AWARD NUMBER: W81XWH-14-1-0571

TITLE: Bright Light Therapy for Treatment of Sleep Problems Following Mild TBI

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REPORT DATE: 29 DEC 2019

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
29 DEC 19	Final Report	30 SEP 14 – 29 SEP 19

4. TITLE AND SUBTITLE

Bright Light Therapy for Treatment of Sleep Problems Following Mild TBI

5a. CONTRACT NUMBER
W81XWH-14-1-0571

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective in this project was to facilitate recovery from mild traumatic brain injury (mTBI) by regulating sleep and circadian rhythms via targeted blue light (BL) exposure. In a pilot study, we found that 30-minutes of daily morning BL for 6-weeks was associated with a significant phase shift in sleep-wake timing, improved daytime sleepiness, enhanced executive functioning, and associated changes in brain structure and function. The present study expanded the original sample by 31 additional participants who underwent the 6-week treatment (Treatment Arm) and included a second sample of healthy normal individuals who underwent a single exposure to BL, followed by functional neuroimaging (Effect Localization Arm). The project has been completed. The Effect Localization Arm showed that BL increased cognitive performance and was associated increased brain activation/neural efficiency. The Treatment Arm confirmed and expanded the pilot findings, suggesting that daily morning BL improved daytime sleepiness and was associated with changes in regional brain volume and functional connectivity. Findings suggest that morning BL can provide a useful adjunctive treatment to facilitate sleep and neurocognitive recovery in patients with mTBI. Further research into this potentially effective treatment for concussion is warranted.

15. SUBJECT TERMS

TBI, traumatic brain injury, concussion, DWI, white matter, brain imaging, light therapy neuropsychological performance, neurocognitive performance, structural connectivity

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	745	19b. TELEPHONE NUMBER *(include area code)* (520) 621-0605

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1. INTRODUCTION

Mild traumatic brain injury (mTBI), or concussion, is among the most common injuries to military personnel (Hoge et al., 2008). For a significant proportion of individuals who sustain a mTBI, post-concussive symptoms (PCS) may persist for years after the injury and interfere with daily functioning (Hoge et al., 2008). Persistent sleep disruption is one of the most common complaints in patients with mTBI (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Castriotta et al., 2007; Makley et al., 2008; Parcell, Ponsford, Redman, & Rajaratnam, 2008; Rao et al., 2008; Verma, Anand, & Verma, 2007; Williams, Lazic, & Ogilvie, 2008), with as many as 40 to 65% complaining of insomnia (Beetar, Guilmette, & Sparadeo, 1996; Dikmen, McLean, & Temkin, 1986; Orff, Ayalon, & Drummond, 2009). Because sleep is critical to the neurogenesis and neural plasticity necessary for recovery from mTBI, sleep enhancement via circadian modulation may be an ideal candidate for direct intervention or adjunct treatment to facilitate recovery. A potentially effective treatment for the sleep problems common in patients with mTBI is selective application of bright light. Exposure to bright blue-wavelength light (BL) has been shown to stimulate melanopsin receptors in the retina, which are directly linked to the suprachiasmatic nucleus, a part of the hypothalamus that regulates sleep-wake cycles (Brainard et al., 2008; Phipps-Nelson, Redman, Schlangen, & Rajaratnam, 2009; Revell & Skene, 2007; Smith, Revell, & Eastman, 2008). Targeted morning stimulation with BL entrains the circadian rhythm, leading to improved sleep quality and daytime alertness (Lack, Gradisar, Van Someren, Wright, & Lushington, 2008; Lack & Wright, 2007; Skene, 2003). There is evidence that BL treatment reduces fatigue in patients who have experienced mTBI (Ponsford et al., 2012; Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014), but until now, no study has directly examined the structural and functional brain changes associated with BL treatment and its influence on sleep following mTBI. We recently completed a small pilot study of the effects of 6-weeks of BL on recovery from mTBI, with evidence of significant improvement (Bajaj, Vanuk, Smith, Dailey, & Killgore, 2017; Killgore, Vanuk, Shane, Weber, & Bajaj, 2019). Thus, the present study aims to: 1) extend our earlier pilot work to double the overall sample size to 60 participants (30 from previous study and 30 from current study, with 30 per light condition—Treatment Arm); 2) evaluate the longevity of treatment effects using actigraphy monitoring for six weeks after treatment; and 3) identify the brain regions most affected by blue relative to amber light exposure by assessing the acute effects of a single 30-minute exposure to blue light versus amber placebo light in 30 healthy control participants (Effect Localization). This Effect Localization Arm will inform focal regions of interest (ROIs) for in-depth analysis of treatment-related changes in neural activation and connectivity in the mTBI treatment portion of the study.

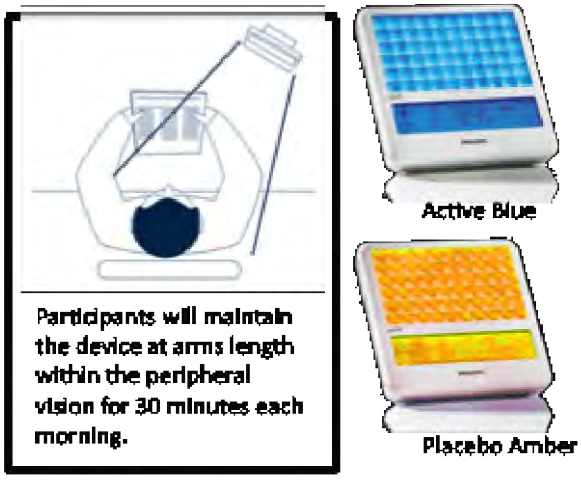


Figure 1. The blue (active) and amber (placebo) light devices.

2. **KEYWORDS**

mTBI, mild traumatic brain injury, concussion, post-concussive syndrome, brain imaging, neuroimaging, functional magnetic resonance imaging, fMRI, actigraphy, blue light therapy, circadian rhythm, neuropsychological performance, neurocognitive performance, structural connectivity, sleep disruption

3. **ACCOMPLISHMENTS:**

- **What were the major goals and objectives of the project?**

The following major tasks were proposed in the Statement of Work (SOW):

EFFECT LOCALIZATION ARM:

Major Task 1: Prepare Regulatory Documents and Research Protocol for both arms of study. **(**Y1: Q1-2**)**

Completed*:* 25 AUG 2014

Major Task 2: Acquire necessary materials and equipment for effect localization arm. (Y1: Q1-2)

Completed*:* 01 DEC 2014

Major Task 3: Hire and Train Study Staff. (Y1: Q2)

Completed*:* 01 DEC 2014

Major Task 4: Collect data for effect localization arm. (Y1: Q3 – Y2: Q3)

Completed*:* 01 APR 2015

TREATMENT ARM:

Major Task 1: Acquire necessary materials and equipment for treatment arm (Y1: Q1-2)

Completed*:* 01 DEC 2014

Major Task 2: Collect data for treatment arm

Completed: 10 May 2019

- **What was accomplished under these goals?**

Recruitment:

Recruitment is completed for both arms of the study. All data collection concluded in May of 2019. Various recruitment methods were utilized including email listservs and flyers posted on University of Arizona campus and at local Tucson businesses.

Figure 2 summarizes the recruitment process for the mTBI Treatment Arm of the study. Cumulatively 1076 individuals completed a telephone screen or online interest form to indicate their interest. Of these, 61 individuals were eligible to participate and 1015 were deemed

ineligible to participate. Of the 61 eligible participants, 51 were enrolled to participant and 31 successfully completed the study. In total 11 participants were deemed ineligible after enrollment and 8 participants discontinued participation in the study. The remaining 11 participants that were deemed eligible either did not return our phone calls or did not show up for scheduled study visits. Amendments to the protocol are listed below.

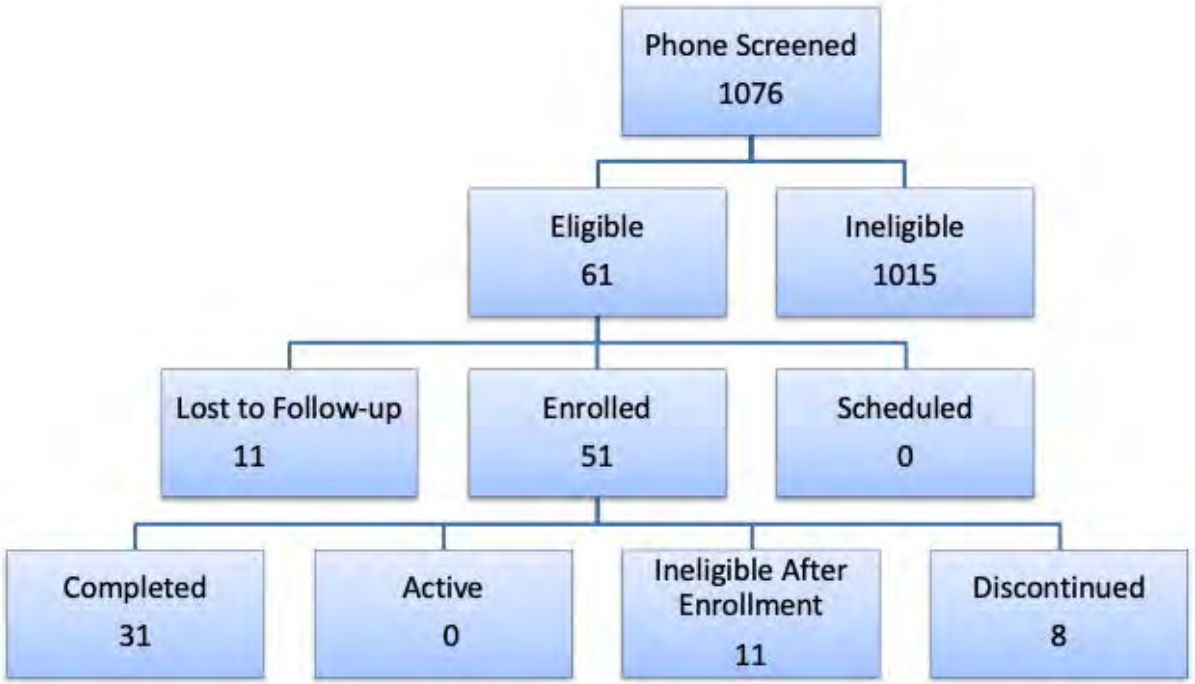


Figure 2. Participant flow diagram for the Treatment Arm.

Amendments:

- Amendment #1 (Approved by local IRB: 25 APR 2014):
  - Updating medical monitor as listed
- Amendment #2 (Approved by local IRB: 02 JUL 2014):
  - Adding FITBIR to all pertinent documents
- Amendment #3 (Approved by the local IRB: 04 AUG 2014):
  - VOTF changes
- Amendment #4 (Approved by local IRB: 16 SEP 2014):
  - Adding Health Control/Effect Localization Arm to F200, ICF
- Amendment #5 (Approved by local IRB: 10 OCT 2014):
  - Adding forms, updating forms, updating ICF, F200, VOTF
- Amendment #6 (Approved by local IRB: 18 NOV 2014):
  - Adding CoC language, forms, updated HC compensation, F200, ICF, VOTF

- Amendment #7 (Approved by local IRB: 02 DEC 2014):
    - Adding DSIQ (HC), EEG Script, FADT & FRT, updating F200, ICF, forms
- Amendment #8 (Approved by local IRB: 06 JAN 2015):
    - Updated ICF, GUID, Phone Screen (HC), VOTF
- Amendment #9 (Approved by local IRB: 03 MAR 2015):
    - Updated VOTF
- Amendment #10 (Approved by local IRB: 15 APR 2015):
    - Increased enrollment numbers and add removal of subjects per PI discretion to ICF. F200
- Amendment #11 (Approved by local IRB: 17 JUL 2015):
    - Updated VOTF and updated F200 - added forms (BDI-II, ISI, Light device Instructions, Symptoms Checklist, and BL2 Flyer), removed forms (Sway and mobility test, EKG in scanner and mail return language)
- Amendment #12 (Approved by local IRB: 07 AUG 2015):
    - Increased enrollment numbers for health control arm to 50 from 40
- Amendment #13 (Approved by local IRB: 22 DEC 2015):
    - Updated VOTF
- Amendment #14 (Approved by local IRB: 03 MAY 2016):
    - Updated F200 to add the SWLS form
- Amendment #15 (Approved by local IRB: 18 MAY 2016):
    - Updated ICF to clarify subjects won't have access to study data until after study finishes
- Amendment #16 (Approved by local IRB: 25 JUL 2016):
    - Updated VOTF
- Amendment #17 (Approved by local IRB: 30 AUG 2016):
    - Added recruitment ads and updated VOTF
- Amendment #18 (Approved by local IRB: 15 NOV 2016):
    - Updated F200 to include EPIC data access, added ads for dorm recruitment, and updated VOTF
- Amendment #19 (Approved by local IRB: 03 FEB 2017):
    - Updated F200: detailed how the EPIC database will be used to recruit participants, removed self-report sleep problems as an eligibility criteria; Updated ICF; Updated phone script; Updated VOTF
- Amendment #20 (Approved by local IRB: 05 APR 2017):
    - Updated VOTF
- Amendment #21 (Approved by local IRB: 10 MAY 2017):
    - Updated ICF, added consent script updated F200 regarding these changes
- Amendment #22 (Approved by local IRB: 31 MAY 2017):
    - Updated F200 - added Qualtrics online screening survey
- Amendment #23 (Approved by local IRB: 18 AUG 2017):
    - Updated F200 - added Pima recruitment and updated ICF
- Amendment #24 (Approved by local IRB: 25 AUG 2017):
    - Updated DSIQ

- Amendment #25 (Approved by local IRB: 11 SEP 2017):
    - Added BPAQ form and updated F200 to reflect this change
- Amendment #26 (Approved by local IRB: 03 OCT 2017):
    - Updated F200 – BPAQ will be given to current participants and new participants; updated VOTF
- Amendment #27 (Approved by local IRB: 19 DEC 2017):
    - Updated DSIQ form
- Amendment #28 (Approved by local IRB: 22 MAR 2018):
    - Updated F200 – added Twilio as a way to communicate with participants
- Amendment #29 (Approved by local IRB: 21 JUN 2018):
    - Updated F200 – added Research Associate Program (RAP) as a means of recruitment
- Amendment #30 (Approved by local IRB: 17 JUL 2018):
    - Updated F200 to remove handedness from exclusion criteria; updated flyers to reflect the change in exclusion criteria; updated VOTF; added RAP referral instructions
- Amendment #31 (Approved by local IRB: 31 JUL 2018):
    - Updated F200, ICF and consent script – made 6-week post-treatment sleep monitoring portion of the study optional follow-up and increased compensation for completion of this (now) optional portion of the study
- Amendment #32 (Approved by local IRB: 17 AUG 2018):
    - Updated F200 to add PSY101 mass screening survey as a source of recruitment
- Amendment #33 (Approved by local IRB: 26 AUG 2018):
    - Updated VOTF

Data preprocessing and quality control:
As outlined by the SOW, all neuroimaging data were uploaded to secure computer workstations, pre-processed, and checked for errors in acquisition as they were collected. The Lab Manager and the Departmental Regulatory Coordinator oversaw compliance with IRB/HRPO regulations via periodic audit of data storage and test administration by study staff. Behavioral data were dually entered and verified by Research Technicians and all collected data was backed up routinely and checked periodically to ensure high inter-reliability scoring across the study.

PRIMARY FINDINGS/RESULTS

As described earlier, the project included two separate data collection arms: 1) Effect Localization Arm, and 2) Treatment Arm. The Effect Localization Arm was designed to examine the effects of a single 30-minute dose of blue-wavelength light on immediate subsequent brain activation in healthy individuals to allow more precision in setting regions of interest for the second arm of the study, which involved individuals with mTBI. The Treatment Arm was designed as a 6-week randomized placebo-controlled intervention study that involved daily 30-minute morning exposure to a light therapy device and pre- and post-treatment assessments to

measure effects on sleep and cognitive functioning. In the sections that follow, we will describe each arm of the study separately and the associated findings.

RESULTS—EFFECT LOCALIZATION ARM:

The purpose of this arm of the study was to obtain an independent sample of healthy individuals from which to derive focal anatomical regions of interest (ROIs) for in-depth analysis in the treatment portion of the study. This arm of the project involved collecting data from healthy control participants exposed to a single half hour dose of either blue- or amber-wavelength light followed by functional neuroimaging within 30-minutes of light cessation.

Data collection for the Effect Localization Arm was completed during Year 1 of the project. Briefly, prolonged exposure to blue wavelength light has been shown to have an alerting effect and enhances performance on some cognitive tasks (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Maquet, & Dijk, 2009; Vandewalle, Schmidt, et al., 2007). A small number of studies have also suggested that relatively short exposure to blue light leads to changes in functional brain responses during the period of exposure. However, the extent to which blue light continues to affect brain functioning during a cognitively challenging task during the period after cessation of the light (i.e., roughly 30 minutes or longer), is not well understood. Therefore, for the Effect Localization Arm, we conducted a between-group comparison of blue versus amber placebo control light exposure.

Total Sample Characteristics

For the Effect Localization Arm, a total of 36 healthy participants were recruited to undergo a single day experiment involving exposure to either blue (n = 18) or amber (n = 18) wavelength light for 30 minutes in a darkened room, followed immediately by functional magnetic resonance imaging (fMRI) while undergoing several different cognitive and emotional tasks (described below). All participants were right handed, primary English speakers, who were free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 20:00 and 01:00. Demographic data for the total sample are presented in Table 1 below and show that there were no significant baseline differences in general demographic factors.

Demographics	Blue (active)		Amber (placebo)		
	M	SD	M	SD	p-value
Age	21.61	2.83	22.28	4.03	.57
Education	14.11	1.97	13.94	1.83	.79
Height (inches)	67.56	3.96	65.89	4.24	.23
Weight (pounds)	152.89	26.70	151.83	46.11	.93
Full Scale IQ	106.83	14.46	107.17	11.74	.94
Male/Female (n)	9/9	--	8/10	--	.74

Table 1. Demographic data for the Effect Localization Arm (n = 36).

General Procedure

In this Effect Localization arm of the study, participants arrived at the lab in the morning and began data collection at 08:15. Participants first completed a number of questionnaires about sleep habits and mood, followed by administration of the Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II) as a measure of intellectual ability.

Beginning at 09:05, participants completed the first portion of the California Verbal Learning Test (CVLT-II), which involved 5 trials during which they were read a list of 16 words and were asked to try to recall as many words as possible. A distractor list was then given, followed by an immediate recall trial for the previously learned list. Participants provided a saliva sample for melatonin baseline, a Stanford Sleepiness Scale (SSS), and then underwent a controlled light exposure while sitting in an otherwise completely darkened room. All participants began with a 30-minute light *Washout Period* that involved sitting in a dark room while only exposed to two amber light devices (described below) mounted on a desk at a distance of approximately 80 cm from participant nasion, with each light centered at a 45-degree angle from midline (see Figure 2 Left). Actual distance and angle of the light devices were adjusted manually until the pair of amber devices used during the initial washout period resulted in a 20-lux reading as measured by a light meter (Digital Lux Meter LX1330B) on each side of the participant's nose. During the *Exposure Period,* light was administered by a similar configuration of four light devices, also centered at 45 degrees to each side of the participant with a distance of approximately 80 cm from the participant's nasion (see Figure 2). During the *Exposure Period*, the light devices were either blue or amber depending on random assignment (see Figure 2 Right). Blue light exposure utilized an array of commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). Each device consisted of a plastic table-mounted chassis with a 10 x 6 array of light emitting diodes (LEDs), encased in 1 x 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and panel irradiance (mW/cm^2) = 1.23 at 20 cm). The amber devices were provided by the manufacturer for research purposes and were essentially identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and total irradiance (mW/cm^2) = 0.35).

Participants were exposed to the 4-light array for 30-minutes. During this time, they completed a 10-minute psychomotor vigilance test (PVT), several practice tasks to be completed in the scanner later, and another PVT at the end of the session. A second saliva sample and SSS was collected at the end of the light session. Upon termination of the light, participants donned amber colored glasses and were escorted next door to the MRI scanner where they completed a 90-minute session of structural and functional MRI scans. After the scans, participants provided a third saliva sample and completed another SSS. Participants were then released for the remainder of the day at 13:00 and were required to return to the lab for a fourth melatonin sample and SSS at 20:45. Figure 2 (bottom) shows the general timeline for study activities.

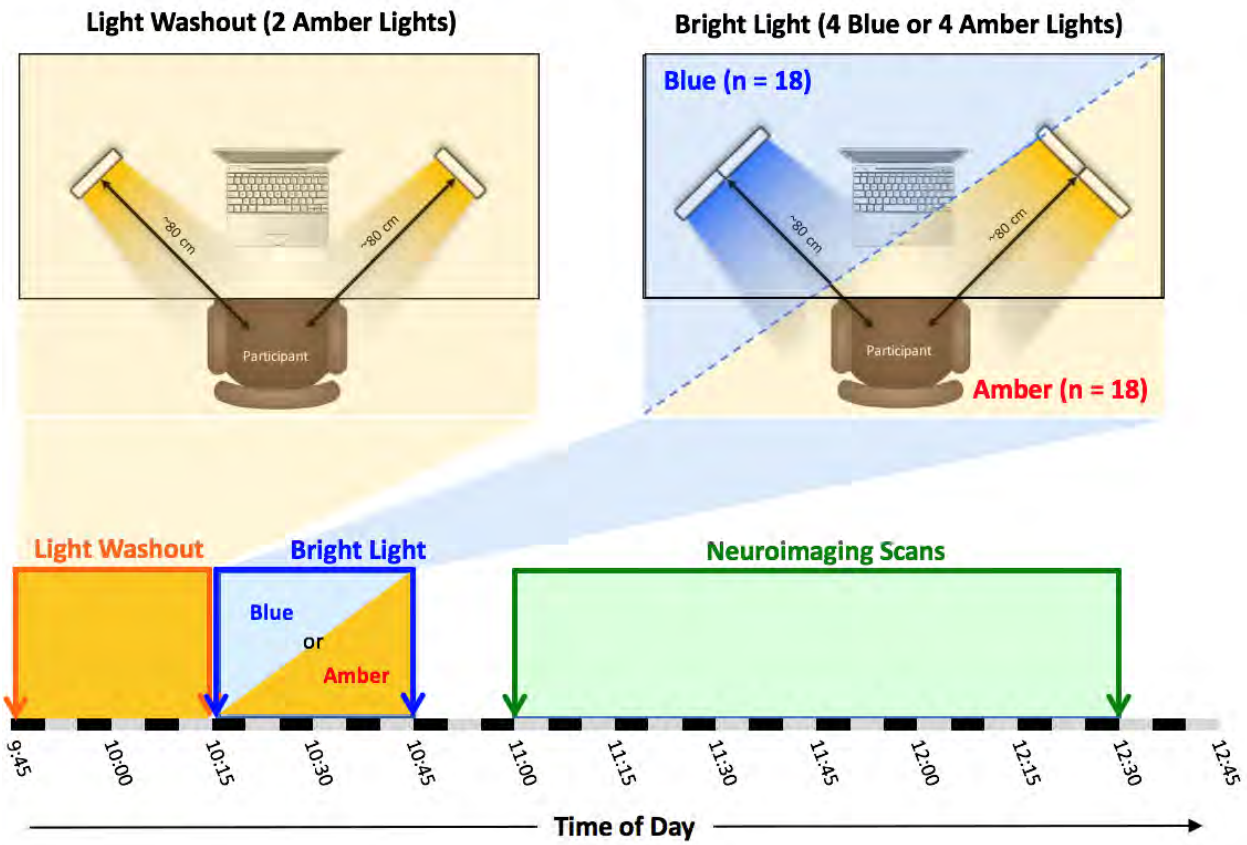


Figure 2. Experimental conditions and schedule. All participants began the study session by completing a 30-minute "light washout" period from 9:45 a.m. to 10:15 a.m. to minimize prior exposure to ambient blue light. During that time, participants sat in a darkened room facing two amber light devices at 45-degree angles from the center of fixation. During this time, participants completed a 5-minute practice session with the Multi-Source Interference Task (MSIT) on a laptop computer. Beginning at 10:15 a.m., participants were randomly assigned to receive 30-minutes of blue or amber bright light exposure. Bright light exposure was provided by four light devices (either all blue or all amber) in the same location as the previous amber light washout devices. After the bright light exposure period, participants were escorted to the neuroimaging scanner to undergo functional magnetic resonance imaging. The MSIT task began at ~11:17 a.m. and ended at ~11:25 a.m..

Long-Term Memory

California Verbal Learning Test (CVLT-II). Acute exposure to light within the blue wavelengths has been shown to enhance alertness and vigilance, and lead to improved speed on reaction time tasks, possibly due to activation of the noradrenergic system (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle et al., 2009; Vandewalle, Schmidt, et al., 2007). It remains unclear, however, whether the effects of blue light extend beyond simple alertness processes to also enhance other aspects of cognition, such as memory performance. Here, we aimed to investigate the effects of a thirty-minute pulse of blue light versus placebo (amber light) exposure in healthy normally rested individuals in the morning during verbal memory consolidation (i.e., 1.5 hours after memory acquisition) using the California Verbal Learning Test (CVLT-II), an individually administered test of verbal memory and associated cognitive processes. Participants completed the immediate recall, short-delay, and long-delay free recall parts of the CVLT-II. Participants were read a list of words and told they would be

asked to repeat as many words as possible. This test-recall procedure was repeated 5 times (*immediate recall, trials 1-5*). The list consisted of 15 neutral words evenly divided into the following categories: animals, furniture, vegetables, and modes of transportation. After the 5th trial, participants were read a second list (i.e., distractor list) and asked to repeat only words from the second list. Immediately following recall of the second list, participants were asked to recall only words presented in initial list (*short-delay free recall*). Approximately 1.5 hours after the short-delay free recall subtest, participants were asked to recall as many words from the initial list (*long-delay recall*). Raw scores (i.e., total number of words recalled) as well as standard scores (i.e., raw scores converted to norm-referenced scores) were calculated for each trial.

Statistical Analysis. Change in performance from CVLT-II short-delay free recall to long-delay free recall raw and standard scores between the blue and amber light exposure groups were analyzed using repeated-measures analysis of covariance (ANCOVA), using WASI-FSQI and BDI-II scores as covariates.

Preliminary analyses. In order to rule out any group differences prior to the light exposure, independent samples t-tests were conducted comparing performance on the CVLT-II between the blue and amber light group. There were no differences in standard scores on the CVLT between the two groups at trial 1 ($t(28) = .56$, $p = .57$), trial 5 ($t(28) = -1.29$, $p = .21$), or on total performance standard scores (sum of trials 1-5) ($t(28) = .17$, $p = .87$). These findings suggest that the two groups did not differ in their initial learning or retention of the word list prior to exposure to the light conditions. In addition, the two groups did not differ in age, sex, sleep duration the night before the day of testing, number of caffeinated products consumed on the morning before testing, WASI-II FSQI total and Vocabulary subscale scores. Participants also did not differ on habitual bedtime, or habitual sleep duration. However, participants in the amber light group did report significantly earlier habitual wake times (7:20 am; SD = 60 min) than participants in the blue light group (8:07 am; SD = 54 min; $t(28) = -2.15$, $p = .04$). Participants' habitual wake times were therefore included as an additional covariate in the analyses below.

Hypothesis testing. The repeated-measures ANCOVA showed a significant main effect of time ($F(1, 25) = 5.06$, $p = .03$, $d = .09$) as well as a group x time interaction ($F(1, 25) = 4.39$, $p = .05$, $d = .84$). Post-hoc pairwise comparisons showed that while there was no significant difference from pre- to post-light exposure for the blue light group ($p = .13$), there was a significant decline in CVLT standard scores from pre- to post-light exposure for the amber light group ($p<.001$). In addition, there was no difference between the two groups for CVLT short-delay recall scores ($p=.92$), and there was no significant difference between the two groups for the CVLT long-delay recall score ($p = .20$).

As standard scores can be difficult to interpret because they include corrections for age and gender, we re-ran the analysis using CVLT raw scores. While, there was no significant main effect of time ($F(1, 25) = 2.45$, $p = .13$, $d = .62$), there was a significant group x time interaction ($F(1, 25) = 4.50$, $p = .04$, $d = .85$). Figure 3 shows participants in the blue light group forgot an

average of 0.19 words, whereas participants in the amber light group forgot an average of 1.88 words from short-delay to long-delay recall. This translates to an average decline of only 1.48% in delayed verbal recall for individuals receiving the active blue light treatment, but an average decline of 14.62% for individuals in the amber placebo light group.

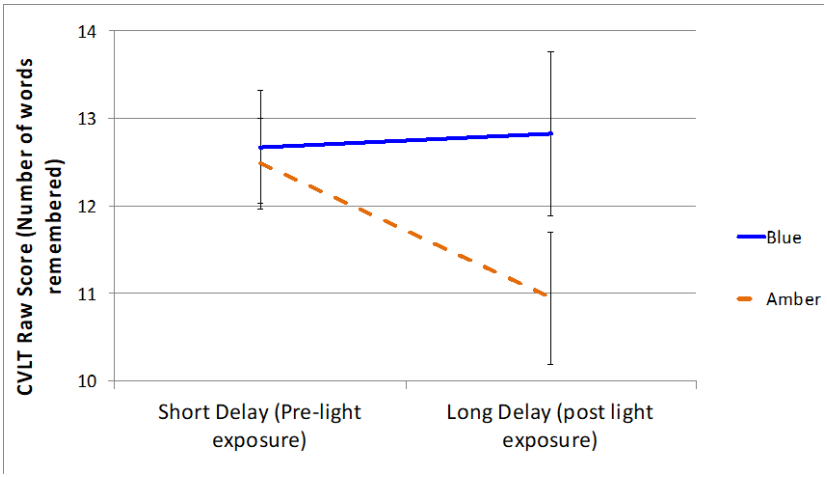


Figure 3. The estimated marginal means and error bars (1SE) for CVLT –II short-delay and long-delay raw scores for individuals in the blue (n = 12) and amber (n =18) light groups are displayed. CVLT-II: California Verbal Learning Test (Version 2). Blue light sustained memory performance over the delay period while amber placebo light was associated with a decay in memory.

In summary, exposure to 30-minutes of blue wavelength light during memory consolidation led to better subsequent delayed verbal memory recall, when compared to an amber (placebo) light condition. These findings may have important implications for clinical populations with memory impairments, as well as for healthy individuals who want to improve their ability to retain newly learned material. Considering this is the first study to investigate whether 30 minutes of blue light exposure can influence memory performance, future research will be necessary to confirm this effect, and to investigate the precise mechanisms, optimal dose/timing of administration, and possible application to clinical samples. This finding was published in the journal PLoS One in 2017 (Alkozei, Smith, Dailey, Bajaj, & Killgore, 2017).

Neuroimaging

N-Back Task. It was of interest to determine whether blue light was more effective than amber placebo light at activating prefrontal brain regions during working memory. We hypothesized that during a standard working memory task, participants who had received 30-minutes of exposure to blue-wavelength light would show greater activation within the dorsolateral prefrontal cortex relative to those receiving the placebo amber light condition. The N-Back is a classic working memory task that has been widely used in functional magnetic resonance imaging (fMRI) studies. The *N*-back task used in this study was a letter variant of the visually presented *N*-back task (Gevins & Cutillo, 1993) to assess working memory. The letter variant of the N-back task, in addition to auditory and visuospatial versions, is a widely used variant of the N-back task (Owen, McMillan, Laird, & Bullmore, 2005). Participants were presented with a black screen with centered white letters, appearing one letter at a time (see Figure 4). The *N*-back task was split into three different conditions. In the one-back condition, participants responded using the index or middle finger of their right hand to indicate whether the current letter presented was identical to the letter presented in the immediately preceding trial. In the two-back condition, participants responded whether the current letter presented was

identical to the letter presented two letters previously. In addition, participants completed a control condition (i.e., “zero-back”), whereby they were asked to identify whether the letter on the screen matched a predetermined letter (e.g., “P”). Each condition was presented three times for 52 seconds in a pseudorandom order. Participants saw a crosshair for 10 seconds, then saw a screen indicating the instructions for the next block (0-back, 1-back or 2-back) for 6000ms. Sixteen letters were presented in each condition and each letter was presented for 500ms. Participants had 1750ms to respond to each item. The task ended with a final crosshair for 10 seconds. The whole task lasted 7 minutes and 58 seconds. Participants practiced one version of the task outside of the scanner, which involved completing each condition once with feedback to ensure that they understood the task before completing it in the scanner. Verbal instructions were given to participants while in the scanner and they were encouraged to ask any questions that they might have had before beginning the task.

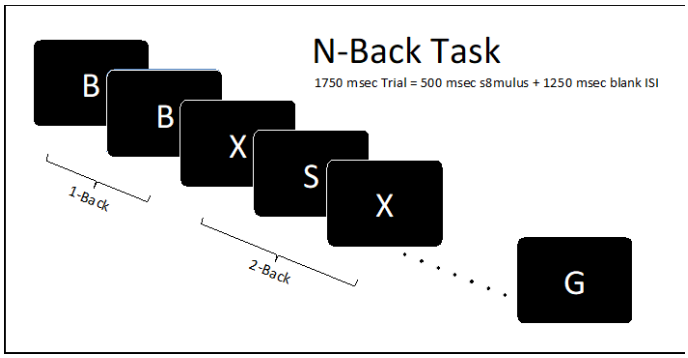


Figure 4. N-Back Task. This is a working memory task where the participant must press a key each time the letter on the current screen matches a letter seen on a previous screen, either 1-back or 2-back.

Usable data were available from 35 participants (17 male; 18 female). There was no difference in accuracy and response time between the blue and amber placebo groups for the zero-back condition, but participants in the blue group responded faster during the one- ($t(33) = -2.26$, $p=.03$) and two-back conditions ($t(33) = -1.98$, $p = .05$) than participants in the amber placebo group.

Neuroimaging Methods. Participants underwent fMRI immediately after completion of the 30-minute exposure to either blue or amber light. Neuroimaging scans were collected on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.33 ms/ 12 degree) over 176 sagittal slices (256 x 256) and a slice thickness of 1.00 mm (voxel size = 1 x 1 x 1). T2*-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/ 25.0 ms/ 90 degree) with 239 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 x 64 acquisition matrix.

Image Processing. Processing and analysis of neuroimaging scans was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; *http://www.fil.ion.ucl.ac.uk/spm*). Raw functional images were first preprocessed by realigning and unwarping the functional images, and then co-registering the newly created mean functional image to each subject’s structural T1 scan. Forward deformation fields were used to normalize the images from subject native space to Montreal Neurological Institute (MNI) coordinate space. Finally, the images were spatially smoothed (6 mm full-width at half maximum), and resliced to 2 x 2 x 2 mm voxels. A high pass filter with a 128 second cut-off period was used to remove low

frequency confounds. The standard canonical hemodynamic response function in SPM was employed, and serial autocorrelation was corrected with an autoregressive model of 1 (+white noise). Motion artifacts exceeding 3 SD in mean global intensity and scan-to-scan motion that exceed 1.0mm were regressed out using the Artifact Detection Tool (*http://www.nitrc.org/projects/artifact_detect/*).

Statistical Analysis. On an individual basis, a general linear model (GLM) was specified to contrast activation between the two-back > zero-back condition. These contrast images were entered into a second-level independent samples t-test analysis with light group (blue versus amber) as the independent variable. Based on our *a priori* hypotheses and previous findings from a large meta-analysis of normative functional neuroimaging studies using the *N*-back task (Owen et al., 2005), spheres of a 10 mm radius centered on stereotaxic coordinates derived from the previous meta analysis were placed in areas of the DLPFC and VLPFC. The Talairach coordinates reported in Owen et al. (2005)(Owen et al., 2005) were transformed to MNI coordinates using the MNI2TAL online program from Lacadie et al. (2009) (Lacadie, Fulbright, Rajeevan, Constable, & Papademetris, 2008) (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). The following MNI coordinates were used: DLPFC (x = 41, y = 31, z = 30; x = -37, y = 45, z = 21; x = -46, y = 19, z = 22), and VLPFC (x = -31, y = 21, z = 4; x = 34, y = 23, z = 1). Analyses were thresholded at $p < .001$ (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, family wise error (FWE) corrected at $p < .05$, and k (extent) ≥10 contiguous voxels.

In addition to the primary analysis of our hypothesized effects, we also conducted an exploratory whole brain analysis to provide complete data for future hypothesis generation. Here, we used a slightly more liberal height threshold of $p < .005$, while protecting against Type I error through a cluster-corrected extent threshold of 201 voxels, which represents an FWE correction of $p < .05$ (Woo, Krishnan, & Wager, 2014). Because this analysis was exploratory, we had no *a priori* hypothesis and merely present these supplemental findings for completeness and to obviate bias in reporting.

Descriptive Statistics. According to self-report, participants slept on average 7.2 hours (SD = .94) per night, and obtained 6.8 hours (SD = .72) of sleep the night before the assessment. Participants reported going to bed on average at 11:32pm (SD = 1:04 hours) and waking at 7:37am (SD = 1:02 hours) on weekdays. Participants were told to adhere to their normal caffeine use patterns so that excess or withdrawal patterns did not affect the data. Participants reported drinking an average of 0.93 (SD = 0.89) caffeinated products per day and eight participants (4 in each group) reported having had one caffeinated product prior to the assessment, which was consistent with their normal morning consumption patterns. Groups did not differ on age, gender, years of education, mean number of hours slept on weeknights, number of hours slept the previous night, waking and bed times, mean number of caffeinated products consumed per day, and general levels of intelligence as measured using the WASI-II.

Behavioral Results. A repeated-measures ANOVA showed no differences in self-reported sleepiness, as measured with the SSS, over the three time points ($F(2, 31) = .12$, $p = .88$). There was no difference in accuracy and response time between the blue and amber placebo groups for the zero-back condition, but participants in the blue group responded faster during the one- ($t(33) = -2.26$, $p=.03$) and two-back conditions ($t(33) = -1.98$, $p = .05$) than participants in the amber placebo group.

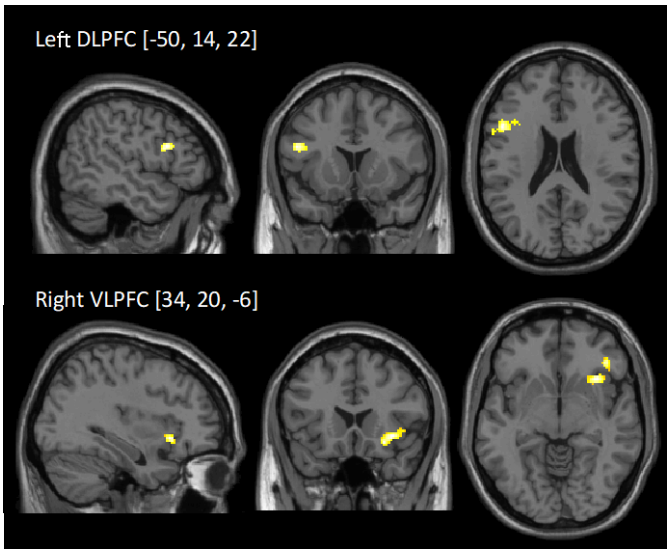


Figure 5. SPM images showing the clusters of significant activation where Blue > Amber for the N-Back task (2-back > 0-back). Based on the a priori regions of interest, this comparison revealed that the blue light condition was associated with significantly greater activation within the left dorsolateral prefrontal cortex (DLPFC) and the right ventrolateral prefrontal cortex (VLPFC) when compared to the amber light condition during complex working memory. Clusters are significant at p < .05, FWE corrected, but are displayed at p < .005 for ease of visualization.

Neuroimaging results. For the two-back > zero-back contrast, individuals in the blue light group showed significantly greater activation in a cluster within the left DLPFC ($k = 29$; $p_{FWE} = .03$; $t = 4.12$; $x = -50$, $y = 14$, $z = 22$, small volume corrected) and a cluster within the right VLPFC ($k = 17$, $p_{FWE} = .006$, $t = 4.83$; $x = 34$, $y = 20$, $z = -6$, small volume corrected) than individuals who were exposed to the amber placebo light (see Figure 5). There were no regions within the brain where amber placebo light exposure was associated with faster response times than blue light exposure.

In order to investigate the association between regional activation and behavioral responses, we extracted the activation for the unadjusted cluster eigenvariate for both brain regions and conducted Pearson's correlations between the eigenvariate and response time and performance metrics during the two-back condition. There was a negative correlation between the VLPFC activation and response time ($r = -.35$, $p = .04$). This correlation was present among the sample as a whole and was not driven by one group in particular (see Figure 38). No significant associations with accuracy were found. In addition, no significant associations were found between activation within the DLPFC and performance on the working memory task. Thus, individuals in the blue group who showed greater VLPFC activation showed faster response times.

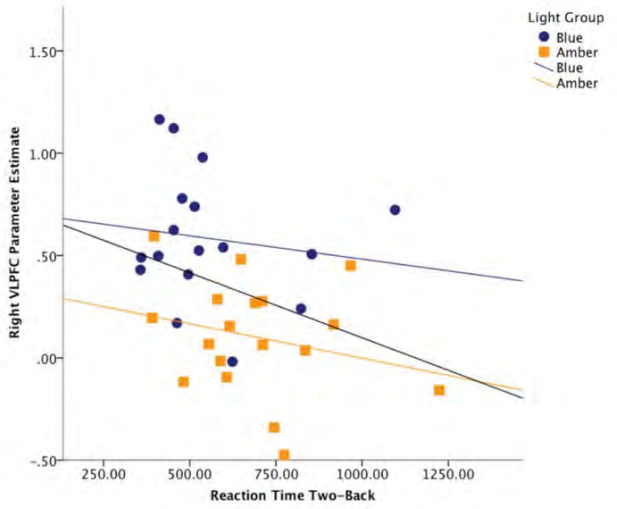


Figure 38. The scatterplots illustrate the association between the activation within the right ventrolateral prefrontal cortex (VLPFC) and reaction time during the two-back condition for the blue and amber light groups, and the sample as a whole.

To investigate whether participants were more 'efficient' with increases in working memory (i.e., the number of correct responses per second), a measure of cognitive throughput was calculated ((Accuracy x (1/RT) *1000)) (Thorne, 2006). Throughput provides a quantitative metric of the speed versus accuracy tradeoff. While there was no difference in throughput between the two groups in the zero-back condition ($t(33) = -1.60$, $p = .19$), participants in the blue group showed enhanced throughput in the one-back ($t(33) = -2.57$, $p = .01$), and marginally higher throughput in the two-back condition ($t(33) = -1.92$, $p = .06$) than the amber placebo group. In other words, participants in the blue light group provided a greater number of correct responses per unit of time than participants in the amber placebo group (see Figure 7). Given that the groups were essentially equivalent with regard to accuracy, this difference suggests that exposure to blue light led to faster response times with no loss in accuracy.

Finally, exploratory whole brain analysis was undertaken for the purpose of facilitating future hypothesis generation, with a peak height threshold of $p < .005$, and cluster-corrected extent threshold of $p < .05$ (FWE corrected). Again, comparing the two-back > zero-back contrast, we found that the blue-wavelength light exposure group showed significantly greater activation than amber placebo light within several distributed regions including left and right VLPFC (i.e., inferior frontal gyrus/insula), left and right middle temporal gyrus, right posterior cingulate gyrus, left middle occipital cortex, brainstem, and thalamus (see Figure 8 below). There were no regions in the brain showing greater activation to the amber placebo control light compared to blue light during the working memory task.

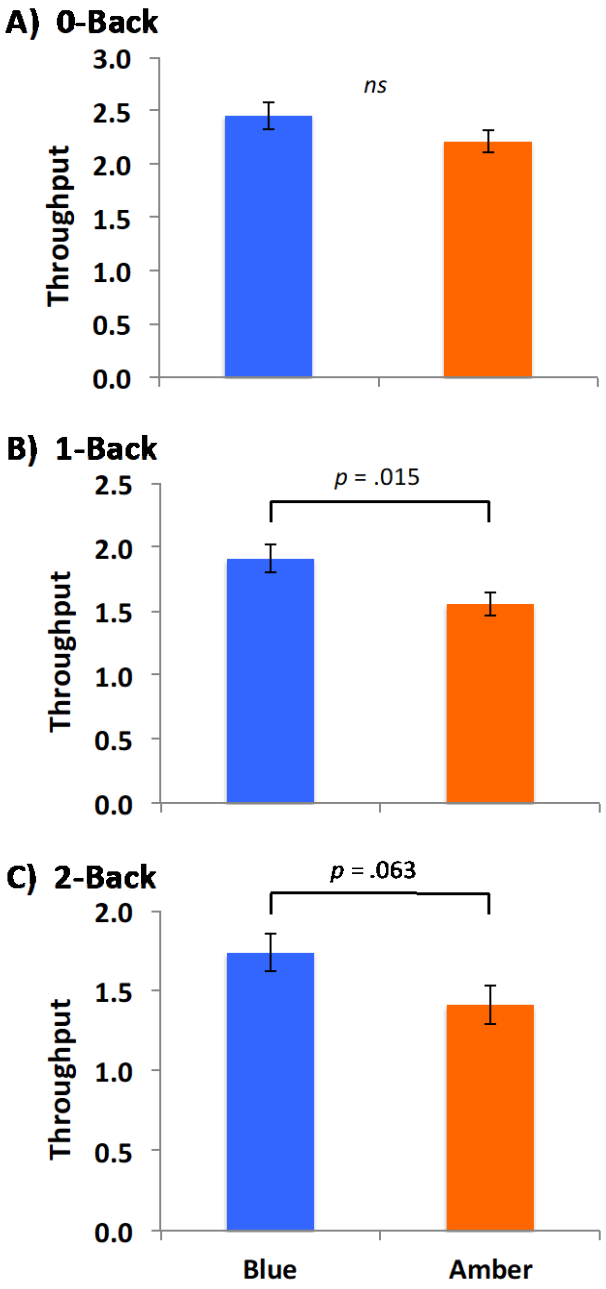


Figure 7. The figure shows group differences in working memory cognitive throughput ((Accuracy x (1/RT) *1000)), which is a measure of the speed x accuracy trade-off. A) There was no difference between the blue and amber groups with regard to throughput performance on the 0-back task. B) On the 1-back task, the blue light group showed significantly enhanced throughput performance compared to the amber control group. C) On the 2-back task, there was a marginally significant trend toward greater throughput for the blue compared to the amber placebo group.

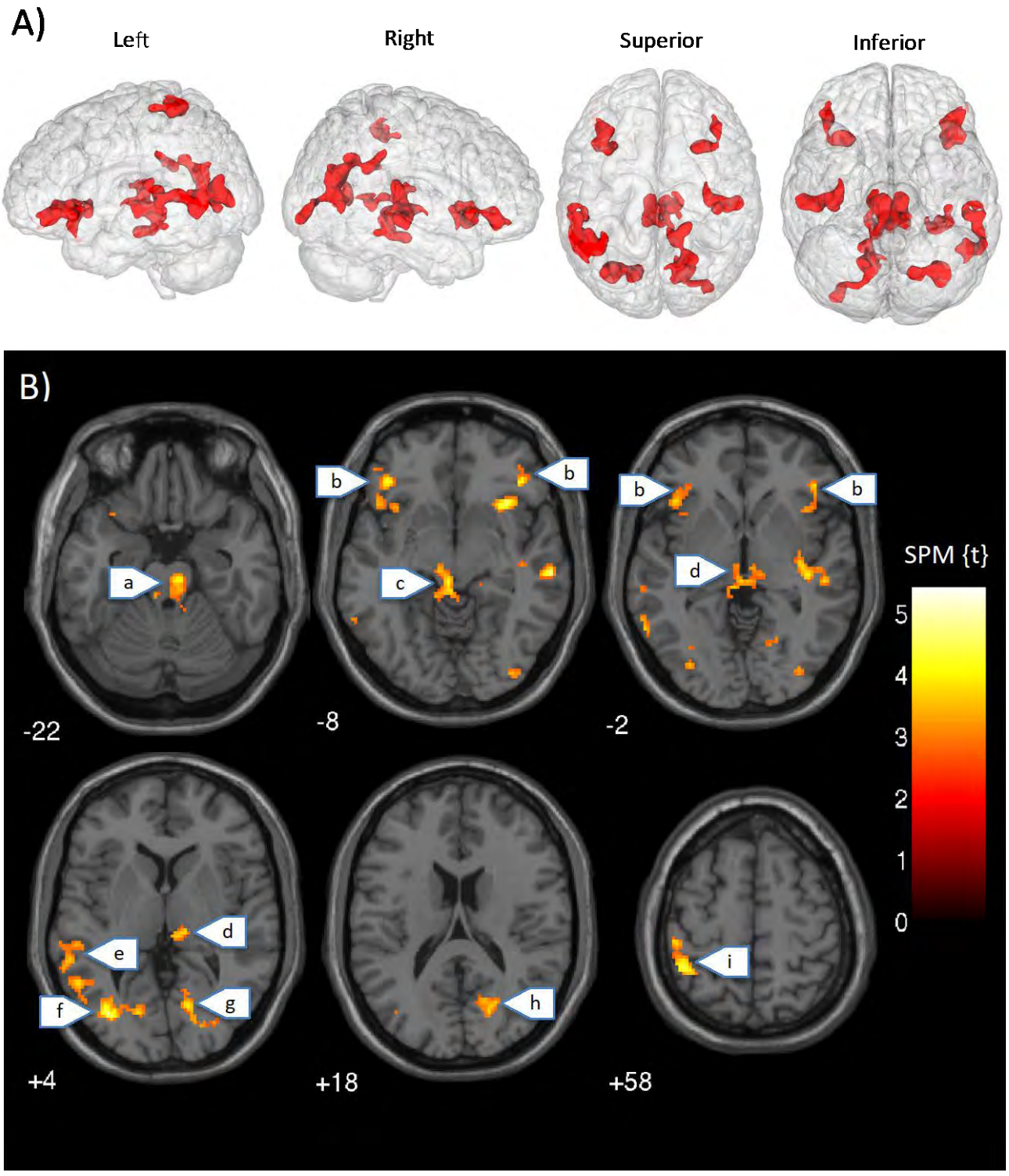


Figure 8. The scatterplots illustrate the association between the activation within the right ventrolateral prefrontal cortex (VLPFC) and reaction time during the two-back condition for the blue and amber light groups, and the sample as a whole.

This paper was published in the journal SLEEP (2016), 3, 1671-1680 (Alkozei, Smith, Pisner, et al., 2016) . Overall, this finding represents the first published study to suggest that a relatively brief, single exposure to blue light has a subsequent beneficial effect on working memory performance, even after cessation of exposure, and leads to temporarily persisting functional brain changes within prefrontal brain regions associated with executive functions. These findings may have broader implication for using blue-enriched light in a variety of work settings where alertness and quick decision-making are important.

Melatonin Changes. Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle, with profound increases in circulating levels during the nighttime and nearly non-existent levels during daylight hours (Cajochen, Krauchi, & Wirz-Justice, 2003). While melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and executive function. We measured the change in salivary melatonin from mid- to late-morning in a subsample of the participants described above who completed the N-Back task. As described above, participants provided saliva samples at three time points: 09:45 (MEL1), 10:45 (MEL2), and 12:45 (MEL3).

Saliva Assays. All materials for salivary melatonin collection were acquired from Salimetrics (State College, PA). Saliva was collected via passive drool method and stored in a 2 mL cryovial made of polypropylene. Within 3 minutes of collection, samples were placed in a Styrofoam cooler with ice packs and subsequently transferred to and stored in a freezer set and monitored to maintain sample storage at a temperature of -20 degrees Celsius. Samples were analyzed using Salimetrics Salivary Melatonin EIA kits according to standard procedures (https://www.salimetrics.com/assets/documents/1-3402n.pdf).

Statistical Analysis. Our interest was to examine the brain activation responses predicted by changes in salivary melatonin from pre- to post-light exposure. Therefore, melatonin data from the 0945 (MEL1) sample were subtracted from the mean of the 1045 (MEL2) and 1245 (MEL3) samples (i.e., ([MEL2+MEL3]/2) - MEL1) to derive a melatonin change score (MEL Change). The individual contrast images for the N-Back task, as described above, were entered as the dependent variable in an SPM12 linear regression analysis with MEL Change as the independent variable. Significant clusters were identified by initially thresholding the statistical maps at $p < .001$, and then applying a $p < .05$ false discovery rate (FDR) cluster extent threshold. The data from significant clusters were extracted and transferred for further analysis in IBM SPSS 20. Further regression analyses were conducted to determine the individual and combined effects of light exposure, MEL Change, and their interaction on brain activation.

There was considerable individual variability in the magnitude and direction of change in melatonin across the morning, with 14 individuals showing a decline and 11 showing an increase from mid- to late-morning. Consequently, when the sample was considered as a whole, salivary melatonin levels did not decline significantly during the study period (Mel Change $M = -.18$, $SD = 3.01$, $t[24] = -0.31$, $p = .76$), and this change did not differ significantly between the blue ($M = -.59$, $SD = 3.53$) and amber ($M = .33$, $SD = 2.24$) light groups, $t(23) = 0.75$, $p = .46$. Behaviorally, greater decline in melatonin levels was associated with marginally

better throughput (i.e., the number of correct responses per second; [% correct/RT]*1000) for the 0-Back (r = -.32. p = .055, 1-tailed), but not for the 1-Back (r = -.22, p = .14, 1-tailed) or 2-Back (r = -.15, p = .23, 1-tailed) conditions, suggesting that declines in melatonin were associated with improved vigilance.

Our primary hypothesis focused on the association between changes in melatonin and brain activation associated with working memory. However, it was first important to rule out any potential effects of melatonin change on simple vigilance performance. Thus, we first conducted three correlational analyses to examine the relation between melatonin change and brain activation for the pure vigilance (0-Back > Fixation), and low working memory load (1-Back > Fixation), and low working memory minus vigilance conditions (1-Back > 0-Back). At our a priori statistical threshold of p < .001, with cluster correction of p < .05, we found no activations that survived in any of these correlation analyses.

However, for our primary hypothesis regarding activation during high working memory load, the decline in melatonin levels during the morning was associated with increased task-related activation in two clusters within the prefrontal cortex for the 2-Back > 0-Back contrast (see Figure 9). The first was a cluster (k = 75) located within the left medial superior frontal gyrus (MNI Coordinates: x = -12, y = 28, z = 54, T = 5.21, *p* = .046, FDR cluster corrected, Figure 2a), and the second was a cluster (k = 76) located within the right inferior frontal gyrus (MNI Coordinates: x = 48, y = 36, z = 10, T = 4.85, *p* = .046, FDR cluster corrected, Figure 2b). As shown in the scatterplots of Figure 2, MEL Change accounted for more than 50% of the variance in brain responses in these two regions.

Activation within the medial prefrontal cortex cluster was significantly associated with better throughput (i.e.,

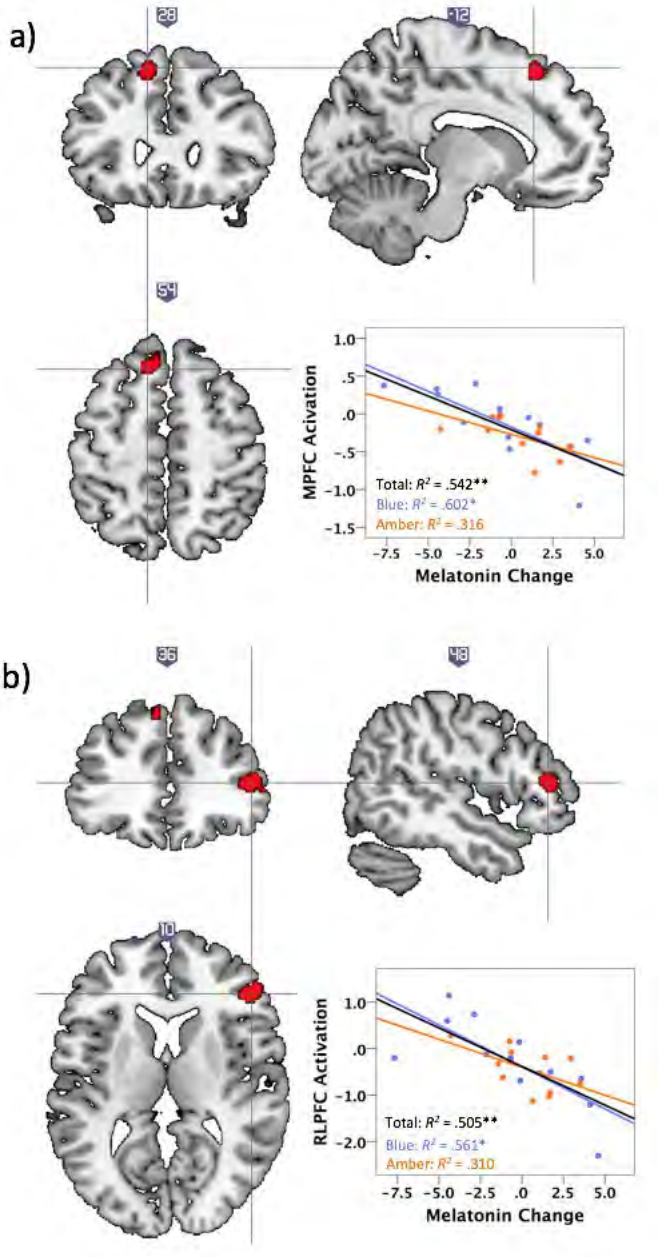


Figure 9. Three dimensional views of the cortical regions showing significant (p < .05, FDR cluster corrected) correlation with melatonin change for the contrast of interest (i.e., 2-Back > 0-Back), including a) the left superior medial frontal gyrus [x, y, z: -12, 28, 54], and b) the right inferior frontal gyrus (trigone region) [x, y, z: 48, 36, 10]. The scatterplots show the association between melatonin change from baseline to the time of the scan and its association with prefrontal activation for the group as a whole (black line), and the blue and amber light conditions separately. *p < .005, **p < .001.

correct responses per second) performance on the 0-Back (r = .34, p = .047, 1-tailed), and marginally so for the 1-Back (r = .29, p = .08, 1-tailed), but not the 2-Back (r = .22, p = .14, 1-tailed) conditions. The activation cluster in the lateral prefrontal cortex was not significantly associated with any level of N-Back performance (all *r*s < .25).

It was also of interest to determine whether the associations between MEL Change and brain activation differed as a function of the light exposure. We therefore conducted a stepwise multiple linear regression analysis to evaluate the contribution of light category to the models. For the first cluster, located in the left medial superior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (Change in R^2 = .016, p = .38) above and beyond the effects of MEL Change, and the addition of the light condition x MEL Change interaction term also did not contribute significant prediction to the model (Change in R^2 = .013, p = .44). Similarly, for the second cluster located in the right inferior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (Change in R^2 < .001, p = .998), and the addition of the light condition x MEL Change interaction term also did not contribute significantly to the model (Change in R^2 = .012, p = .45).

We conclude that changes in morning salivary melatonin were associated with functional brain responses during a working memory task. The magnitude of decline in salivary melatonin during the late morning hours was associated with increased brain activation within dorsomedial and lateral prefrontal cortex, brain regions involved in vigilance, action selection, and cognitive control. These changes were modestly associated with improved vigilance performance during the task, but not with complex executive function. These findings suggest that changes in morning melatonin levels are associated with differences in prefrontal cortex functioning. We interpret these associations as reflecting individual differences in circadian phase of melatonin and their potential impact on the morning establishment of prefrontal functioning in the hours following awakening.

Emotional Anticipation Task. It is well established that light exposure has positive effects on mood and emotional functioning. We were, therefore, also interested in whether blue-wavelength light would affect emotional processing within the brain. The goal of the was to examine the effects of acute exposure to blue wavelength light on immediate post-exposure responses within neural systems implicated in affective regulation. Such systems, which include the amygdala, insula, anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC), among others, have been shown to be dysregulated in individuals with depression and anxiety, particularly when perceiving threatening stimuli (Lee et al., 2007; Stein, Simmons, Feinstein, & Paulus, 2007) and when anticipating aversive stimuli (Nitschke et al., 2009; Straube, Mentzel, & Miltner, 2007; Strigo, Simmons, Matthews, Arthur, & Paulus, 2008). It has been shown that in anticipation of reward, firing of neurons within the ACC increases as reward approaches (Shidara & Richmond, 2002); interestingly, depressed individuals show reduced activation of the ACC during reward anticipation (Smoski et al., 2009), and this resolves with successful treatment (Dichter et al., 2009). Further, synaptic plasticity within the ACC (which may underlie the learning rate within the aforementioned decision-making functions) appears to be facilitated by greater norepinephrine release under conditions of 'certain reward' anticipation (Izumi & Zorumski, 1999; Katsuki, Izumi, & Zorumski, 1997; Silvetti, Alexander, Verguts, &

Brown, 2014); as blue light is known to increase norepinephrine release from the LC (which itself has extensive projections to the ACC), this suggests that, under such conditions, blue light should increase the synaptic activation within the ACC associated with the integration of reward prediction-error and related learning mechanisms (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Florin-Lechner, Druhan, Aston-Jones, & Valentino, 1996). In this part of the project, we measured functional brain responses during three conditions of anticipation ('certain threat' cues, 'certain reward' cues, or 'uncertain event' cues) in healthy adults following a single dose of thirty minutes of blue wavelength versus an equal exposure to an amber wavelength light condition. We aimed to explore how exposure to thirty minutes of blue wavelength light would lead to functional brain changes within the amygdala, insula, ACC and mPFC during anticipation of 'certain threat', 'certain reward' and 'uncertain event' stimuli, in comparison to an equal dose of placebo (amber) light.

The Emotional Anticipation Task (EAT) was designed to evaluate the brain activation associated with anticipating a positive, negative, or uncertain stimulus (see Figure 10). The task was adapted from Aupperle et al.'s (2013) (Aupperle et al., 2013) study design and lasted a total of 460 seconds. Participants completed the task in the MRI scanner by viewing images on a translucent projection screen and viewed through the mirror mounted on the head coil. For each trial, participants were presented with a grey background with a black arrow that alternated randomly pointing either left or right (baseline condition). For each image, participants were instructed to indicate via button press the direction the arrow was pointing. Participants were told that occasionally the screen color would change to signify that another type of image was to follow. Specifically, when the screen turned yellow, a negative picture would soon appear ('certain threat' anticipation). If the screen turned blue, a positive picture would soon appear ('certain reward' anticipation), and if the screen turned green, either a positive *or* a negative picture would soon appear ('uncertain event' anticipation). The anticipation period always lasted 6 seconds, and the baseline period varied in duration from 4 seconds to 8 seconds. Each anticipation condition was presented 9 times in pseudorandom order and each anticipation period was preceded by a baseline condition. The picture stimuli were presented for 2 seconds

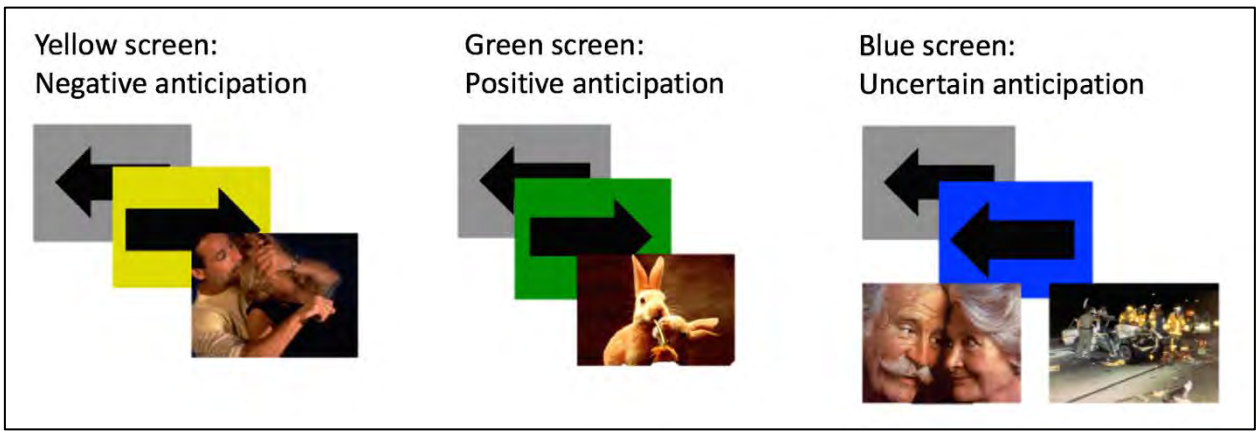


Figure 10. The Emotional Anticipation Task (EAT). Participants are required to press a button indicating the direction of an arrow on the screen. When the screen changed color behind the arrow, that indicated that an image would follow. When a yellow screen appeared, it was always followed by an emotionally aversive unpleasant image. When a green screen appeared, it was always followed by a pleasant image. However, when a blue arrow appeared, it could be followed by EITHER an unpleasant or a pleasant image.

each and consisted of positive and negative pictures from the International Affective Picture System (IAPS). The most unpleasant (e.g., mutilated bodies) (mean valence = 1.62, SD = 1.09, mean arousal = 6.87, SD = 2.14) as well as the most pleasant (e.g., animals) pictures (mean valence ratings = 7.48, SD = 1.53 mean arousal = 5.42, SD = 2.29) were chosen from the picture set.

Neuroimaging Methods. The same participants described above for the N-back task provided data on the anticipation task (17 male; 18 female). Participants underwent neuroimaging on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.33 ms/ 12 degree) over 176 sagittal slices (256 x 256) and a slice thickness of 1.00 mm (voxel size = 1 x 1 x 1). T2-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/ 25.0 ms/ 90 degree) with 230 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 x 64 acquisition matrix.

Image Processing. Methods are identical to those described above for the N-Back task.

Statistical Analysis. On an individual basis, a general linear model was specified to contrast activation between all anticipation periods and baseline periods, as well as between the anticipation periods themselves. These contrast images were entered into a second-level independent samples t-test analysis with light group as the independent variable. Based on our a priori hypotheses, bilateral search territories were created using the Wake Forest University PickAtlas Utility (Maldjian, Laurienti, Kraft, & Burdette, 2003) and the boundaries defined by the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002b), focusing on the vmPFC, amygdala, insula, and ACC bilaterally. Analyses were thresholded at $p < .001$ (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, false discovery rate (FDR) corrected at the cluster level at $p < .05$, and k (extent) ≥10 contiguous voxels. In order to ensure that the results were not explained by participant's depression scores, which may have an impact on functional brain responses within these areas, analyses were re-run controlling for Beck Depression Inventory (BDI) scores.

Neuroimaging Results. We compared the contrasts between the various conditions as described below:

Anticipation > Baseline. There were no significant differences in activation within the a priori ROIs between the two light groups for the following contrasts: 'certain threat' > baseline, 'certain reward' > baseline or 'uncertain event' > baseline.

Anticipation condition contrasts. There were no significant differences in activation within the ROIs between the two groups for the following contrasts: 'certain threat' > 'certain reward', and 'certain threat' > 'uncertain event'.

'Uncertain event' > 'Certain reward'. For the 'uncertain event' > 'certain reward' contrast, an independent samples t-test between the placebo (amber) > blue light group focusing on the a priori ROIs showed a significant difference in activation comprising two large clusters within the left rostral ACC (238 voxels, p<.001, t = 4.72, x = -6, y = 42, z = 10; and 108 voxels, t = 4.35, x = -4, y = 42, z = -4). Participants in the blue light condition showed reduced activation within those areas in comparison to participants in the placebo light condition (see Figure 11). When controlling for BDI scores in the analysis, the difference between the amber versus the blue light group was particularly pronounced for a large cluster within the rostral ACC (560 voxels, p<.001, cluster-level FDR corrected, and peak-level FWE-corrected at p = .03; *t* = 5.10, *x* = -6, *y* = 42, *z* = 10).

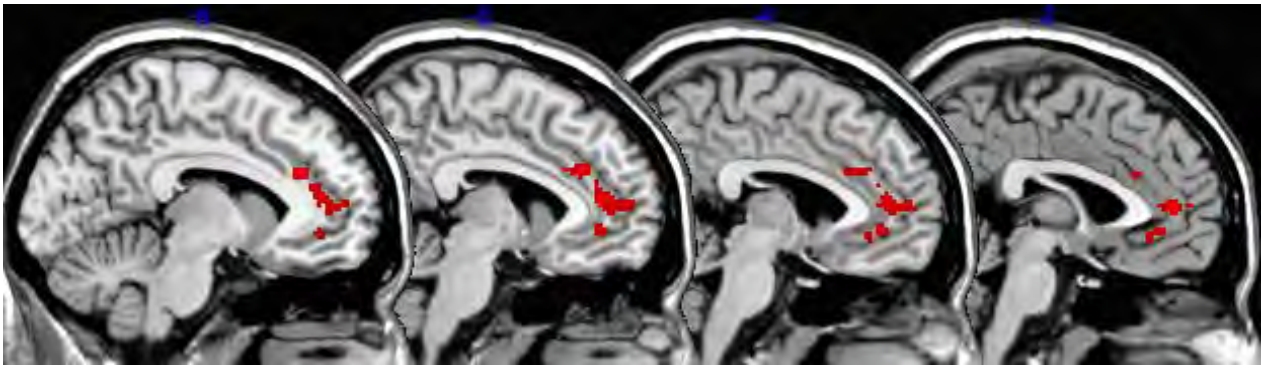


Figure 11. There was a significantly greater activation difference between uncertain event anticipation > certain reward anticipation in the amber versus the blue light group after 30 minutes of light exposure within two clusters in the left ACC (MNI: x = -6, y = 42, z = 10, and x = -4, y = 42, z = -4)..

In sum, we found that a single dose of thirty minutes of blue light exposure immediately preceding the scanning session was associated with a reduced activation difference (relative to amber light exposure) within the left rostral ACC between 'uncertain' anticipation of negative or positive stimuli ('uncertain event' anticipation) and 'certain' anticipation of positive stimuli ('certain reward' anticipation). That is to say, the degree to which left rostral ACC activation was stronger during 'uncertain' than 'certain' anticipation was significantly greater in the amber light condition than the blue light condition. We suggest that this result may be explicable in terms of the known role of the ACC in the integration of uncertainty and valence-related information in decision-making and reinforcement learning. The findings suggest that blue wavelength light has the potential to enhance activation within the ACC during 'certain reward' anticipation, possibly due to an increase in norepinephrine, leading to an increase in the effectiveness of dopaminergic reward prediction-error signals. This increase in the learning rate during reward anticipation may partly explain the beneficial effect of blue light as a treatment for individuals with depression. These findings may help explain some of the positive mood enhancing aspects of light exposure, and suggest the possibility that blue-wavelength light could be applied in clinical settings to improve responses to ongoing therapy. This set of findings was published in 2016 in the journal Neuroscience Letters (Alkozei, Smith, & Killgore, 2016).

Multi-Source Interference Task. The aforementioned findings suggest that a brief single exposure to blue-wavelength light can sustain emotional anticipation and working memory performance for at least a half-a-hour after the light pulse ends, if not longer. However, the potential of blue light exposure to subsequently affect the efficiency of higher-level cognitive processing, such as minimizing the effects of cognitive interference on task performance, has not been explored. Therefore, we further examined the effects of a 30-minute dose of blue-wavelength light on subsequent functional brain activation and performance during the Multi-Source Interference Test (MSIT)(Bush & Shin, 2006; Bush, Shin, Holmes, Rosen, & Vogt, 2003), a popular and well-validated neuroimaging task designed to assess cognitive interference resolution. The MSIT produces robust and reliable activation within a network of regions comprising the dorsal anterior cingulate cortex (dACC)/supplementary motor area/medial prefrontal cortex (Deng, Wang, Wang, & Zhou, 2018). We hypothesized that exposure to blue light would enhance the efficiency of cortical systems involved in resolving cognitive interference on the MSIT. Therefore, based on the predictions of the neural efficiency hypothesis (Neubauer & Fink, 2009), we expected that blue light would thus reduce task positive activation to the MSIT interference condition while also reducing suppression of default mode activation compared to a matched placebo light exposure.

While undergoing fMRI, participants completed the MSIT, a well-validated cognitive interference task that produces consistent and robust activation patterns within the cingulo-frontal-parietal attention network during fMRI (Bush & Shin, 2006; Bush et al., 2003; Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012). The MSIT consists of an alternating series of two conditions that are performed within the MRI scanner. During each trial, the participant is presented with a row of three digits on a video screen. As shown in Figure 12, on each presentation, two of the digits are always the same and one digit differs from the others, and participants are required to indicate the location of the inconsistent digit by making a key press on a button box in their right hand. For the "control" trials, the two distractor digits are always "0" and the inconsistent digit was always congruent with its physical position in the series and therefore matches its location on the button box (e.g., "100" = press button "1"; "020" = press button "2"; "003" = press button "3"). For the "interference" trials, the distractor digits were numbers other than zero and the inconsistent digit was never in the same spatial position as the required button press (e.g., "331" = press button "1"; "211" = press button "2"; "232" = press button "3"). During each trial, the digit sets were presented for 1750 ms, with a prerelease of 500 ms, yielding a stimulus presentation of 1250 ms and an interstimulus interval of 500 ms. Four blocks of control trials were alternated with four blocks of interference trials, with each block consisting of 24 digit set presentations, yielding a total of 192 sets presented over a

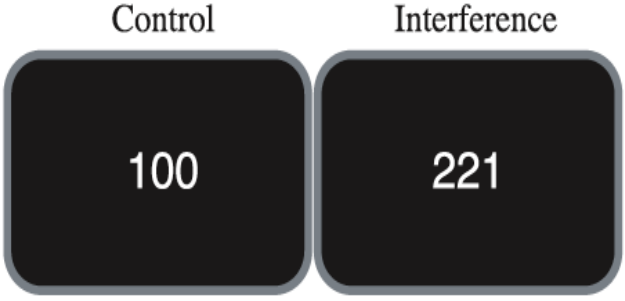


Figure 12. Multi-Source Interference Task (MSIT). Each screen presents a 3-digit number. The task alternates between a simple *Control* condition where participants must press a button based on the *spatial location* of the number that is different from the others, and an *Interference* condition where participants must press the button that corresponds to the *value* of the digit that is different from the others.

total run time of 6 min and 36 s. The task was generated in E-Prime software and presented from a laptop computer via a high-resolution, rear projection system to a translucent screen viewed through the mirror mounted to the head coil.

Neuroimaging Methods. The same participants described earlier participated in the MSIT task as well, although data from several individuals was not usable due to technical malfunctions. Therefore, the final sample included thirty (16 male; 14 female) right-handed, primary English speaking, healthy adults ranging in age from 18 to 32 years (M = 22.3, SD = 3.6). Of these, 14 were in the blue light (8 male; 6 female) and 16 (8 male; 8 female) in the amber placebo light condition. Structural and functional neuroimaging data were acquired on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. For structural imaging, a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.33 ms/ 12 degree) over 176 sagittal slices (256 x 256) and a slice thickness of 1.00 mm (voxel size = 1 x 1 x 1 mm) was acquired. For the functional MSIT scans, T2*-weighted echoplanar MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm (voxel size 2.5 x 2.5 x 2.5 mm) using an interleaved sequence (TR/TE/flip angle = 2.0 s/ 25.0 ms/ 90 degree) with 198 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 x 64 acquisition matrix.

Image Processing. Processing methods are identical to those described above for the N-Back and Emotion Anticipation tasks.

Statistical Analysis. At the individual level, a general linear models (GLM) was specified to contrast activation between the interference trials and the control trials for each participant (i.e., interference > control). At the group level, individual contrast maps (interference > control) were entered into a one-sample t-test in SPM12. From this analysis, the positive contrast identified regions that showed increased activation during the interference task (vs control), while the negative contrast indicated regions that showed reduced activation (vs control) during the interference task. A highly conservative threshold was used for this initial analysis, employing a whole-brain family-wise error (FWE) correction of $p < .001$ (corrected) and a minimum cluster size of 8 (i.e., twice the cluster-wise False Discovery Rate threshold, FDR = 4 as indicated by SPM12). The first eigenvariate representing total combined activation from the full set of surviving clusters was extracted as a whole-brain network from the positive and negative contrasts respectively and entered into IBM SPSS version 26 for further analysis. The extracted whole brain activation of each of these networks was then compared between the blue and the amber conditions using one-way analysis of variance and zero-order correlations.

Neuroimaging Results. We compared the contrasts between the various conditions as described below:

The MSIT produced activation in expected brain networks even at highly stringent thresholds (see Figure 13). Specifically, the interference > control contrast led to significant positive task-related activation throughout a network of regions including bilateral occipital, parietal, and middle cingulate cortex (see Table 2). Collectively we identify this pattern of activation as the

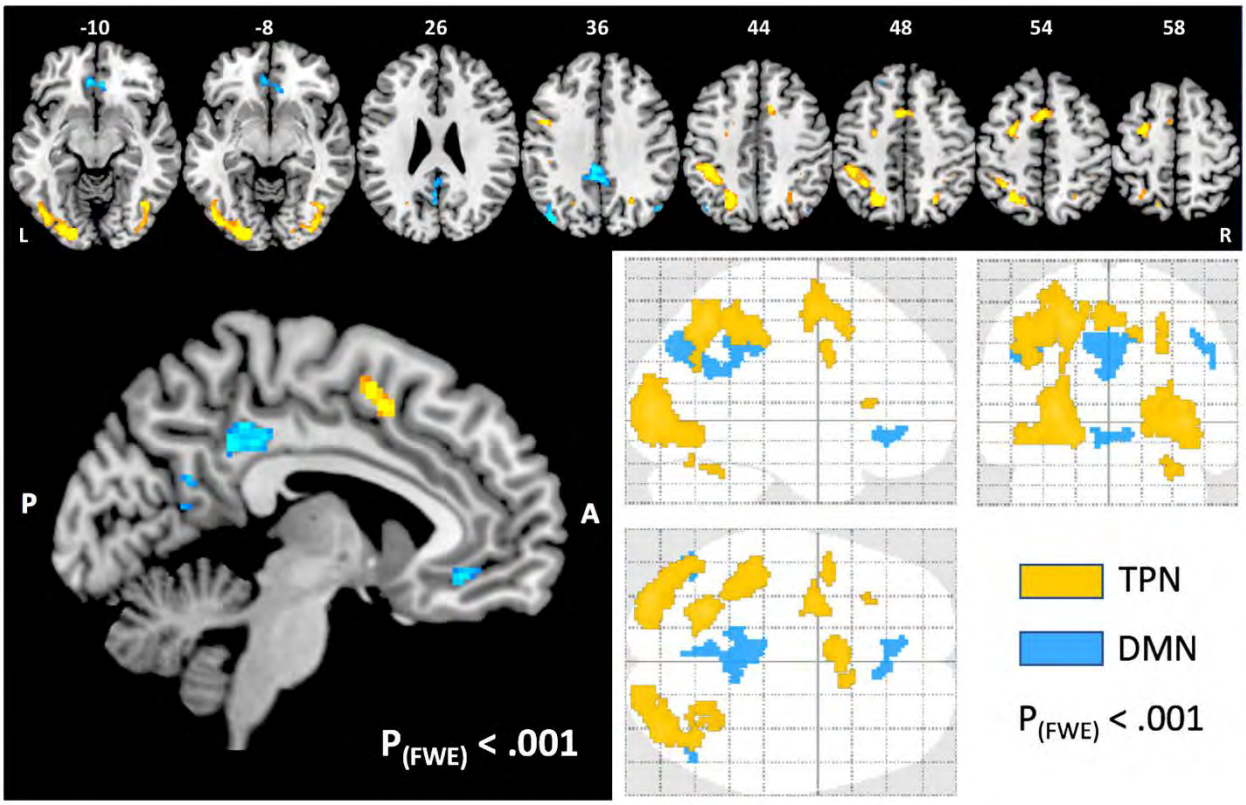


Figure 13. Group brain activation patterns for the Multi-Source Interference Task (MSIT). Data are shown for the contrast "interference > control" in multiple axial slices (top), midline sagittal slice (bottom left), and "glass brain" maximum intensity projection (bottom right). Warm colors represent activation of the task positive network (TPN) for the interference > control contrast, while cool colors represent task-related deactivations, which conform roughly to the default mode network (DMN). All data are whole brain corrected for family-wise error (FWE) at $p < .001$, and a cluster threshold of 8 voxels (twice the cluster-wise false discovery rate (FDR) threshold).

task positive network (TPN) for the MSIT interference condition. Significant deactivations during the interference condition were observed within the angular gyri bilaterally, as well as medial cortical structures including the middle/posterior cingulate gyrus, and anterior cingulate gyrus/medial orbitofrontal gyrus (see Table 1). We identify this collective pattern of activation as the *default mode network* (DMN). The total activation (i.e., first eigenvariate across all regions combined) was extracted for the TPN and DMN separately.

As shown in Figure 14a, total activation of the TPN was significantly lower among participants completing the blue light condition relative to the amber placebo light condition ($F(1, 28) = 5.70$, $p = .024$, partial $\eta^2 = .169$), showing a large effect size. In contrast, the two groups did not differ in total suppression of the DMN ($F(1,28) = 0.01$, $p = .910$, partial $\eta^2 = .000$). These analyses were repeated after controlling for WASI-II full-scale intelligence, but the results remained virtually unchanged.

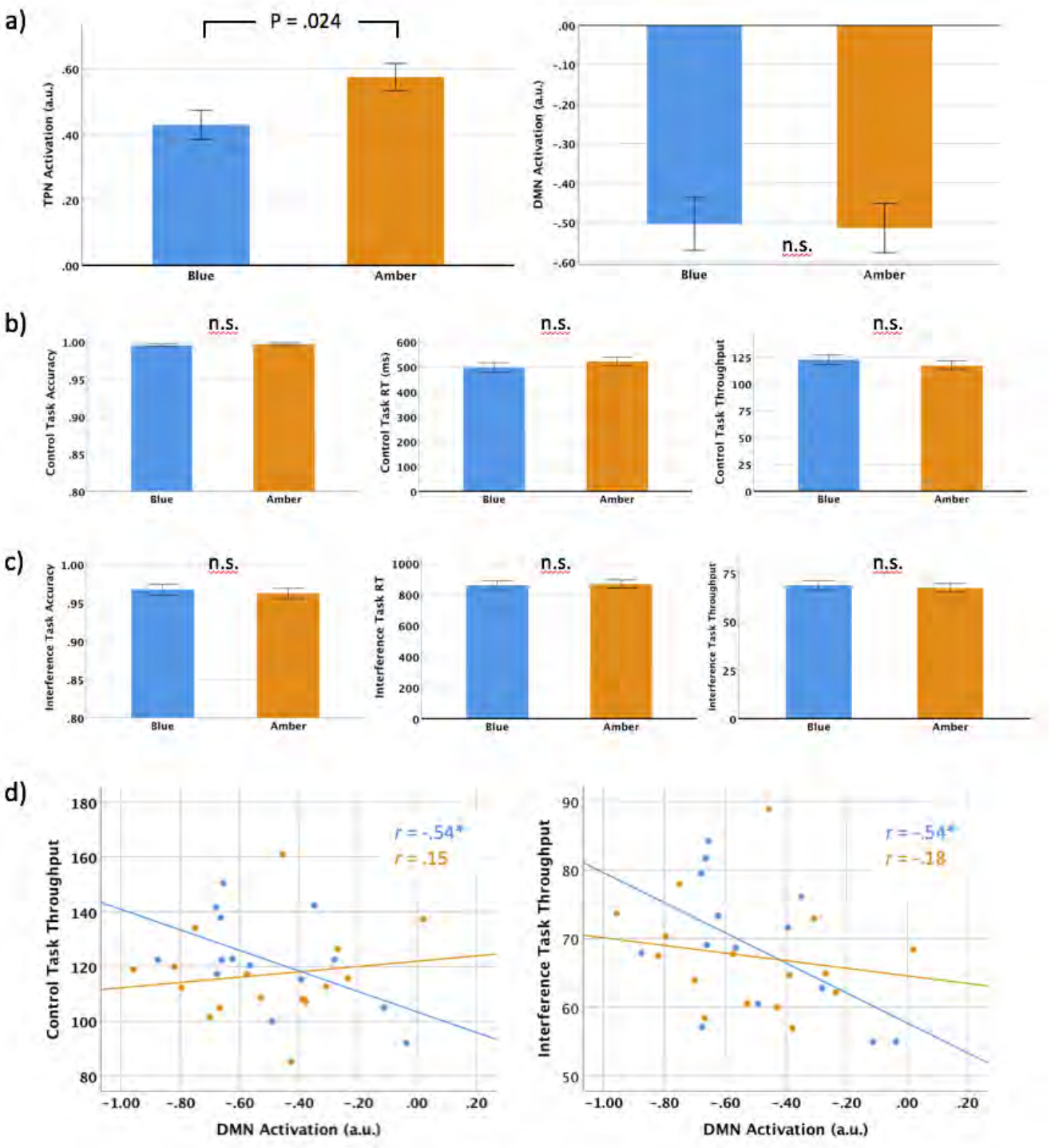


Figure 14 Group mean comparisons between primary variables during the Multi-Source Interference Task (MSIT). a) Mean activation within the task positive network (TPN) was significantly (p = .024) lower for the blue group than the amber group (left), but did not differ between groups for the default mode network (right); b) Mean performance variables for the MSIT Control condition showed no between-groups difference for accuracy (left) response time (RT; middle), or cognitive throughput (i.e., number of correct responses per working minute; right); c) Mean performance variables for the MSIT Interference condition showed no between-groups difference for accuracy (left) response time (RT; middle), or cognitive throughput (i.e., number of correct responses per working minute; right); d) Scatterplots showing the association between default mode activation and Cognitive Throughput, which was significant for the blue group in the Control (left) and Interference conditions but not the amber group. a.u. = arbitrary units; ns = nonsignificant; *p < .05.

Behavioral task data from the MSIT were scored in three ways. First, accuracy was the percent of correct responses for all trials for a particular condition. Second, response time was the mean time taken to press one of the three response keys. Third, a metric of "cognitive throughput" (i.e., (% correct/mean response time) x 600)), which indicates the number of correct responses per working minute. Behavioral data showed that the blue and amber groups did not differ in terms of accuracy ($F(1, 28) = 0.26$, $p = .615$, partial $\eta^2 = .009$), response time ($F(1, 28) = 0.86$, $p = .363$, partial $\eta^2 = .030$), or throughput ($F(1, 28) = 0.75$, $p = .394$, partial $\eta^2 = .026$) for the control task (see Figure 3b). Similarly, the groups did not differ in terms of accuracy ($F(1, 28) = 0.27$, $p = .609$, partial $\eta^2 = .009$), response time ($F(1, 28) = 0.03$, $p = .864$, partial $\eta^2 = .001$), or throughput ($F(1, 28) = 0.16$, $p = .688$, partial $\eta^2 = .006$) for the interference task (see Figure 14c).

Target Region	Cluster Size	MNI coordinates			*T*
		x	y	z	
Task Positive Network					
Left Middle Occipital Gyrus	**748**	**-30**	**-88**	**4**	**14.83**
Right Inferior Occipital Gyrus	656	38	-84	-2	13.76
Left Superior Parietal Lobule	**300**	**-24**	**-60**	**48**	**13.48**
Left Middle Frontal Gyrus	174	-28	-4	54	11.62
Left Supplementary Motor Area/Middle Cingulate Gyrus	**129**	**-2**	**10**	**50**	**10.88**
Left Inferior Parietal Lobule	361	-44	-34	42	10.32
Left Precentral Gyrus	**62**	**-42**	**4**	**30**	**9.80**
Right Middle Cingulate Gyrus	19	12	14	44	9.19
Right Superior Occipital Gyrus	**75**	**26**	**-62**	**38**	**9.03**
Right Cerebellum	27	32	-60	-26	8.71
Right Cerebellum	**8**	**28**	**-68**	**-22**	**8.62**
Left Insula	8	-28	26	6	8.29
Default Mode Network					
Left Angular Gyrus/Middle Occipital Gyrus	124	-42	-78	36	12.09
Left Middle/Posterior Cingulate Gyrus	**350**	**-4**	**-44**	**36**	**10.13**
Left Medial Obitofrontal/Anterior Cingulate Gyrus	64	-4	36	-10	9.06
Right Angular Gyrus	**21**	**48**	**-70**	**36**	**8.52**

Table 2. Overall brain activation regions during the MSIT.

Finally, we examined the correlations between brain network activation and behavioral performance (i.e., MSIT throughput) within each group. There was no association between TPN activation and control or interference throughput for either the blue or amber groups. In contrast, for the DMN, the correlation between network deactivation and performance was significant within the blue group for both the control task (r = -.54, p = .046) and the interference task (r = -.54, p = .046), but not for the amber group (see Figure 14d).

These findings have implications for methods to enhance or optimize cognitive processing among military personnel. While task performance was equivalent between groups with regard to accuracy, response time, and cognitive throughput, the blue light condition showed significantly lower activation of the TPN relative to the amber placebo condition. Consistent with the neural efficiency hypothesis (Neubauer & Fink, 2009), this suggest that a single half-hour exposure to blue light reduced metabolic demands on task-related cortical resources without compromising task performance. However, contrary to our hypothesis, we did not find any difference between conditions in global suppression of the DMN.

The neural efficiency hypothesis posits that individuals with greater cognitive capacity require less brain activation (i.e., fewer neural resources) to complete the same cognitive tasks when such tasks are of low to moderate difficulty (Neubauer & Fink, 2009). The MSIT conditions used here are consistent with this difficulty requirement, as the accuracy level for the control task was 99.6% blue and 99.7% for amber, and the accuracy for the interference task was 96.7% for blue and 96.2% for amber, with no differences observed between groups in performance (see Figure 3b and 3c). Similar outcomes were found for MSIT response time and throughput. Thus, both tasks were completed nearly perfectly by all participants, but those in the blue group required significantly less brain activation to complete the more demanding (yet relatively easy) interference task than those in the amber placebo group. Furthermore, this difference was not accounted for by differences in measured intelligence. Apparently, exposure to blue-wavelength light for 30-minutes allowed the task to be completed equally well with less demand on TPN neural resources, regardless of baseline intelligence. Of course, this begs the question: by what mechanism does light exposure produce this enhanced efficiency?

While there have been many proposed neurobiological mechanisms underlying neural efficiency (Poldrack, 2015), we posit that the most likely mechanism here is optimized allocation of attentional resources due to the effects of light on norepinephrine regulation by the locus coeruleus (LC). The LC is crucial for promoting wakefulness, arousal, attention, and efficiency of cognitive processing (Glennon et al., 2019; Vazey, Moorman, & Aston-Jones, 2018). Further, the LC appears to amplify neural gain to focus cognition on prioritized cognitive tasks (Clewett, Huang, Velasco, Lee, & Mather, 2018), and has been shown to be particularly responsive to light exposure (Szabadi, 2013; Vandewalle, Schmidt, et al., 2007). Blue light has been shown to acutely activate the LC and downstream cortical regions when task performance coincides with light exposure (Vandewalle et al., 2009). While speculative, we propose that these stimulating effects may continue to prime cognitive networks for efficient functioning for at least a half an hour after the cessation of light exposure. Analogous to the way a “warm up” before athletic activity allows more efficient and precise muscle movement, this pre-activation of cortical attention systems would potentially allow fewer redundant or unnecessary cognitive resources to be engaged to carry out a simple cognitive task (i.e., greater neural efficiency). Of course, these suggestions are speculative and will require further research before they can be accepted.

These findings build upon prior work showing that acute exposure to blue light can enhance cognitive performance and brain functioning (Alkozei et al., 2017; Alkozei, Smith, & Killgore, 2016; Alkozei, Smith, Pisner, et al., 2016; Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle et al., 2009; Vandewalle, Schmidt, et al., 2007). These acute effects of light likely involve different mechanisms than longer-term treatment with blue light for recovery from traumatic injury or mood dysfunction. For instance, we have recently shown that six-weeks of blue light exposure leads to neuroplastic changes in gray and white matter and concomitant cognitive improvements among individuals recovering from mild traumatic brain injury (Bajaj et al., 2017; Killgore et al., 2019). However, these changes likely reflect the effects of daily morning blue light on circadian and sleep patterns, which in turn, may have contributed to structural and functional recovery. Thus, blue light exposure may have differential effects on the brain across several timeframes, ranging from acute effects on brain activation over the course of seconds to minutes, to slightly longer effects on cortical neural efficiency on the time scale of at least half an hour, as seen here, and finally longer term neuroplastic changes and associated functional outcomes due to sleep and circadian entrainment that may emerge over the course of weeks or months.

We, therefore, conclude that single 30-minute exposure to blue-wavelength light was associated with greater neural efficiency than an equal duration exposure to amber placebo light, as evidenced by reduced activation of the TPN and sustained performance during a task requiring ongoing resolution of cognitive interference. These findings provide further evidence that blue-wavelength light has acute enhancing effects on some aspects of cognition.

Heart Rate Variability in Healthy Controls. Heart Rate Variability (HRV) has been shown to increase at the onset of sleep. Interestingly, exposure to blue wavelength light prior to sleep can inhibit this increase, suggesting a possible biomarker of increased alertness. In addition, acute exposure to blue light has been demonstrated to increase alertness, reduce sleepiness, and increase performance on the Psychomotor Vigilance Test (PVT), but this has not been directly associated with HRV. We hypothesized that blue light exposure would decrease HRV and increase performance on the PVT. Twenty healthy 18-30 year olds underwent a half hour baseline acclimation period in low amber light at 9:45 a.m., followed by a half hour exposure to bright blue light (469 nm; n=10) or bright amber light (578 nm; n=10). HRV was assessed during a 5-minute resting condition at baseline and during bright light exposure. A change score was calculated between these two resting periods. As a measure of sustained attention, the PVT was administered during the final 10 minutes of the bright light exposure.

There was no significant difference in baseline HRV, performance on the PVT, or sleepiness between the two light conditions. Both groups showed an increase in HRV between baseline and the bright light exposure (p=.001). However, smaller HRV change scores were associated with fewer lapses in vigilance (p=.003) and faster reaction time (p=.001) on the PVT (see Table 3).

		Reaction Time PVT 1	Reaction Time PVT 2	Lapses PVT 1	Lapses PVT 2
Baseline HRV	Correlation Coefficient	-.391	-.397	-.174	-.302
	Sig. (2-tailed)	.088	.083	.462	.195
	N	20	20	20	20
Post Light Exposure HRV	Correlation Coefficient	-.030	-.002	.163	-.025
	Sig. (2-tailed)	.900	.995	.493	.917
	N	20	20	20	20
Change in HRV	Correlation Coefficient	**.486***	**.602****	**.473***	**.469***
	Sig. (2-tailed)	**.030**	**.005**	**.035**	**.037**
	N	**20**	**20**	**20**	**20**

Table 3. Correlations between heart rate variability (HRV) and reaction time on the psychomotor vigilance test (PVT) at each administration in healthy normal individuals.

Contrary to expectations HRV increased for both wavelengths of bright light. However, consistent with our hypotheses, individuals with inhibited HRV increases during light exposure, regardless of wavelength, had better performance on the PVT (see Figure 15). Findings suggest that smaller increases in HRV during bright light exposure, regardless of wavelength, may be associated with better sustained attention. Future work may focus on the role of individual differences in HRV during exposure to light on performance during various cognitive tasks.

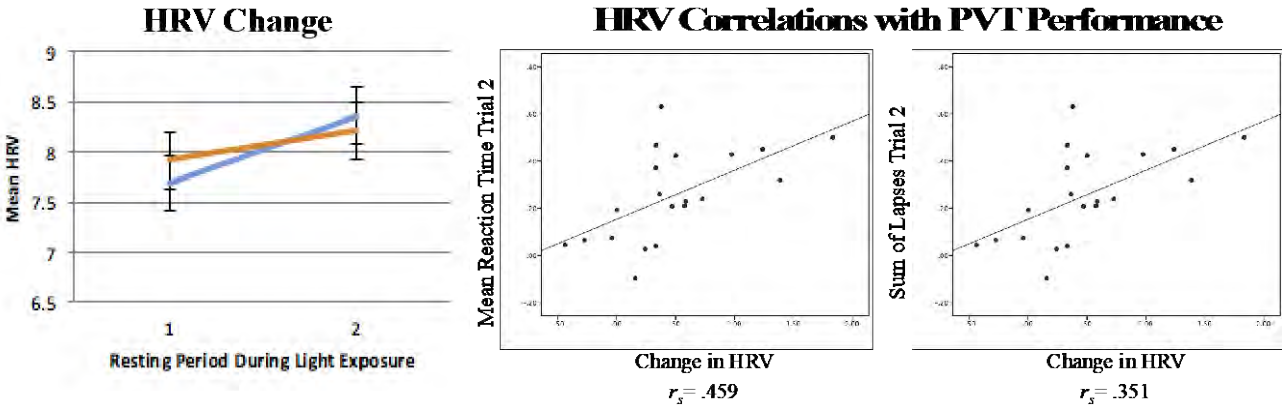


Figure 15. Changes in heart rate variability correlate with psychomotor vigilance in healthy individuals.

Light Induced Changes in HRV are Associated with Frontoparietal Connectivity: Acute exposure to blue light increases alertness and performance on the Psychomotor Vigilance Task (PVT). Preliminary data from our lab has also shown that smaller changes in heart rate variability (HRV), a measure of cardiac reactivity, can predict PVT performance during bright light exposure. We hypothesized that individuals who show smaller increases in HRV during light exposure (presumably reflecting greater alertness and associated sympathetic tone) would have greater post-exposure frontoparietal connectivity. A subsample of the group described above (n = 20), ranging in age from 18-30, underwent a six-minute resting state functional magnetic resonance imaging (fMRI) scan at 3T within 10 minutes of cessation of light exposure (described above). Regions of interest were placed in frontal and parietal areas of the cortex as defined by the Automated Anatomical Labeling Atlas. Functional connectivity was analyzed utilizing the CONN toolbox and SPM12, with $p<.05$, FDR corrected. Smaller change in HRV from baseline in response to the bright light exposure, and better PVT performance, correlated positively with increased functional connectivity between the Left Angular Gyrus, and Left Middle Frontal Gyrus; in contrast, it was associated with greater negative functional connectivity between the Left Middle Frontal Gyrus and Right Superior Frontal Orbital Gyrus (see Figure 16). During light exposure, attenuated change in HRV was associated with increased functional connectivity within the left fronto-parietal attention network, and better vigilance performance (see Figure 17). Findings suggest a link between sympathetic vagal tone as measured by HRV and brain function that is directly associated with faster response times. The HRV response to

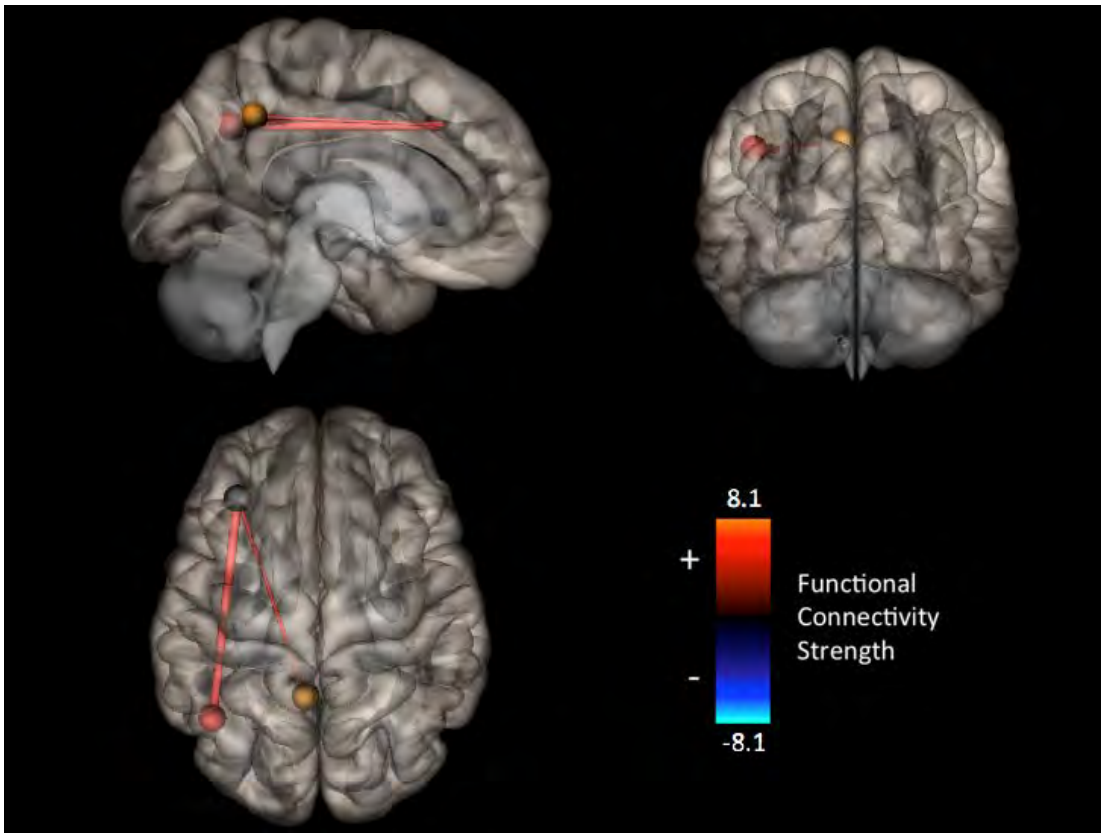


Figure 16. Associations between heart rate variability and fronto-parietal functional connectivity.

light exposure might potentially serve as a trait marker of vulnerability to cognitive decline during sleepiness or fatigue.

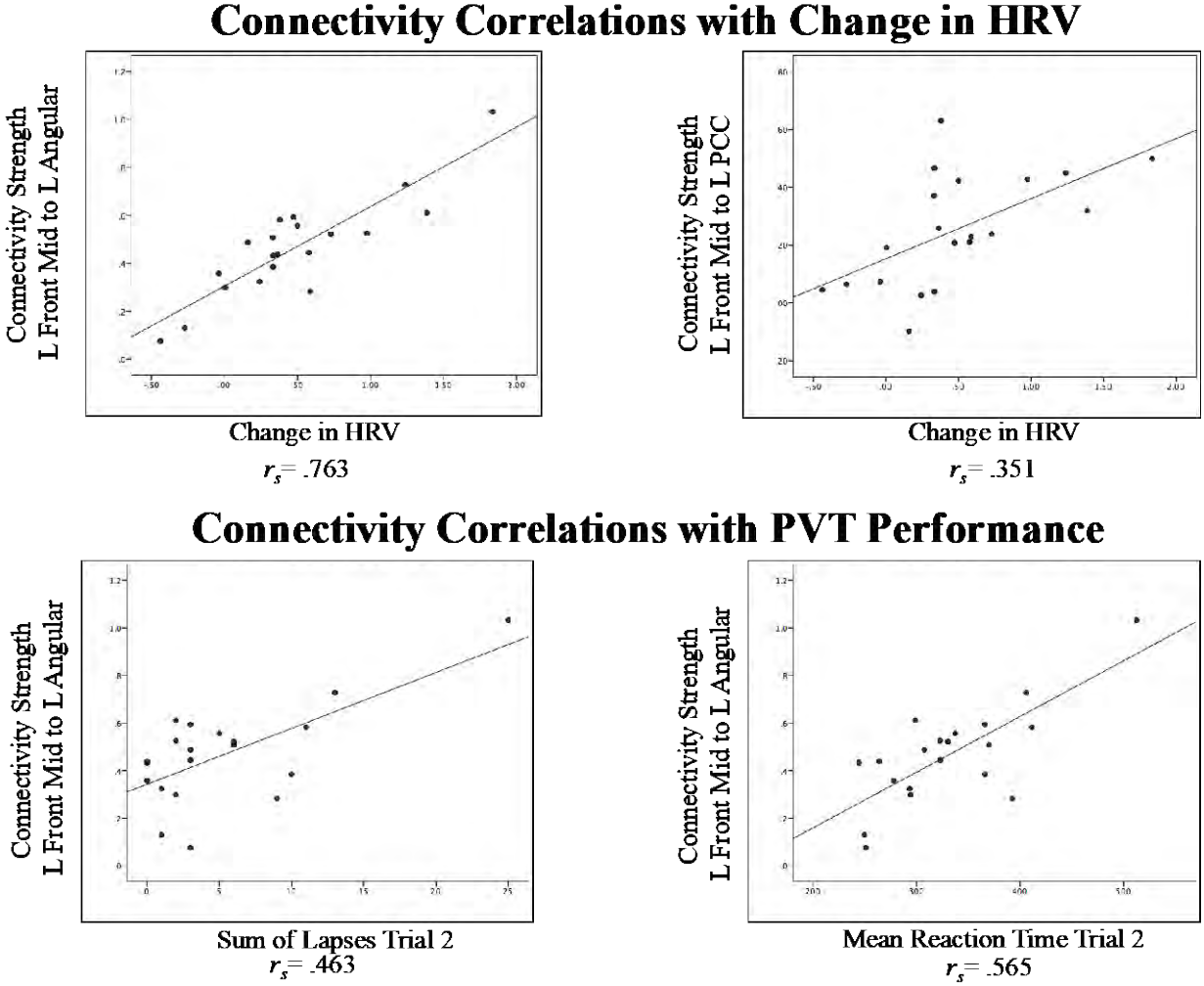


Figure 17. Correlations between the strength of fronto-parietal functional connectivity and changes in heart rate variability (HRV; TOP) and performance on the psychomotor vigilance test (PVT; BOTTOM) in healthy normal individuals.

General Summary of Effect Localization Arm

The objective of the Effect Localization Arm was to identify the brain circuitry that is affected by acute exposure to blue-wavelength light. We were successful in accomplishing this objective. Our findings suggest that blue-wavelength light has immediate alerting effects that appear to be separate from its effects on the circadian-melatonin system. In a series of several publications, we have now shown that a single 30-minute exposure to blue-wavelength light leads to an increase in functional activation within the dorsolateral and ventrolateral regions of the prefrontal cortex, which is associated with improved efficiency of performance on a standard working memory task. Interestingly, 30-minutes of blue-wavelength light also is associated with reduced activation of the Task Positive Network on a challenging interference task, without affecting

performance, suggesting that blue light may also improve the neural efficiency of complex brain functioning. Blue light also led to improved processing of emotional uncertainty by enhancing activation of the anterior cingulate cortex during an emotional anticipation task. Behaviorally, we also find that when blue light is administered immediately following learning of a list of words, participants retain more of this learned information after a delay period. Together, these findings suggest that, in addition to the well-established circadian effects of blue-light, this intervention may also have direct effects on an immediate alerting system that facilitates cognitive and affective processing. We speculate that this system may specifically activate the locus coeruleus, a region involved in immediate norepinephrine release, which enhances alertness and cognitive performance. We aim to conduct future work to examine the potential use of blue light to sustain performance in military personnel under adverse conditions such as sleep deprivation.

RESULTS—TREATMENT ARM:

Purpose: Each year in the United States, in excess of 1.5 million mild traumatic brain injuries (mTBIs) and sports-related concussions are sustained by military service members, athletes, and the general public (Defense and Veterans Brain Injury Center, 2018)(Langlois, Rutland-Brown, & Wald, 2006). These injuries, characterized by disrupted brain function following a blow to the head or body, result in a wide range of alterations in cognitive and motor performance as well as changes in mental health, pain, and sleep (Alsalaheen, Stockdale, Pechumer, Broglio, & Marchetti, 2017; Galea, Cottrell, Treleaven, & O'Leary, 2018; Manley et al., 2017; Mantua et al., 2018; McCrory et al., 2017). Though the majority of the overt cognitive and motor deficits generally resolve quickly, sleep complaints often persist months to years post-injury in the absence of specific intervention (Farrell-Carnahan et al., 2015; Kaufman et al., 2001; Theadom et al., 2015; Wiseman-Hakes, Gosselin, Sharma, Langer, & Gagnon, 2019).

Following a mTBI, as many as 90% of individuals report new or worsened insomnia, poor quality sleep, as well as daytime fatigue that impairs function (Mantua et al., 2018; Mathias & Alvaro, 2012; Ouellet, Beaulieu-Bonneau, & Morin, 2006; Wiseman-Hakes et al., 2019). Additional evidence suggests that individuals with prior mTBIs may experience more frequent wakefulness following sleep initiation, overall poorer sleep efficiency (i.e., the percentage of time spent asleep compared to the time spent in bed), and greater night-to-night variability in sleep duration, sleep onset latency, and sleep efficiency compared to individuals without current or previous mTBIs (Arbour et al., 2015; Mantua, Henry, Garskovas, & Spencer, 2017; Raikes, Satterfield, & Killgore, 2019; Raikes & Schaefer, 2016; Sufrinko, Howie, Elbin, Collins, & Kontos, 2018; Williams et al., 2008).

Critically, insufficient and low-quality sleep may adversely impact physiological recovery from a mTBI, as it can affect clearance of neurotoxins from the brain (Xie et al., 2013). Furthermore, both sleep disruption and daytime fatigue are associated with post-mTBI symptom and depression severity (Sullivan, Berndt, Edmed, Smith, & Allan, 2016; Towns, Silva, & Belanger, 2015), increased musculoskeletal injury and mTBI risk (Raikes, Athey, Alfonso-Miller, Killgore, &

Grandner, 2019), as well as impaired cognitive, motor, and emotional function (Bloomfield, Espie, & Evans, 2010; Heaton, Maule, Maruta, Kryskow, & Ghajar, 2014; Mantua et al., 2017; Patrick et al., 2017). Given the prevalence of post-mTBI sleep disruption and the wide range of adverse effects resulting from sleep disruption, identifying and implementing sleep-related treatments following a mTBI is essential. However, to date, no widely accepted, evidence-based, efficacious treatments have been identified for this population (Sullivan et al., 2018; Wickwire et al., 2018).

One promising intervention is blue light therapy (BLT) (Raikes & Killgore, 2018). Blue light, particularly in a narrow spectral band from $\lambda \sim 460\text{-}480$ nm, selectively stimulates intrinsically photosensitive retinal ganglion cells (ipRGCs) that synapse with the suprachiasmatic nucleus, the brain's master circadian clock (Berson, Dunn, & Takao, 2002). When stimulated by blue light, these ipRGCs signal melatonin suppression, resulting in greater wakefulness and a phase shift in subsequent circadian rhythms, depending on the timing of administration (Dacey et al., 2005) (Dewan, Benloucif, Reid, Wolfe, & Zee, 2011; Hattar, Liao, Takao, Berson, & Yau, 2002). When applied in a therapeutic manner, blue light can be used to induce wakefulness (ideal for shift-work requiring wakefulness at out-of-phase periods) as well as circadian shifts (earlier sleep onset) when applied early in the day (Alkozei, Smith, & Killgore, 2016; Alkozei, Smith, Pisner, et al., 2016; Chellappa et al., 2011; Phipps-Nelson, Redman, Dijk, & Rajaratnam, 2003; van Maanen, Meijer, van der Heijden, & Oort, 2016). Several prior studies have employed light therapy, including blue light specifically (Killgore et al., 2019), as an adjunctive treatment for mTBI (Bajaj et al., 2017; Sinclair et al., 2014). These studies have demonstrated that morning light therapy reduces daytime fatigue (Sinclair et al., 2014) and blue light in particular may help to shift sleep onset times to earlier in the night (circadian phase advance) (Killgore et al., 2019) as well as contribute to improved white matter integrity (Bajaj et al., 2017).

Experimental paradigm:

Participants: Participants with a recent mTBI (< 18 months post-injury) were recruited to complete the experimental protocol outlined below. Mild traumatic brain injuries were defined consistent with the VA/DoD criteria, including 1) a transient alteration in consciousness subsequent to a blow to the head or body; 2) loss of consciousness < 30 minutes; 3) post-traumatic amnesia lasting < 24 hours; and 4) a maximal Glasgow Coma Scale score between 13-15 within 24 hours of injury (when collected). All individuals provided head injury documentation from a medical provider or third-party witness prior to enrollment. All participants reported a mTBI between 4 weeks and 18 months prior to participation.

Exclusionary criteria included 1) any other history of neurological illness, current DSM-IV Axis I disorder, lifetime history of psychotic disorder, or head injury with loss of consciousness > 30 minutes; 2) complicating medical conditions that might influence neuropsychological assessment or functional imaging (e.g., brain tumor); 3) abnormal visual acuity uncorrected by contact lenses; 4) metal within the body (including those made of materials considered "MRI safe," such as permanent dental retainers or braces), claustrophobia, or other contraindications for neuroimaging; 5) less than 9th grade education; 6) excessive current alcohol use (more than

2 instances of 5+ drinks (men) or 4+ drinks (women) when drinking in the past two months, and/or on average drinking > 2 drinks per day (men); > 1 drinks per day (women) during the past two months; 7) history of alcoholism or substance abuse; 8) significant use of illicit drugs; 9) history of marijuana use within the past 4 weeks, use of marijuana before the age of 16, and/or history of greater than moderate marijuana use throughout the participant's lifetime; and 10) shift-work, night work, or individuals who have substantially desynchronized work-sleep schedules (i.e., sleeping later than 10:00 a.m. more than once a week). All procedures were reviewed and approved by the Institutional Review Board of the University of Arizona as well as the U.S. Army's Human Research Protection Office and all participants provided written informed consent prior to participation.

Procedures: The overall experimental paradigm is presented in Figure 18. Interested individuals completed a screening visit to confirm eligibility. Those meeting eligibility criteria were then provided a wrist-worn accelerometer for sleep quantification (Philips Respironics Actiwatch Spectrum) and scheduled for a baseline visit approximately one week later. Baseline and post-treatment visits were separated by six weeks, with each visit consisting of a comprehensive neuropsychological and self-report battery, as well as neuroimaging. At the baseline visit, participants were randomly assigned to either the blue light treatment (BLT; $\lambda \sim 480$ nm) or

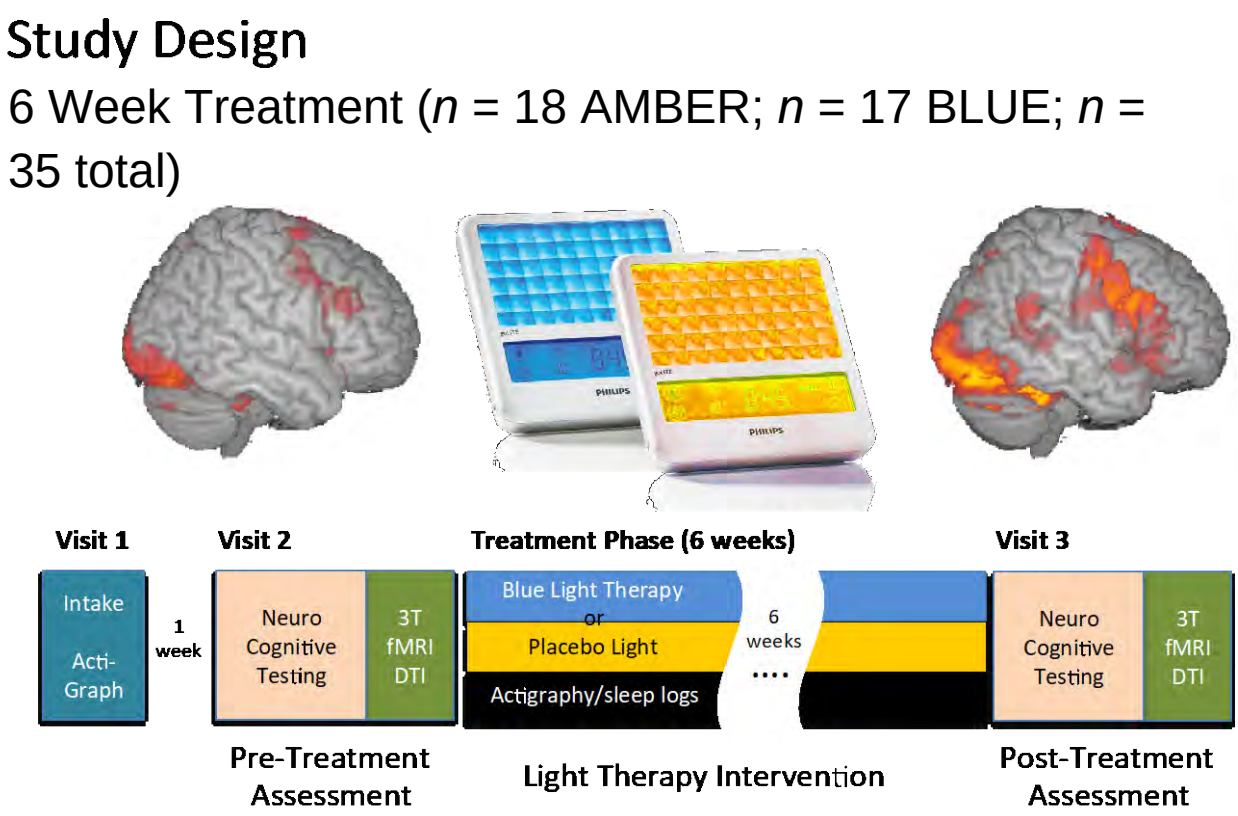


Figure 18. Study Design. Participants completed 3 visits to the lab. Visit 1 involved an intake session and fitting with an actigraphic sleep monitor, which was worn for the duration of the entire study. One week later, participants returned to the lab for Visit 2 to complete a comprehensive neurocognitive testing battery and a series of structural and functional MRI scans. Participants were then randomly assigned to one of two treatment conditions (BLUE or AMBER light). For the next 6 weeks, participants used the assigned BLUE or AMBER device for 30-minutes each morning, within two hours of awakening. At the completion of 6 weeks, participants returned to the lab for Visit 3, and completed the final post-treatment assessment.

placebo amber light treatment (ALT; λ ~ 530 nm) group and provided with the appropriate light box (BLT: Philips goLITE BLU®, Philips Electronics, Stamford, CT; ALT: Custom lightbox provided by Philips Electronics). Participants completed six weeks of at-home, 30-minutes daily morning light treatment. Light treatment was self-administered within 30 minutes of waking each morning (instructed to be between 0800 and 1000) via the light box, placed at arm's length on a table at approximately 45° off center from the participant's primary direction of gaze (i.e., indirect light exposure; Figure 2). Participants were not restricted from performing other activities as long as they remained in front the light box.

Measures: Table 4 identifies the primary behavioral and actigraphy measures of interest.

Self-report	**Computerized and Cognitive Assessments**
Pittsburgh Sleep Quality Index (PSQI)	Automated Neuropsychological Assessment Metrics (ANAM)
Epworth Sleepiness Scale (ESS)	Wechsler Abbreviated Scale Intelligence – 4 (WASI-4)
Spielberger State-Trait Anxiety Inventory (STAI)	Personality Assessment Inventory (PAI)
Evaluation of Risks Scale (EVAR)	Repeated Battery for the Assessment of Neuropsychological Status (RBANS)
Invincibility Beliefs Index (IBI)	Balloon Analog Risk Task (BART)
Morningness-Eveningness Questionnaire (MEQ)	Psychomotor Vigilance Task (PVT)
Functional Outcomes of Sleep Questionnaire (FOSQ)	Go/No Go
9-item Patient Health Questionnaire (PHQ9)	Multi Source Interference Task (MSIT)
Rivermead Post-concussion Symptom Questionnaire (RPCSQ)	N-back
Beck Depression Inventory -2 (BDI-II)	
Satisfaction with Life Scale (SWLS)	
Stanford Sleepiness Scale	
Neurobehavioral Symptom Inventory (NSI)	

Neuroimaging: All participants completed a multimodal neuroimaging protocol on a 3-T Siemens Skyra housed at the University of Arizona at both pre- and post-treatment. This included

- a T1-weighted magnetization prepared rapid acquisition gradient echo scan (echo time (TE) = 2.3ms; repetition time (TR) = 2100ms; inversion time (TI) = 1100ms; flip angle 12°; slice thickness = 1mm; field of view (FOV) = 256x256; matrix size = 256x256; voxel size = $1mm^3$)
- a seven-minute single shot, gradient-recalled echo planar imaging resting-state functional neuroimaging scan (eyes open with a fixation cross; TE = 25ms; TR = 2000ms; flip angle = 90°; slice thickness = 2.5mm; FOV = 210x210; matrix size = 84x84; voxel size = 2.5mm x 2.5mm x 3.5mm)
- an eight-minute gradient-recalled echo planar imaging functional neuroimaging scan (eyes open with a fixation cross; TE = 25ms; TR = 2000ms; flip angle = 90°; slice thickness = 2.5mm; FOV = 210x210; matrix size = 84x84; voxel size = 2.5mm x 2.5mm x 3.5mm) while completing the N-back task

- a six-and-a-half-minute gradient-recalled echo planar imaging functional neuroimaging scan (eyes open with a fixation cross; TE = 25ms; TR = 2000ms; flip angle = 90°; slice thickness = 2.5mm; FOV = 210x210; matrix size = 84x84; voxel size = 2.5mm x 2.5mm x 3.5mm) while completing the MSIT task
- a single shot echo planar (TE = 88ms; TR = 9600ms; FOV: 256 x 256; matrix size = 128x128; voxel size = $2mm^3$) diffusion weighted scan

Actigraphy: All participants wore an Actiwatch Spectrum throughout pre-baseline (between screening and baseline visits) and treatment phases to quantify daily sleep habits. Data were collected 24-hours today with a 1-minute epoch-to-epoch time. Actigraphy data were processed in Philips Respironics Actiware 6 using the Cole-Kripke algorithm (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992) provided in the software. All scoring was visually inspected by trained technicians. Scoring inaccuracies and ambiguous recordings were reconciled using the participants' daily sleep diaries and scoring was adjusted based on the MESA scoring guidelines (MESA: Multi-Ethnic Study of Atherosclerosis, 2016).

Data from the week of pre-baseline visit sleep monitoring, as well as the final seven days of the treatment phase, were considered. Extracted values included daily sleep onsets and offsets, total time in bed (TIB), total nighttime sleep time (TST), sleep efficiency (total sleep time / total in-bed time; SE), and normalized wake after sleep onset (minutes awake after sleep initiation/total sleep time; $WASO_{norm}$). For each phase (pre-baseline, end of treatment), participants were required to have a minimum of five valid nights of actigraphy in the seven-day window in order to be included for analyses. Data were aggregated per participant per phase as a mean value as well as the coefficient of variation (standard deviation/mean) as an indicator of night-to-night variability.

Pretreatment Characteristics: The final sample included a total of 35 individuals who completed the screening and baseline visits and 31 individuals who completed all phases of the study. 17 individuals were randomized to receive daily morning blue light therapy (12 females, 5 males) and 18 individuals were randomized to receive the placebo amber light (10 females, 8 males). After randomization 4 individuals dropped out of the trial (n = 3 in the blue light group; n = 1 in the amber light group). Table 5 shows the pre-treatment demographic characteristics of the sample. Overall, the two groups were reasonably well-match on key features. The blue group had sustained, on average, less than one more mTBI than the amber group, though this difference was statistically significant. As is evident in Table 5, the groups are reasonably well-matched at baseline, though the amber group self-reported better general productivity via the FOSQ than did the blue group at baseline. Likewise, Table 5 demonstrates that there were minimal differences in objective sleep outcomes between the groups at baseline. The Appendix contains additional tables of baseline between-group descriptive statistics across the primary and secondary measures of interest.

Table 5. Demographic, self-report, and actigraphy characteristics							
	Amber		Blue		Baseline differences (Blue – Amber)		
Measure	Baseline	Post-treatment	Baseline	Post-treatment	Effect size [95% CI]	*t*	*p*-value
Demographics							
Age	26.23 ± 7.62	-	25.53 ± 8.65	-	-0.097 [-0.242, 0.051]	1.297	0.195
Days Post-injury	281.72 ± 198.57	-	270.00 ± 134.28	-	-0.067 [-0.210, 0.077]	0.923	0.356
Number of mTBIs	1.97 ± 1.22	-	2.18 ± 1.62	-	***0.161 [0.015, 0.304]***	***2.154***	***0.032***
Self-reported outcomes							
ESS	8.72 ± 3.32	9.33 ± 3.74	8.17 ± 3.28	6.82 ± 3.11	-0.161 [-0.835, 0.513]	0.489	0.628
BDI	9.28 ± 6.03	9.67 ± 6.69	9.76 ± 6.01	7.29 ± 5.29	0.079 [-0.597, 0.750]	0.239	0.812
PSQI							
Sleep quality	1.44 ± 0.70	1.28 ± 0.67	1.76 ± 0.66	1.35 ± 0.70	0.457 [-0.243, 1.234]	1.384	0.176
Sleep latency	1.61 ± 0.92	1.44 ± 0.70	2.06 ± 0.90	1.59 ± 0.80	0.482 [-0.234, 1.166]	1.458	0.154
Sleep duration	0.78 ± 1.00	0.67 ± 1.03	0.71 ± 0.69	0.53 ± 0.80	-0.081 [-0.716, 0.611]	0.249	0.805
Sleep efficiency	0.78 ± 0.81	0.50 ± 0.92	0.94 ± 1.25	1.17 ± 1.24	0.153 [-0.552, 0.795]	0.457	0.652
Sleep disturbance	1.44 ± 0.51	1.39 ± 0.50	1.35 ± 0.49	1.24 ± 0.44	-0.178 [-0.911, 0.502]	0.539	0.593
Sleep medication use	0.33 ± 0.77	0.39 ± 0.85	0.18 ± 0.39	0.06 ± 0.24	-0.249 [-0.853, 0.380]	0.768	0.450
Daytime dysfunction	1.17 ± 0.71	1.17 ± 0.62	1.18 ± 0.95	0.94 ± 0.66	0.011 [-0.666, 0.684]	0.034	0.973
Total score	7.56 ± 3.29	6.83 ± 3.26	8.18 ± 3.36	6.88 ± 3.28	0.181 [-0.488, 0.866]	0.549	0.587
FOSQ							
Activity level	3.29 ± 0.40	3.23 ± 0.46	3.20 ± 0.64	3.17 ± 0.57	-0.154 [-0.817, 0.531]	0.459	0.650
Vigilance	3.34 ± 0.44	3.13 ± 0.59	3.11 ± 0.84	3.32 ± 0.60	-0.338 [-0.963, 0.347]	1.006	0.325
Relationships	3.56 ± 0.66	3.63 ± 0.50	3.54 ± 0.59	3.77 ± 0.40	-0.031 [-0.832, 0.655]	0.089	0.930
General productivity	3.59 ± 0.68	3.35 ± 0.44	3.26 ± 0.65	3.51 ± 0.45	***-0.603 [-1.137, 0.061]***	***1.798***	***0.084***
Social outcomes	3.53 ± 0.55	3.58 ± 0.60	3.50 ± 0.73	3.73 ± 0.50	-0.042 [-0.781, 0.649]	0.121	0.905
Total score	17.10 ± 2.18	16.28 ± 1.88	15.37 ± 3.82	17.33 ± 2.39	-0.549 [-1.157, 0.121]	1.637	0.114
RPCSQ							
Acute	3.28 ± 2.97	3.00 ± 2.43	3.47 ± 2.50	2.71 ± 2.69	0.068 [-0.607, 0.744]	0.208	0.836
Chronic	12.28 ± 13.01	12.78 ± 11.08	15.94 ± 7.97	11.06 ± 8.27	0.329 [-0.396, 1.097]	1.011	0.321
Somatic	9.06 ± 8.38	8.44 ± 7.45	11.00 ± 4.95	7.76 ± 5.89	0.274 [-0.454, 1.007]	0.841	0.407
Cognitive	3.50 ± 4.05	4.28 ± 3.39	4.88 ± 3.48	3.71 ± 3.75	0.357 [-0.338, 1.073]	1.085	0.286
Emotional	3.00 ± 4.16	3.06 ± 4.02	3.53 ± 3.71	2.29 ± 2.71	0.131 [-0.533, 0.829]	0.398	0.693
Actigraphy							
TIB	475.89 ± 58.99	471.82 ± 56.62	503.39 ± 48.17	503.67 ± 40.76	0.478 [-0.219, 1.201]	1.417	0.167
TST	392.05 ± 46.52	389.78 ± 50.57	406.07 ± 39.44	418.77 ± 38.87	0.316 [-0.373, 1.030]	0.935	0.357
SOL	16.37 ± 10.85	15.97 ± 8.05	25.25 ± 15.73	19.53 ± 14.95	***0.645 [-0.089, 1.284]***	***1.877***	***0.072***
SE	82.53 ± 4.83	82.56 ± 4.20	80.98 ±4.71	83.43 ± 5.11	-0.317 [-0.994, 0.375]	0.933	0.358
$WASO_{norm}$	11.20 ± 3.02	11.66 ± 2.91	11.97 ± 3.23	10.40 ± 3.32	0.240 [0.452, 0.920]	0.706	0.486
Sleep onset time (hours after 00:00)	0.45 ± 0.99	0.57 ± 0.86	-0.10 ± 1.15	-0.08 ± 1.31	-0.516 [-1.188, 0.217]	1.512	0.141
Sleep offset time (hours after 00:00)	7.84 ± 1.12	7.38 ± 1.33	7.60 ± 1.25	7.73 ± 0.98	-0.197 [-0.878, 0.516]	0.578	0.567
Actigraphy CV							
TIB	0.20 ± 0.05	0.19 ± 0.07	0.18 ± 0.07	0.18 ± 0.07	-0.300 [-1.022, 0.452]	0.874	0.389
TST	0.22 ± 0.06	0.19 ± 0.08	0.20 ± 0.08	0.18 ± 0.07	-0.220 [-0.936, 0.534]	0.642	0.526
SOL	0.93 ± 0.31	0.94 ± 0.28	0.96 ± 0.42	0.95 ± 0.33	0.095 [-0.618, 0.782]	0.278	0.783
SE	0.06 ± 0.04	0.07 ± 0.03	0.08 ± 0.04	0.06 ± 0.03	0.388 [-0.376, 1.077]	1.144	0.261
$WASO_{norm}$	0.32 ± 0.24	0.33 ± 0.24	0.34 ± 0.20	0.27 ± 0.09	0.114 [-0.491, 0.932]	0.337	0.738

Notes: Negative values in effect sizes indicate outcomes with blue < amber (between-group). Confidence intervals are bootstrapped using 20000 resamples. T-statistics are Welch's t. ***Bold, italicized entries highlight to emphasize outcomes with moderate to large effect sizes (Hedges g > 0.5) with p-values < 0.1 and outcomes effect size confidence intervals not containing 0 regardless of magnitude.*** *Abbreviations: ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory -2; PSQI: Pittsburgh Sleep Quality Index; FOSQ: Functional Outcomes of Sleep Questionnnaire; RPCSQ: Rivermead Post-concussion Symptom Questionnaire; TIB: Time in bed; TST: Total sleep time; SOL: Sleep onset latency; SE: Sleep efficiency;* $WASO_{norm}$*: Normalized wake-after-sleep-onset*

Primary behavioral findings: All data processing and statistical analyses were conducted using R (v. 3.6.1) and Python 3.7. All data were analyzed on an intent-to-treat basis to ensure that all randomized individuals were analyzed regardless of compliance or completion.(Heritier, Gebski, & Keech, 2003) Missing post-treatment data due to withdrawal or drop-out were imputed using a "baseline observation carried forward" (BOCF) method.

Primary analyses: All primary analyses were carried out using the DABEST package in Python. This package was used to provide between- and within-group effect sizes as well as bias-corrected, bootstrapped, accelerated 95% confidence intervals around these estimates, as well as Gardner-Altman estimation plots (between-group comparisons) and slope-graphs (within-group comparisons) plots (Figures 1-5) to visualize individual values within comparisons. Additionally, DABEST reports traditional two-group hypothesis testing outcomes via Student's *t*-, Welch's *t*- and Mann-Whitney *U* tests.

To ensure homogeneity in pre-treatment outcomes, we computed between-group differences (BLT vs. ALT) on all primary self-report and actigraphy values using DABEST. Results are reported as Hedges *g* effect sizes (with 95% confidence intervals), Welch's *t*-statistic and associated *p*-values.

To identify between-group differences following treatment, BOCF-imputed post-treatment values were first residualized on the baseline values using the *lm* function in R. These residuals were then passed to DABEST and analyzed in the same way as the baseline data (between group differences). Additionally, within-group changes were analyzed separately for the BLT and ALT groups using the "paired" option in DABEST (resulting in paired *t*-tests) on the raw baseline and BOCF-imputed post-treatment data. All confidence intervals were produced via bootstrap with 20,000 resamples. For visualization purposes residualized post-treatment scores were rescaled to the original units by adding the mean post-treatment value.

Compared to receiving amber light, daily morning blue light therapy was associated with moderate-to-large and statistically significant improvements in self-reported daytime sleepiness, depressive symptoms, sleep efficiency, sleep-related functional outcomes, as well as chronic and somatic post-concussion symptoms (Table 6). Additionally, blue light therapy resulted in a moderate increase in sleep efficiency and decreased normalized WASO, indicating better sleep quality by post-treatment (Table 6). These findings corroborate previous reports demonstrating the efficacy of light therapy in reducing daytime fatigue and further extend those findings to include measures of mental health, sleep quality, and quality of life.

Table 6. Between- and within-group treatment outcomes for blue and amber light treatment

	Post-treatment differences (Blue – Amber)			Blue within-group changes (Post – Baseline)			Amber within-group changes (Post – Baseline)		
Measure	Hedges *g* [95% CI]	*t*	*p*-value	Hedges *g* [95% CI]	*t*	*p*-value	Hedges *g* [95% CI]	*t*	*p*-value
Self-reported outcomes									
ESS	***-0.882 [-1.435, -0.281]***	***2.643***	***0.013***	***-0.413 [-0.986, -0.034]***	***1.900***	***0.076***	0.169 [-0.050, 0.391]	1.479	0.156
BDI	***-0.684 [-1.338, -0.017]***	***2.086***	***0.045***	***-0.426 [-0.774, -0.130]***	***2.651***	***0.017***	0.060 [-0.294, 0.362]	0.372	0.714
PSQI									
Sleep quality	-0.149 [-0.791, 0.526]	0.452	0.654	**-0.588 [-1.115, -0.206]**	**2.746**	**0.014**	-0.237 [-0.749, 0.210]	1.000	0.331
Sleep latency	-0.152 [-0.779, 0.549]	0.455	0.653	**-0.541 [-1.080, -0.090]**	**2.219**	**0.041**	-0.199 [-0.527, 0.077]	1.374	0.187

Sleep duration	-0.122 [-0.815, 0.594]	0.367	0.717	-0.231 [-0.844, 0.346]	0.824	0.422	-0.107 [-0.445, 0.095]	1.000	0.331
Sleep efficiency	***0.587 [-0.141, 1.304]***	***1.769***	***0.086***	0.184 [-0.315, 0.662]	0.775	0.450	-0.313 [-0.996 0.443]	0.960	0.350
Sleep disturbance	-0.274 [-0.945, 0.431]	0.829	0.413	-0.247 [-0.928, 0.342]	0.808	0.431	-0.107 [-0.672, 0.335]	0.437	0.668
Sleep medication use	-0.443 [-0.838, 0.264]	1.376	0.185	-0.352 [-0.864, 0.00]	1.461	0.163	0.067 [-0.410, 0.625]	0.251	0.805
Daytime dysfunction	-0.389 [-1.026, 0.299]	1.179	0.247	-0.281 [-0.801, 0.147]	1.167	0.260	0.000 [-0.626, 0.465]	0.000	1.000
Total score	-0.088 [-0.740, 0.609]	0.264	0.794	-0.379 [-0.950, 0.091]	1.464	0.165	-0.216 [-0.683, 0.225]	1.054	0.307
FOSQ									
Activity level	0.029 [-0.712, 0.692]	0.085	0.933	-0.052 [-0.679, 0.427]	0.195	0.848	-0.137 [-0.403, 0.094]	1.133	0.273
Vigilance	0.546 [-0.185, 1.180]	1.647	0.109	0.286 [-0.182, 0.787]	1.115	0.281	***-0.396 [-0.793, -0.054]***	***2.052***	***0.056***
Relationships	0.427 [-0.416, 1.137]	1.280	0.212	***0.441 [0.143, 0.849]***	***2.408***	***0.033***	0.115 [-0.248, 0.716]	0.511	0.616
General productivity	0.505 [-0.162, 1.194]	1.525	0.137	***0.434 [0.001, 0.982]***	***1.477***	***0.159***	***-0.560 [-1.071, -0.072]***	***2.271***	***0.036***
Social outcomes	0.364 [-0.336, 0.972]	1.119	0.273	0.363 [0.066, 0.7746]	1.974	0.068	0.094 [-0.330, 0.656]	0.400	0.695
Total score	***0.929 [0.190, 1.605]***	***2.799***	***0.009***	***0.601 [0.318, 1.018]***	***2.746***	***0.014***	-0.392 [-0.935, 0.039]	1.808	0.088
RPCSQ									
Acute	-0.289 [-0.954, 0.371]	0.909	0.370	***-0.288 [-0.671, -0.082]***	***2.748***	***0.014***	-0.100 [-0.453, 0.236]	0.619	0.544
Chronic	***-0.611 [-1.192, 0.077]***	***1.854***	***0.073***	***-0.587 [-1.137, -0.157]***	***3.014***	***0.008***	0.040 [-0.227, 0.416]	0.264	0.794
Somatic	***-0.597 [-1.233, 0.08]***	***1.790***	***0.084***	***-0.581 [-1.152, -0.152]***	***3.138***	***0.006***	-0.075 [-0.286, 0.133]	0.755	0.460
Cognitive	0.491 [-1.129, 0.183]	1.490	0.146	***-0.317 [-0.788, -0.035]***	***1.898***	***0.076***	0.204 [-0.244, 0.691]	0.936	0.362
Emotional	-0.346 [-0.959, 0.361]	1.049	0.302	-0.371 [-0.876, 0.261]	1.301	0.212	0.013 [-0.304, 0.413]	0.077	0.940
Actigraphy									
TIB	0.399 [-0.340, 1.095]	1.170	0.251	0.028 [-0.573, 0.655]	0.096	0.925	-0.069 [-0.457, 0.212]	0.429	0.673
TST	0.529 [-0.199, 1.211]	1.554	0.131	0.316 [-0.222, 0.932]	1.175	0.258	-0.046 [-0.405, 0.289]	0.269	0.792
SOL	-0.010 [-0.746, 0.737]	0.029	0.977	-0.364 [-0.860, 0.233]	1.461	0.165	-0.041 [-0.577, 0.465]	0.161	0.874
SE	0.440 [-0.344, 1.217]	1.278	0.213	0.487 [-0.072, 1.050]	1.935	0.072	0.008 [-0.412, 0.328]	0.045	0.964
$WASO_{norm}$	***-0.667 [-1.293, 0.007]***	***1.965***	***0.058***	***-0.466 [-0.941, -0.130]***	***2.442***	***0.027***	0.152 [-0.254, 0.711]	0.644	0.529
Sleep onset time (hours after 00:00)	-0.259 [-1.003, 0.460]	0.750	0.461	0.016 [-0.317, 0.314]	0.109	0.915	0.017 [-0.190, 0.341]	0.911	0.376
Sleep offset time (hours after 00:00)	0.396 [-0.296, 0.954]	1.185	0.247	0.108 [-0.218, 0.529]	0.608	0.552	-0.368 [-1.038, 0.122]	1.177	0.256
Actigraphy Coefficient of variation									
TIB	-0.061 [-0.751, 0.630]	0.181	0.857	-0.039 [-0.534, 0.465]	0.163	0.873	-0.125 [-0.730, 0.497]	0.436	0.669
TST	-0.164 [-0.818, 0.537]	0.632	0.537	-0.295 [-0.845, 0.208]	1.084	0.295	-0.294 [-0.953, 0.332]	1.026	0.320
SOL	-0.007 [-0.711, 0.694]	0.983	0.694	-0.042 [-0.569, 0.640]	0.143	0.888	0.057 [-0.596, 0.815]	0.167	0.869
SE	-0.398 [-1.120, 0.337]	1.171	0.251	***-0.634 [-1.163, -0.032]***	***2.124***	***0.051***	0.052 [-0.580, 0.525]	0.197	0.847
$WASO_{norm}$	-0.532 [-1.111, 0.159]	1.583	0.124	-0.447 [-0.863, 0.076]	1.657	0.118	0.035 [-0.396, 0.498]	0.246	0.808

Notes: Negative values in effect sizes indicate outcomes with blue < amber (between-group) or post-treatment < baseline (within-group). Confidence intervals are bootstrapped using 20000 resamples. T-statistics are Welch's t (between-group differences) or paired t-test statistics (within-group differences). ***Bold, italicized entries highlight to emphasize outcomes with moderate to large effect sizes (Hedges g > 0.5) with p-values < 0.1 and outcomes effect size confidence intervals not containing 0 regardless of magnitude or statistical significance.*** *Abbreviations: ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory -2; PSQI: Pittsburgh Sleep Quality Index; FOSQ: Functional Outcomes of Sleep Questionnnaire; RPCSQ: Rivermead Post-concussion Symptom Questionnaire; TIB: Time in bed; TST: Total sleep time; SOL: Sleep onset latency; SE: Sleep efficiency; $WASO_{norm}$: Normalized wake-after-sleep-onset*

Primary neuroimaging findings:

In addition to the self-reported and objective sleep outcomes, a major aim of this study was to investigate changes in the brain's structure and function following repeated exposure to daily morning blue light. To accomplish this goal, all individuals underwent a pre- and post-treatment neuroimaging battery that included anatomical, resting-state and task-based functional, and diffusion-weighted scans. We have examined the effects of daily blue light therapy on both the structure and function of the brain as well as the association with primary behavioral outcomes of interest. These are outlined below.

Gray matter volume: Identifying short-term changes in the cortical structure of the brain requires generally large samples. Therefore, the data from the prior and the present study were aggregated to increase the available sample. To identify these changes, all T1-weighted images for the present award and the prior study were preprocessed using the standard longitudinal segmentation process implemented in CAT12 (http://www.neuro.uni-jena.de/cat/). Following segmentation, the gray matter volume (GMV) for each of 400 cortical and 36 subcortical regions of interest (ROIs) was extracted using two standard atlas (Schaefer 400 atlas and the Brainnetome atlas). Additionally, total intracranial volume (TIV) was computed for inclusion as a covariate in the analyses. Between-site data harmonization for the GMV and TIV data was accomplished using ComBat (https://github.com/Jfortin1/ComBatHarmonization)to remove potential scanner-related effects. Following harmonization, baseline and post-treatment GMV for each ROI was adjusted for TIV and age. Sex, number of prior mTBIs, and days post-injury were not significantly associated with GMV in any ROI and therefore not included as covariates. Additionally, post-treatment GMV was adjusted for pre-treatment GMV in each ROI to identify treatment-related effects.

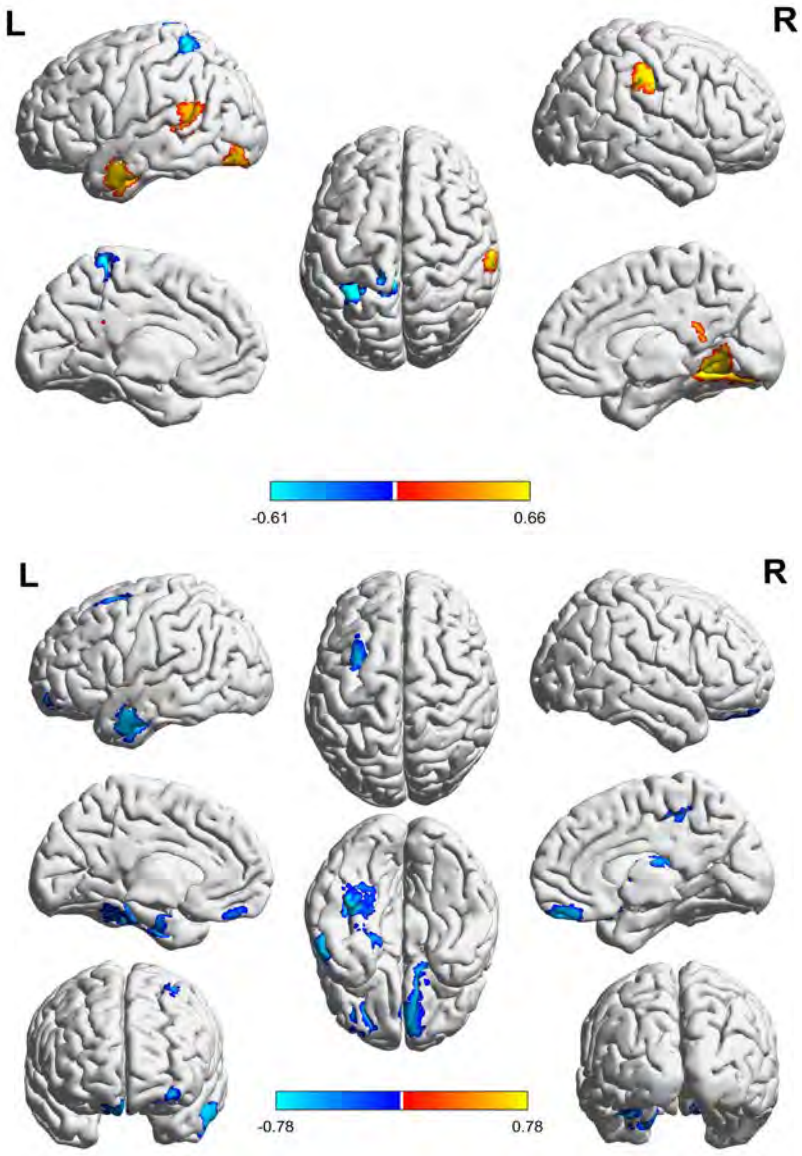


Figure 19. Baseline (left) and baseline-adjusted post-treatment associations (right) between group differences in gray matter volume. Small values indicate blue > amber.

At baseline, moderate differences were observed between the blue and amber groups in 11 ROIs (Figure 19 Top). After adjusting for pre-treatment GMV, individuals receiving blue light exhibited greater GMV than those receiving amber light in 12 ROIs (Figure 19 Bottom). Furthermore, small to moderate increases in GMV were observed within the blue group across 23 ROIs whereas amber light was associated with small to

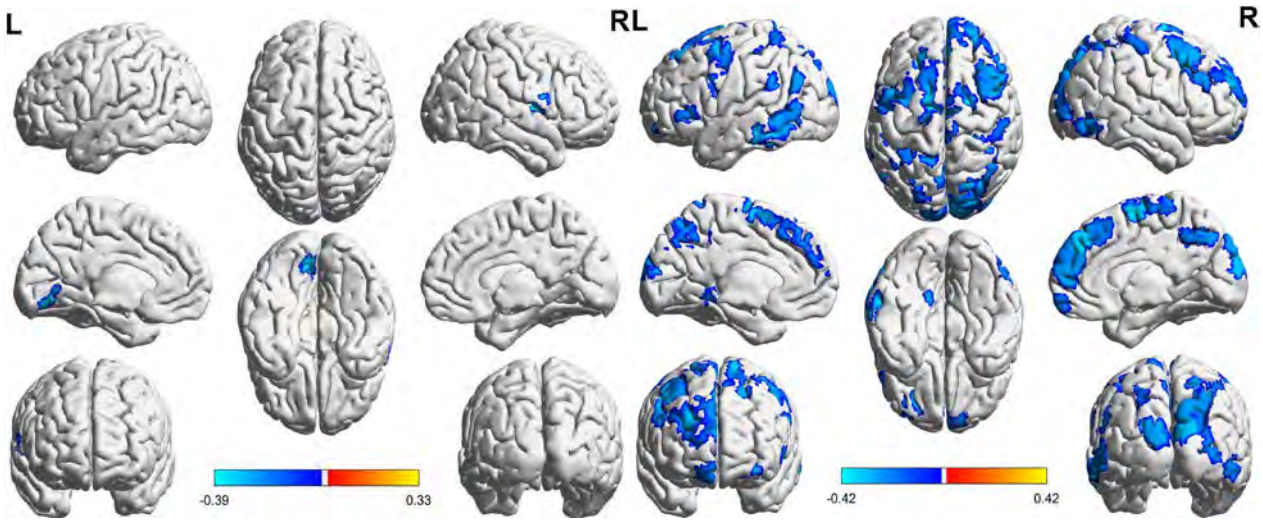


Figure 20. Baseline (left) and baseline-adjusted post-treatment associations (right) between daytime sleepiness and gray matter volume across 400 cortical parcels and 36 subcortical parcels.

moderate decreases in GMV in 7 ROIs and moderate increases in GMV in 5 ROIs (Figure 20 Left and Right respectively).

GMV and daytime sleepiness: In order to identify the association between GMV and behavioral outcomes, we computed bootstrapped correlations (20000 resamples) between baseline and baseline-adjusted post-treatment ESS scores and GMV for all 437 ROIs. To provide conservative estimates of relationships, here we report only the correlations with confidence intervals not containing 0.

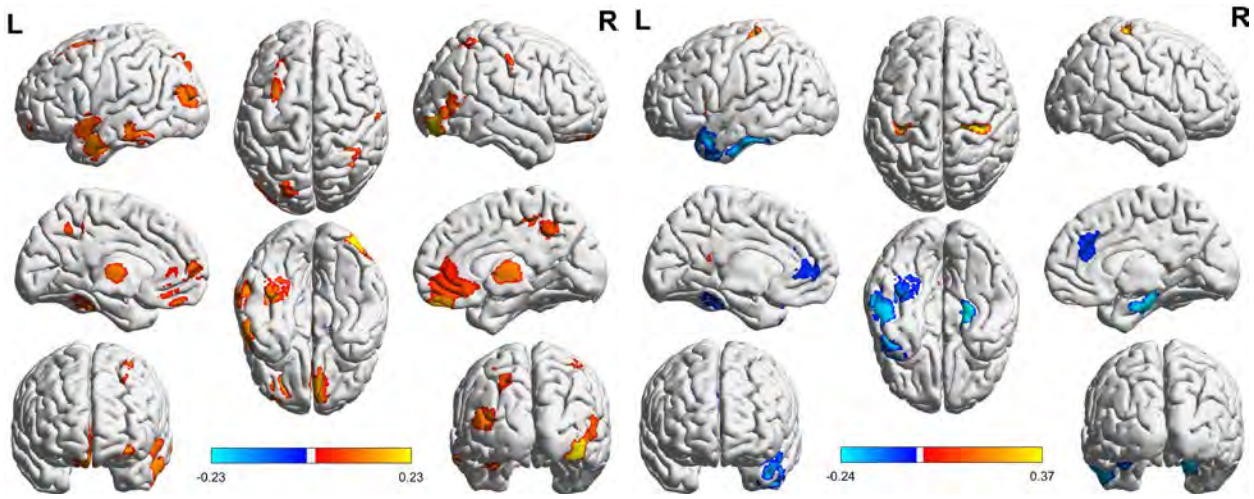


Figure 21. Pre-to-post treatment changes in gray matter volume for blue (left) and amber (right) light treatment. Positive values indicate greater post-treatment volume.

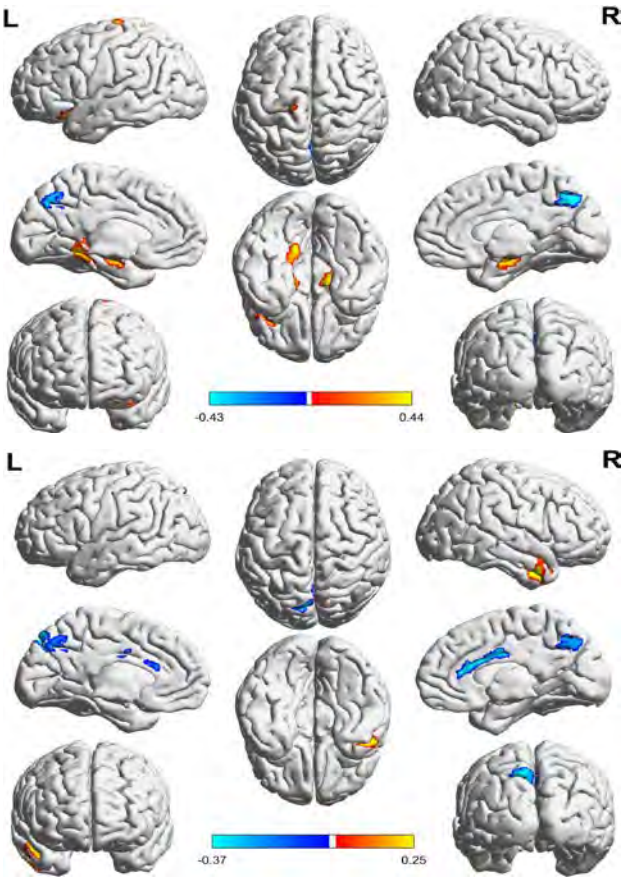


Figure 22. Baseline (top) and baseline-adjusted post-treatment associations (bottom) between depressive symptoms and gray matter volume across 400 cortical parcels and 36 subcortical parcels.

At baseline, greater daytime sleepiness was associated with lower GMV in 2 cortical ROIs and greater GMV in 2 subcortical ROIs (Figure 21). However, following treatment, lower daytime sleepiness was associated with greater GMV in a widespread network of cortical ROIs associated with attention, cognitive control, and visual processing.

GMV and depression: At baseline, greater depression severity was associated with greater GMV in 4 cortical and 2 subcortical ROIs as well as lower GMV in a single cortical ROI. Following treatment, lower depression severity was associated with greater GMV in 5 cortical ROIs associated with mood and internal mentation (Figure 22).

GMV and post-concussive symptoms: Following treatment, decreased acute and chronic post-concussive symptoms were associated with greater GMV across numerous 26 cortical and 11 subcortical ROIs (Figure 23). Notably, this association was observed in a wide network associated with visual processing as well as well as subcortical ROIs include bilateral caudate and putamen.

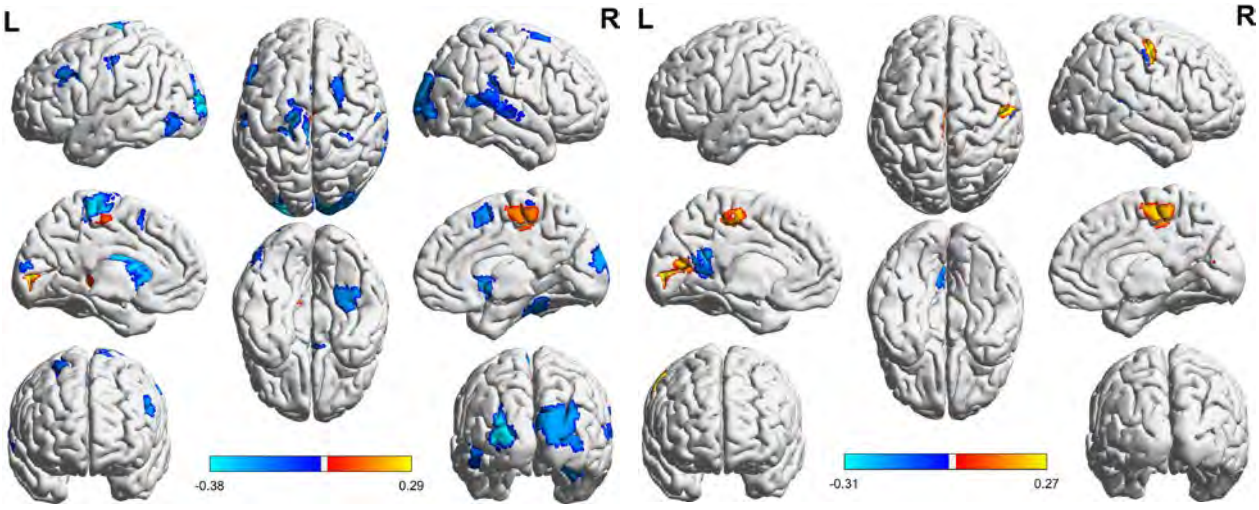


Figure 23. Baseline-adjusted post-treatment associations between acute (RPQ3; left) and chronic (RPQ13; right) symptoms and gray matter volume across 400 cortical parcels and 36 subcortical parcels.

GMV conclusions: Compared with daily amber light therapy, blue light therapy was associated with widespread small to large changes in cortical structure. Differences from pre-treatment to post-treatment were most striking when examining the treatment related effects on daytime sleepiness. There are several plausible explanations for this. The most likely explanation is that self-reported changes associated with blue light (e.g. decreases in daytime sleepiness, depression, and post-concussive symptoms) facilitate engagement in ADLs, sports, and leisure activities – among others – that may have been otherwise inhibited by these self-limiting conditions. Consequently, engagement in these activities creates opportunities for neuroplastic responses that reflect the new, or renewed, engagement in activity. The present findings highlight that daily morning blue light has not only positive effects on self-reported post-mTBI outcomes, but that these effects are associated with discernible changes in the underlying structure of the brain.

Functional connectivity: Concomitant with the observation that blue light induced changes in the cortical structure of the brain, we sought to identify if blue light induced changes in the brain's *functional organization*. Prior work highlights that the brain is organized into large scale networks that can be identified through analyses simultaneous low frequency fluctuations in the blood-oxygen level dependent (BOLD) signal generate during resting-state functional magnetic resonance imaging. These simultaneous fluctuations in multiple regions of the brain (termed *functional connectivity* (FC)) can be identified through bivariate correlation between two areas at the voxel or ROI level. To examine the effects of blue light on the functional connectivity of the brain, we used the same 400-parcel cortical atlas as was used for the GMV analyses and examined the connectivity patterns between these 400 ROIs (79,800 possible connections).

Neuroimaging Processing: fMRIPrep

Results included this manuscript come from preprocessing performed using fMRIPrep 1.3.2 (RRID:SCR_016216),(Esteban, Blair, et al., 2019; Esteban, Markiewicz, et al., 2019) which is based on Nipype 1.1.9 (RRID:SCR_002502).(K. Gorgolewski et al., 2011; K. J. Gorgolewski et al., 2019) Descriptions of this preprocessing are copied from the fMRIPrep boilerplate text under a CC0 license for reproducibility.

Anatomical data preprocessing

A total of two T1-weighted (T1w) images were found within the input BIDS dataset. Both images were corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010) distributed with ANTs 2.2.0 (RRID:SCR_004757)(Avants, Epstein, Grossman, & Gee, 2008). The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. A T1w-reference map was computed after registration of the two T1w images (after INU-correction) using mri robust template (FreeSurfer 6.0.1) (Reuter, Rosas, & Fischl, 2010). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847) (Dale, Fischl, & Sereno, 1999), and the brain mask estimated during the skull-stripping step was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438) (Klein et al., 2017). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (RRID:SCR_008796)(Fonov, Evans, McKinstry, Almli, & Collins, 2009) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both

T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823) (Zhang, Brady, & Smith, 2001).

Functional data preprocessing

For both of the blood oxygen-level dependent (BOLD) rs-fMRI runs per subject (across both sessions, again using the post-treatment rs-fMRI to improve the susceptibility distortion correction described below), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. A deformation field to correct for susceptibility distortions was estimated based on *fMRIPrep's fieldmap-less* approach. The deformation field was that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Huntenburg, 2014; Wang et al., 2017). Registration was performed with *antsRegistration* (ANTs 2.2.0). This process was regularized by constraining deformation to be nonzero only along the phase-encoding direction and modulated with an average fieldmap template (Treiber et al., 2016). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference.

The BOLD reference was then co-registered to the T1w reference using *bbregister* (FreeSurfer), which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using *mcflirt* (FSL 5.0.9) (Jenkinson, Bannister, Brady, & Smith, 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (RRID:SCR_005927)(Cox & Hyde, 1997).

The BOLD time-series were resampled to MNI152NLin2009cAsym standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al. 2014).(Power et al., 2014) The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor) (Behzadi, Restom, Liau, & Liu, 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). Six tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, six components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file.

All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and template spaces). Gridded (volumetric) resamplings were performed using *antsApplyTransforms* (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964).

Many internal operations of fMRIPrep use Nilearn 0.5.0 (RRID:SCR_001362)(Abraham et al., 2014). mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation (https://fmriprep.readthedocs.io/en/1.3.2/).

Neuroimaging processing: XCP Engine

Following the minimal preprocessing steps implemented in fMRIPrep, the BOLD time-series in MNI152NLin2009cAsym space were further processed using a 36-parameter confound regression(Satterthwaite et al., 2013) plus despiking procedure(Cox, 1996) implemented in XCP Engine (https://github.com/PennBBL/xcpEngine).(Ciric et al., 2017) For all participants, this procedure included demeaning the BOLD time-series, despiking using the 3dDespike utility from AFNI 20160207 (RRID:SCR_005927) (Cox & Hyde, 1997), temporal filtering using a 0.01-0.08Hz band-pass filter,(Satterthwaite et al., 2013) and then 36-parameter confound regression using the confounds estimated by fMRIPrep. These 36 parameters included the global signal as well as 6 motion parameters, quadratic terms, and the temporal derivatives of these. Collectively, this procedure demonstrates effective amelioration of in-scanner motion effects on BOLD time-series data. Finally, all data were smoothed to 6mm FWHM. For further details regarding the implementation of these methods, please see the XCP Engine documentation (https://xcpengine.readthedocs.io/).

After these processing steps, the average BOLD signal time series was extracted from n = 400 regions of interest (ROIs) in the Schaefer 400x17 network atlas (Schaefer et al., 2018). This atlas is a multimodal cerebral cortex parcellation derived from Human Connectome Project data. Functional connectivity between ROIs was computed as the Pearson correlation between the mean time series in each ROI, yielding a 400 x 400 functional connectivity matrix.

Baseline differences: Between group differences (blue vs amber) were computed as two-sample t-tests for the present study's dataset (n = 35 participants). Out of 79,800 possible connections, 144 exhibited between group differences (false discovery rate corrected (FDR) $p < 0.01$). Compared to the amber group, mean connectivity in the blue group was higher in 50 and lower 94 of these 144 connections (Figure 24). The majority of these connections were those linking the default mode network (DMN; the brain's primary, resting state, internal mentation network) with the frontoparietal control network (FPC; on-task cognitive switching and

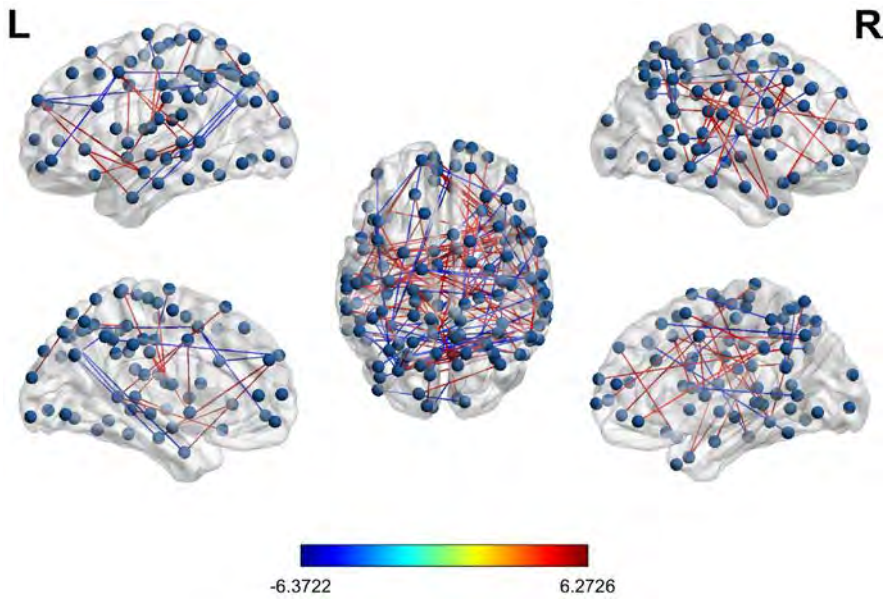


Figure 24. Baseline differences between the blue and amber (amber – blue) groups in functional connectivity across 400 cortical parcels

control) as well as both visually-driven (dorsal attention network; DAN) and salience-drive (salience/ventral attention; VAN) attention networks.

Post-treatment differences: At post-treatment, 51 connections exhibited significant between-group differences (FDR $p < 0.01$), with the major patterns including links between the DMN, FPC, VAN, and DAN as well as internally within the VAN. None of the connections identified at baseline were identified at post-treatment, suggesting that, relative to amber light, blue light induced wide-spread network-related changes that A) ameliorated differences in some connections and B) accentuated differences in others. Among these 51 connections, mean connectivity in the blue group was higher in 33 and lower in 18 compared to the amber group (Figure 25).

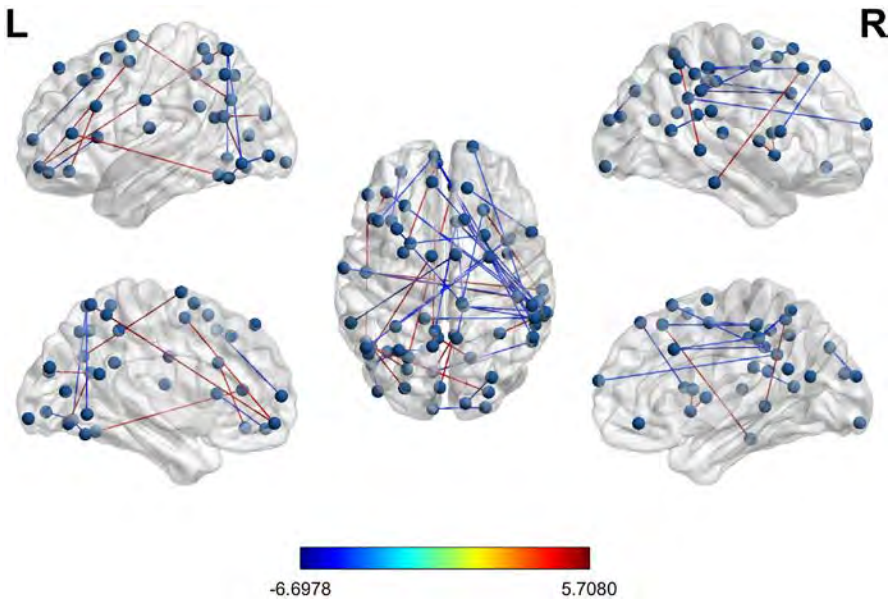


Figure 25. Post-treatment differences between the blue and amber (amber – blue) groups in functional connectivity across 400 cortical parcels

Functional connectivity and daytime sleepiness: We further examined the association between changes in functional connectivity and daytime sleepiness. Constraining the analyses to those connections identified as different between groups at post-treatment ($n = 51$), the correlation between baseline adjusted post-treatment FC and ESS scores was computed for the connection. 13 connections exhibited statistically significant, moderate correlations (uncorrected $p < 0.05$; Figures 26). Lower post-treatment daytime sleepiness was associated with greater functional connectivity among connections linking regions within the VAN, as

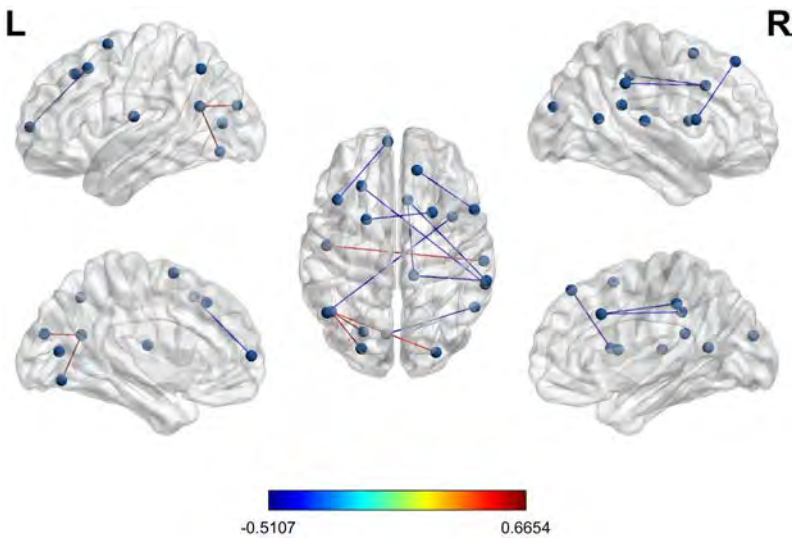


Figure 26. Correlation with ESS sleepiness scores and post-treatment differences between the blue and amber (amber – blue) groups in functional connectivity across 400 cortical parcels

well as the VAN to the FPC while lower daytime sleepiness was associated with lower functional connectivity between regions within the DMN as well as linking the visual network (VN) with the DMN. Collectively, these findings suggest that, in concert with decreased daytime sleepiness, individuals receiving blue light may experience enhanced alertness, attention, and cognitive performance.

Functional connectivity conclusions: Like changes in cortical structure, blue light therapy was associated with widespread changes in the simultaneous resting-state fluctuations between ROIs. These changes included decoupling of areas associated with internal mentation (a drive to think internally about internal states and ruminate on current conditions) and increased coupling of areas associated with attention and cognition. Given the observed effects of blue light on self-reported sleep outcomes, depression, and post-concussive symptoms, it is likely that functional connectivity changes are associated not only with improved well-being but also enhanced performance, or perhaps neural efficiency (requiring fewer neural resources to accomplish tasks without performance decrements) on attention- and cognitively-driven tasks.

Secondary analyses:

In addition to the primary behavioral and neuroimaging analyses, other secondary analyses have been performed on these data. These are described below.

Daytime sleepiness and thalamocortical connectivity: Prior work has consistently demonstrated that daytime sleepiness is associated with thalamocortical connectivity patterns. In addition to the above cortical analyses, we examined the associations between ESS scores and thalamocortical connectivity and changes associated with treatment. Using the same pre-processing pipeline described earlier, we used the Automated Anatomical Labelling (AAL) atlas with 116 distinct nodes between both hemispheres. To identify the relationship between daytime sleepiness and bilateral thalamocortical connectivity, we computed the bivariate correlation between all ROI-to-ROI connections and ESS scores at baseline. To threshold these findings, all correlations were bootstrapped (1000 resamples) and only ROI-to-ROI connections with 95% confidence intervals not including 0 as well as p-values < 0.05 are reported.

At baseline, ESS scores were inversely associated with seven ROI-to-ROI connections attached to the bilateral thalamus (See Figure 27). Many of these connections were specifically associated with the right thalamus and connected to DMN nodes, including the left and right angular gyri as well as the superior medial frontal lobe. These findings further confirm that daytime sleepiness is associated with anti-correlated connections between the thalamus and other areas of the DMN as well as cognitive control areas.

After adjusting for baseline values, these relationships were not evident at post-treatment and rather exhibited positive, though non-statistically significant, correlations. However, between-group differences were evident in several of these connections, with individuals receiving blue light exhibiting increasingly anti-correlated connectivity between these ROIs. Collectively, these findings suggest that for post-mTBI individuals receiving blue light, decreases in daytime sleepiness are associated with altered patterns of thalamic connectivity with in the DMN.

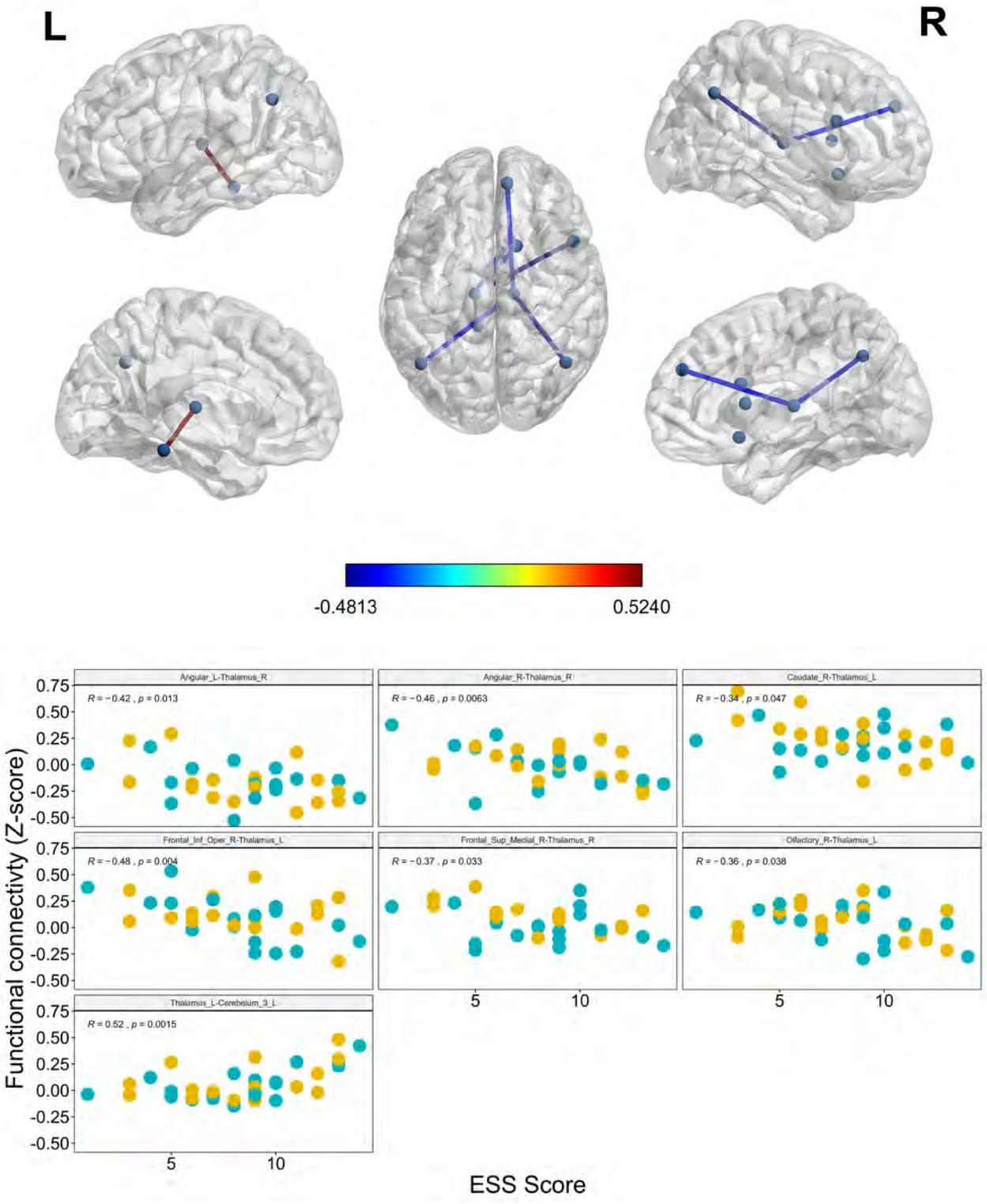
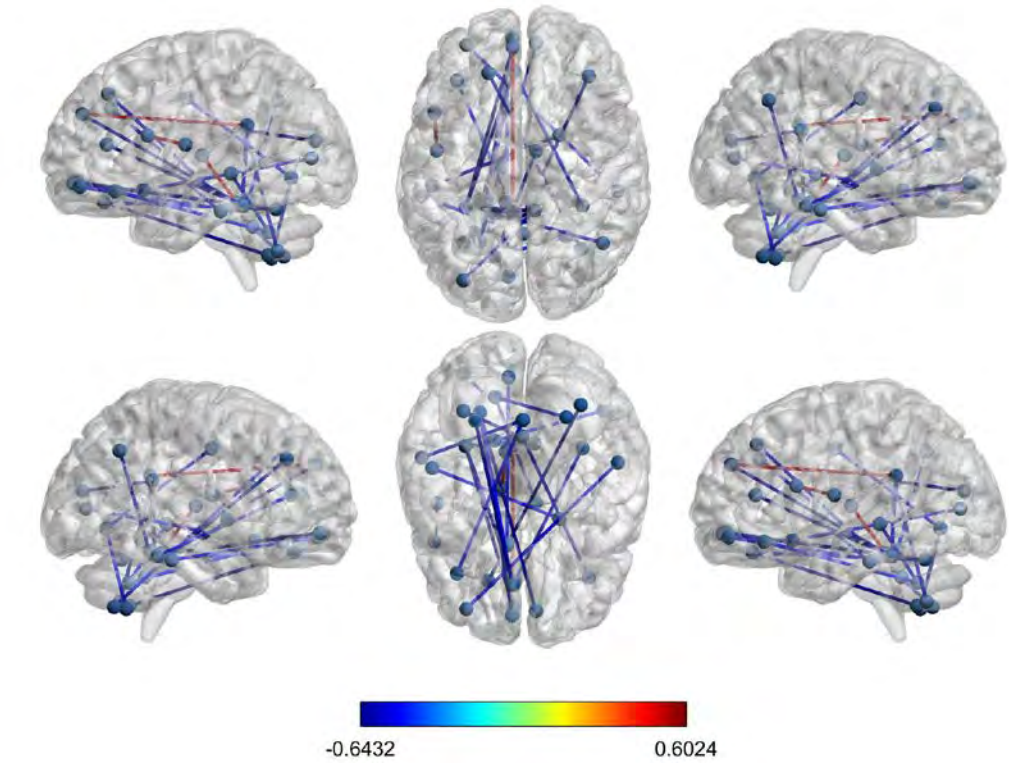


Figure 27 Baseline associations between daytime sleepiness and bilateral thalamic connectivity in the AAL atlas. In general, increased daytime sleepiness is reflected by anticorrelations between the thalami and other DMN nodes

***Changes in functional connectivity and changes in daytime sleepiness*:** While the above analyses highlight that local changes in the thalamic connectivity may underlie improvements in daytime sleepiness, further analyses utilizing all available edges in the AAL atlas reveals widespread patterns of change associated with changes in daytime sleepiness.

Baseline associations between ESS scores and the AAL atlas are shown in Figure 28. These relationships highlight generally anti-correlated nodes linking prefrontal and frontal regions with subcortical gray matter as well as the cerebellum. By contrast, changes in daytime sleepiness were inversely correlated with changes in functional connectivity between nodes linking the DMN (posterior cingulate, superior medial frontal gyrus, parahippocampus) as well as temporal lobe areas and the cerebellum. These patterns, like those observed with the more fine-grained cortical parcellation, further evidence the idea that improved daytime sleepiness following blue light therapy is likely associated with generalized decoupling in the default mode network.



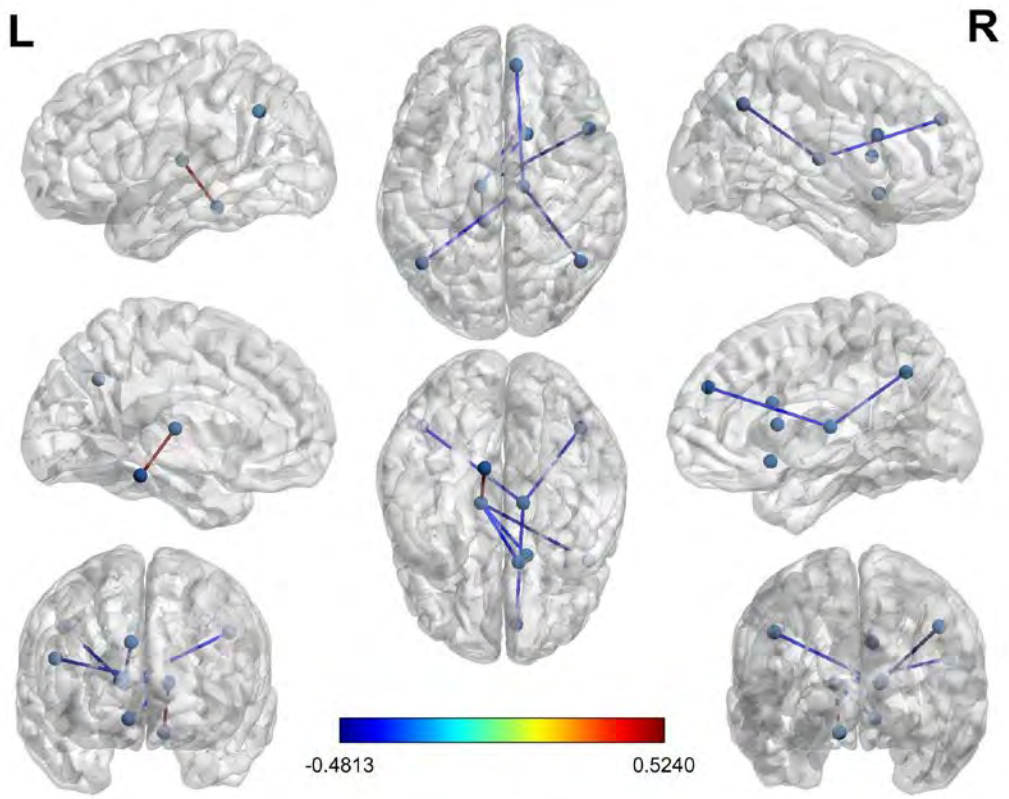


Figure 28. TOP: associations between ESS scores and AAL atlas functional connectivity. In general, daytime sleepiness is associated with anticorrelations between DMN network regions and prefrontal cognitive control regions. BOTTOM: Changes in ESS scores and associated changes in functional connectivity. Improvements in daytime sleepiness were associated with greater decoupling within the DMN.

Neural Correlates of Daytime Sleepiness**:** To describe the relationship between brain structure and daytime sleepiness, we correlated Epworth Sleepiness Scale (ESS) scores at baseline with whole-brain gray matter volume using voxel-based morphometry (VBM) in SPM12. We observed a significant negative correlation between ESS scores and gray matter volume in the middle cingulate gyrus (Figure 29). This region is involved in multiple aspects of emotional processing, learning, and memory. Additionally, this region is implicated in depression. Given the concomitant presence of depression in this sample, it is likely that there is substantial interplay between daytime sleepiness and depression.

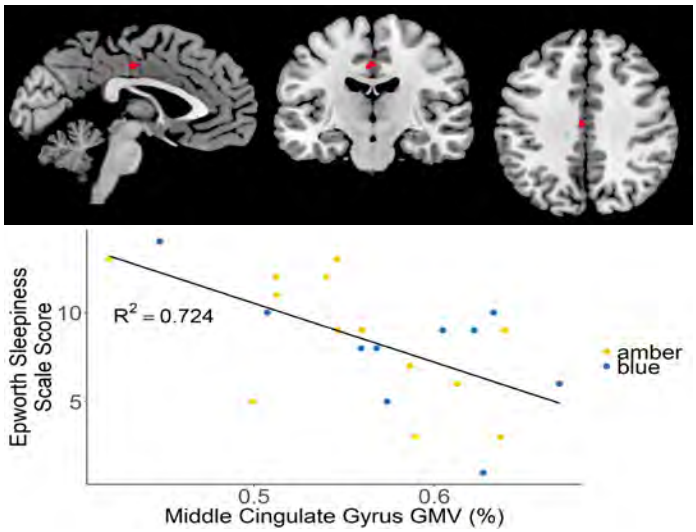


Figure 29. A single cluster (*family-wise error corrected p* < 0.05) demonstrating a negative correlation between gray matter volume and daytime sleepiness.

Whole brain volumetric differences between responders and non-responders: We did observe a significant improvement in daytime sleepiness with blue light therapy. However, our preliminary data have suggested that there is considerable variability in responses, and medical interventions rarely work for all individuals to whom they are applied. To further describe the difference in responses between the blue and amber groups, we computed a reliable change estimate for the Epworth Sleepiness Scale (ESS). The ESS is a self-reported measure of daytime sleepiness, where higher scores indicate greater daytime sleepiness. The reliable change estimate, an estimate of the expected change between two visits above which is likely due to intervention and below which is likely due to chance, was computed based on the original normative sample in the literature (test-retest reliability *r* =0.8; standard deviation = 3.8; $RCI = \sqrt{2 * \left(3.8 * \sqrt{1 - 0.8}\right)^2}$). That reliable change was 2.4, indicating that a change of more than 2.4 points on the ESS from baseline to post-treatment is interpreted as being due to the intervention rather than chance fluctuation. We applied this reliable change to the pre- to post-treatment differences in our data. Individuals in blue group were 3.75x more likely to demonstrate improvement than those in the amber group.

Accordingly, we divided the participants into three groups: Amber, Blue Non-Responders and Blue Responders. To identify possible explanations as to why some individuals did or did not respond to the blue light, we examined differences in whole brain gray matter volume at baseline and post-treatment separately between the Blue Responders and Non-Responders. We observed that individuals who responded to the treatment had lower gray matter volume in multiple regions, including the anterior cingulate (Figure 30, red), superior frontal gyrus (Figure 30, blue), and inferior frontal gyrus (Figure 30, green and yellow). At post-treatment,

Responders persisted in having lower gray matter volume in the inferior frontal gyrus (Figure 30, yellow).

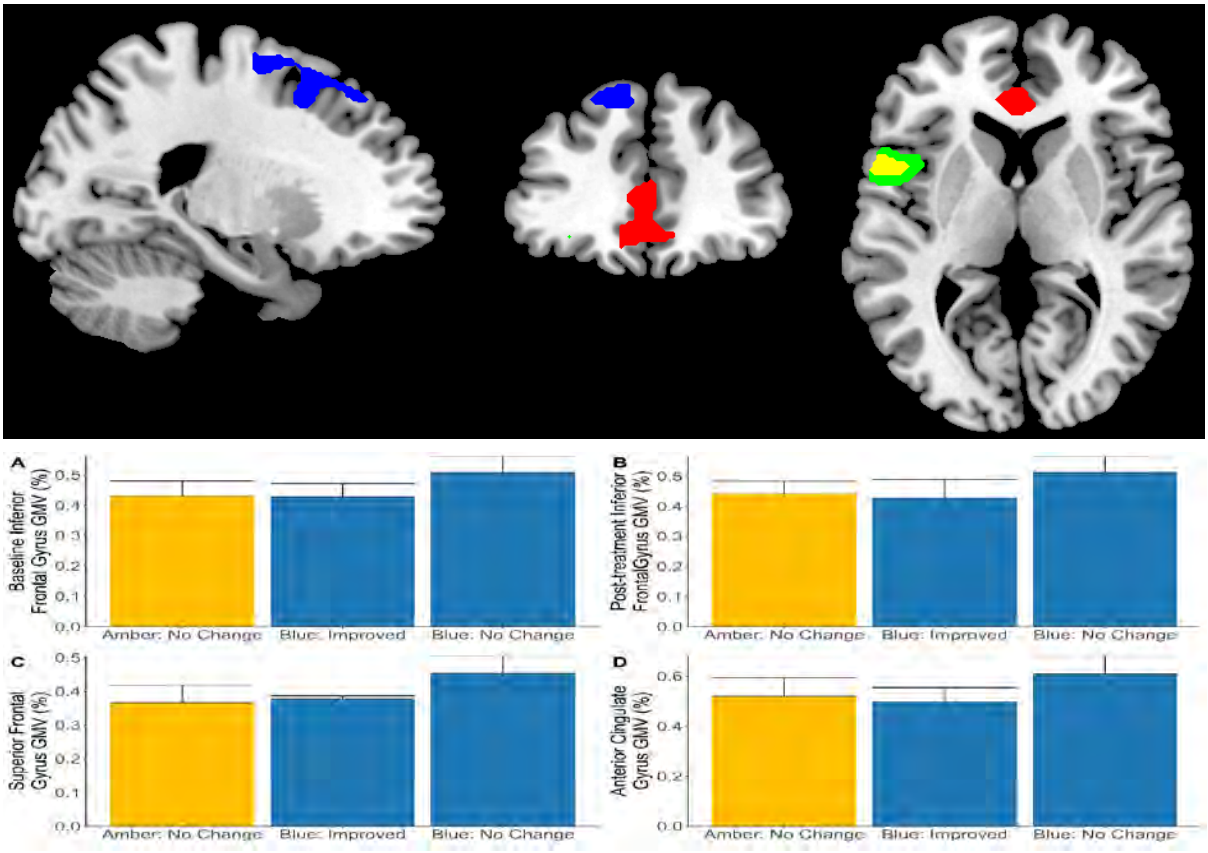


Figure 30. Clusters where blue-light responders had lower gray matter volume at baseline or post-treatment. The red (anterior cingulate), blue (superior frontal gyrus), and green (inferior frontal gyrus) clusters had significantly lower volume (*family-wise error corrected p* < 0.05) at baseline. The yellow cluster, a subset of the green cluster, had significantly lower volume at post-treatment.

These cluster locations have diverse cognitive and emotional functions. In particular the inferior frontal gyrus cluster which was significantly lower in the Blue Responders at both baseline and post-treatment is an area associated with language production. Previous reports in both healthy individuals and individuals with Parkinson's disease have implicated this area as an area of decreased functional connectivity in individuals with excessive daytime sleepiness compared to those without. While the full implications of these findings are not presently clear, they do demonstrate that there may be structural, and perhaps functional, predisposing factors for positive responsiveness to blue light therapy.

Associations between functional connectivity and post-concussive symptoms: Among the many analyses of mild traumatic brain injuries to date, one poorly understood area is the relationship between symptom presentation and underlying psychophysiological characteristics. Despite numerous studies attempting to link symptom patterns to either brain structure or function, there is little consensus to date. One limitation in previous investigations is the reduction of symptoms to singular values (i.e., total symptom scores) rather than considering

that symptom types/clusters may have distinct representations within the brain. Identifying the underlying neurophysiological characteristics that may underpin symptoms may additionally provide opportunities for individualized treatment based on symptoms.

To investigate this brain-behavior relationship, we correlated symptom subscale scores on the Neurobehavioral Symptom Inventory (NSI) with functional connectivity within and between 7 large-scale resting-state networks. Resting state fMRI data were preprocessed as described above and ROI-to-ROI connectivity was fit for a 360 ROI cortical parcellation (Glasser et al., 2016). Each of 360 ROIs was assigned to one of 7 large scale networks (Yeo et al., 2011) and the mean between and within network connectivity was estimated per person. For all participants, symptoms subscale scores were correlated with the network connectivity estimates.

Overall, increased symptom presentation was associated with increased connectivity between the visual and salience networks and concomitantly decreased connectivity between the salience and frontoparietal control networks. Furthermore, increased cognitive, emotional, and vestibular symptom scores were associated with increased connectivity between the visual and salience networks while emotional and somatic symptoms were associated with decreased connectivity between both the salience and dorsal attention and frontoparietal control networks (see Figure 31). Additionally, inter-network connectivity between the limbic network and the

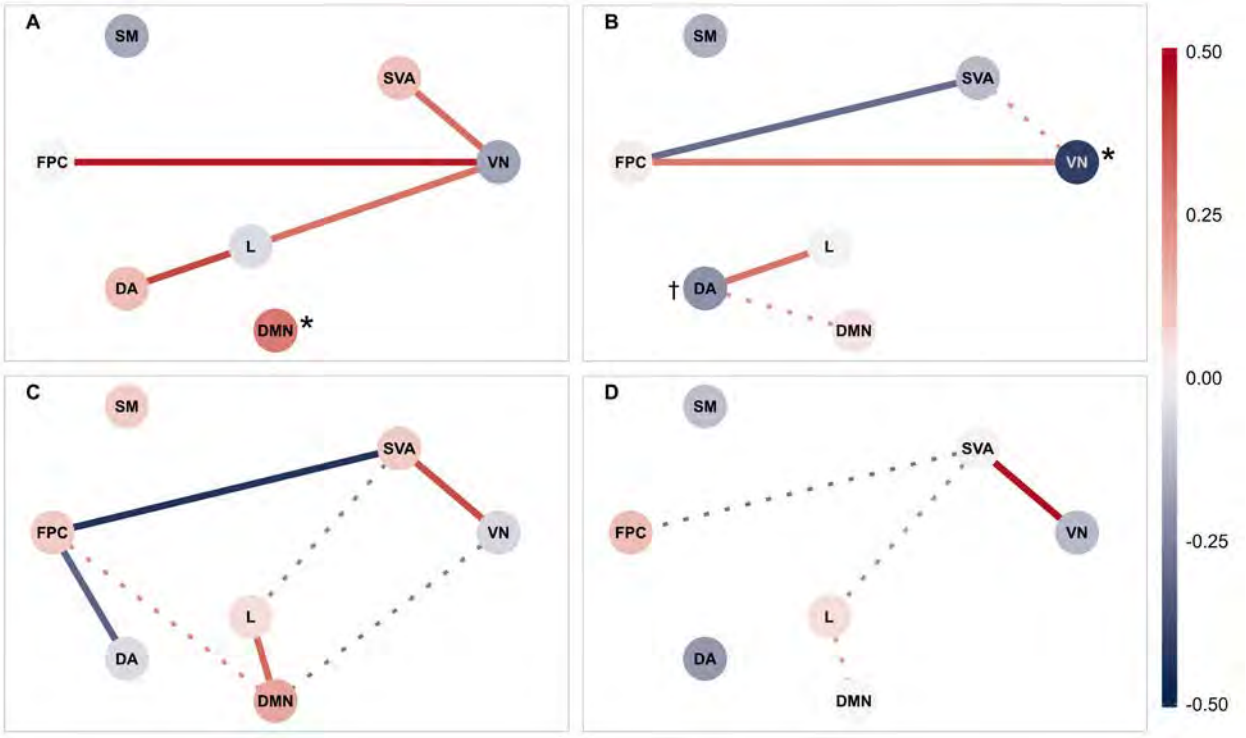


Figure 31. Network schematic describing the correlation between symptom severity and inter-network functional connectivity. Solid (FDR-corrected $p < 0.05$) and dotted (uncorrected $p < 0.05$) lines reflect correlations between vestibular (panel A), somatic (panel B), emotional (panel C), and cognitive (panel D) symptom scores. The color bar indicates the strength (Pearson's r) of the observed correlations. *Intra-network correlation FDR corrected $p < 0.05$; †Intra-network correlation uncorrected $p < 0.05$. Abbreviations: DA: Dorsal attention network; DMN: Default mode network; FPC: Frontoparietal control network; L: Limbic network; SM: Somatomotor network; SVA: Salience/Ventral Attention network; VN: Visual network

visual, attention, and default mode networks was positively associated with increasing symptom presentation.

These findings highlight the following:

1. Vestibular symptoms (i.e., dizziness, loss of balance, clumsiness) may require an increased reliance on visual processing and external attention. Consequently, this may be reflected in increased connectivity between visual, attention, salience, and cognitive control networks.
2. Increased limbic-visual connectivity may be a compensatory mechanism to maintain emotion regulation capacity in the presence of increasing emotional symptoms (see below). Similar findings of increased connectivity between visual and limbic structures have been reported in individuals with perceptual and chronic dizziness. (Indovina et al., 2015; Lee et al., 2018; Riccelli et al., 2017)
3. In addition to the connectivity patterns observed with vestibular symptoms, increased emotional symptoms (e.g., self-reported feelings of anxiety, depression, irritability, and frustration) were associated with decreased connectivity between the frontoparietal control network and both dorsal and ventral attention networks. Decreased connectivity between these networks in relation to emotional symptom presentation is consistent with other work in mTBI and depressive and anxiety symptoms, indicating reduced functional connectivity between these networks (McCuddy et al., 2018). Furthermore, these findings are supported by studies identifying disrupted white matter integrity in pathways connecting cognitive control, attention, and emotion regulation in mTBI patients (Matthews et al., 2011; Raikes et al., 2018; Strain et al., 2013).

Exploratory analyses

Baseline associations between demographics, key self-reported outcomes and secondary outcomes: We thoroughly investigated between-group differences at baseline in the key and secondary self-report and cognitive measures. These revealed few differences, suggesting that the groups were well-matched overall. Additionally, we investigated the bivariate relationships between demographic characteristics (including age, number of mTBIs, and days post injury), symptom presentation (including post-concussion symptoms, depression, and sleep-related outcomes), and secondary cognitive outcomes. At baseline, few associations were observed between any of the key measures of interest, injury characteristics, or cognitive outcomes. Broadly, there were limited associations between injury characteristics, daytime sleepiness, or depressive symptoms on cognitive task performance. Furthermore, associations that were present were generally small and did not substantially influence any of the primary findings. Of note, the primary outcomes were, themselves, correlated at baseline. Additionally, these measures were those that exhibited the greatest changes from pre- to post-treatment, suggesting that blue light imparts highly inter-correlated, positive effects on these measures. Figure 32 provides an exploratory correlation matrix among some of the other variables of interest from this project.

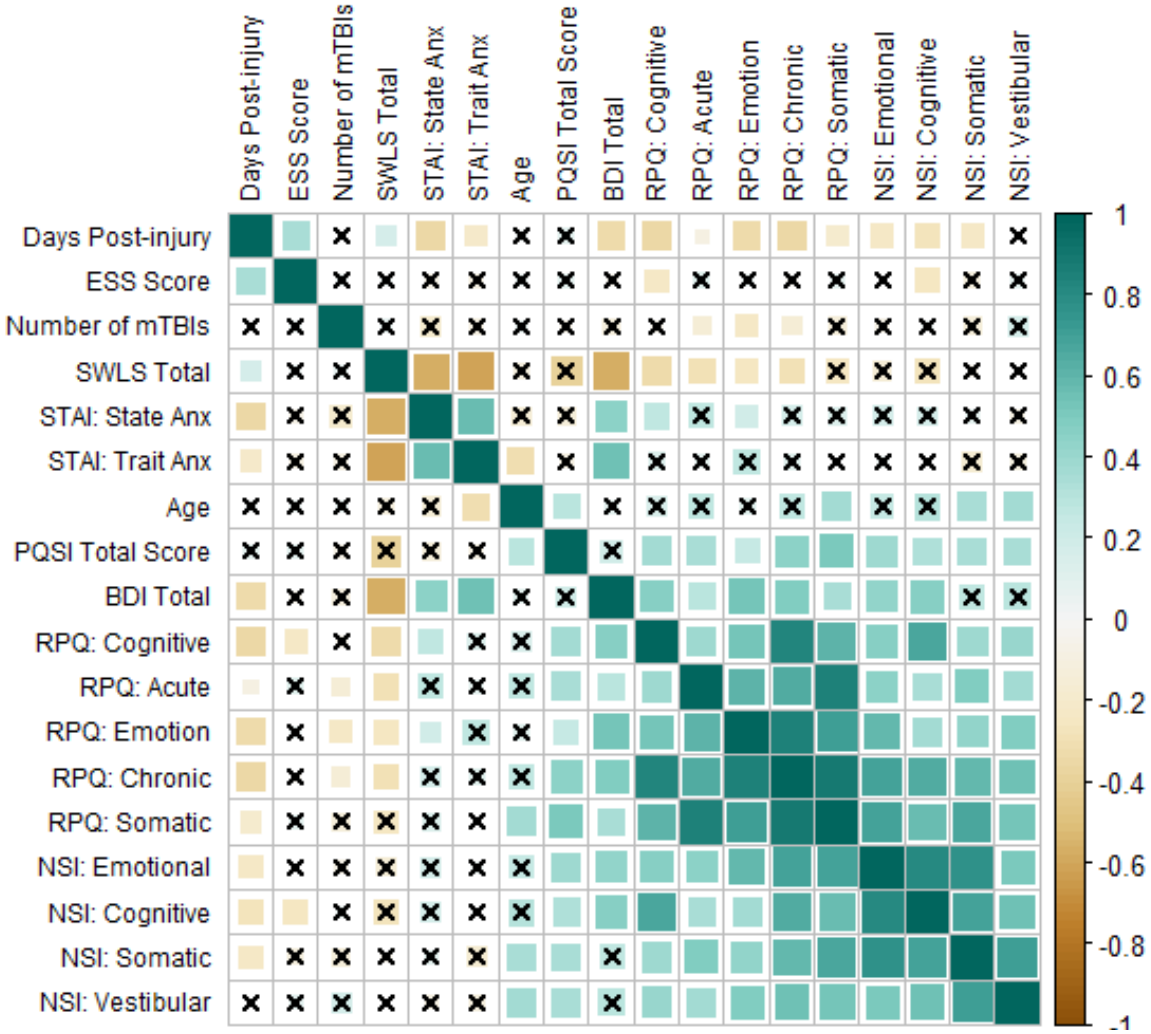


Figure 32. Exploratory correlation matrix between major variables in the project.

Total number of mTBIs exhibited weak, negative associations with symptom reporting on the Rivermead Post-concussion Symptom Questionnaire (RPCSQ). Additionally, days post-injury was weakly, negatively associated with post-concussive symptoms on both the RPCSQ and Neurobehavioral Symptom Inventory (NSI) as well as depression via the BDI (i.e. fewer symptoms as time from injury increases). However, days post-injury was positively associated with daytime sleepiness (increased daytime sleepiness as time since injury increases). This corroborates previous findings suggesting that sleep-related complaints persist long after injury. Symptom scores were positively correlated with each other. Somewhat paradoxically, daytime sleepiness was negatively associated with cognitive symptoms on both the NSI and RPCSQ (i.e., lower daytime sleepiness as associated with more cognitive symptoms).

Overall summary of mTBI treatment arm: Collectively this is the second study trial utilizing blue light we have conducted. Consistent with the previous investigation, daily morning blue light therapy is an efficient and effective method for improving daytime sleepiness and depression symptoms for those recovering from a mTBI. Improvements in these self-reported outcomes – among others – appears to be linked to changes in both brain structure and

function. While the full nature of this relationship remains to be understood (e.g., causal directionality – does improving daytime sleepiness facilitate neuroplasticity or does blue light induce neuroplastic changes resulting in changes in daytime sleepiness), the consistency of the present findings with those previously reported further supports the use of daily morning blue light therapy for those experiencing daytime sleepiness following a mTBI.

To provide a context for the aforementioned findings, we also summarize the primary findings from the previous sample below. Our next step will be to combine the findings from the previous study with those presented here to provide a more comprehensive sample.

Summary of Pilot Study of Blue Light for Facilitating Sleep and Recovery in mTBI:
The present study is an extension of an earlier pilot study of the effects of morning blue-wavelength light treatment on recovery from mTBI. The ultimate goal is to combine the current data with that of the pilot investigation to obtain a more comprehensive sample that includes at least n > 60 participants. Therefore, in the sections that follow, we summarize the primary outcomes from the pilot data, which will eventually be merged with the current data. In the pilot project, we identified the cognitive and neurobiological changes produced by a 6-week intervention of daily morning blue-wavelength light exposure in individuals recovering from a non-complicated mTBI. Specifically, in a randomized, double-blind, placebo-controlled trial, adults with a documented mTBI in the preceding 18 months used an LED lightbox each morning for 30-minutes. Each device was fitted with either BLUE or AMBERLEDs (see Figure 33). Sleep/wake activity was monitored with wrist actigraphy and on-line sleep diaries for one week before treatment, and throughout the 6-week intervention period. Participants also completed a comprehensive neuropsychological assessment battery, a series of objective multiple sleep latency tests (MSLTs), and functional and structural magnetic resonance imaging (MRI) scans on the day preceding the treatment period and immediately upon completion of the intervention. We hypothesized that the blue light intervention would lead to a greater phase advance in the circadian rhythm, improved sleep, and enhanced daytime alertness relative to amber placebo. Further, we hypothesized that compared to the placebo condition, the blue light would produce greater improvement in neurocognitive performance and symptom reduction, which would correspond to increased functional and structural connectivity within brain networks involved in visual attention.

Participants. Individuals with a documented history of an mTBI in the preceding 18 months were recruited from the greater Boston Metropolitan area to participate. Interested volunteers first underwent a rigorous telephone screening interview, followed by a detailed in-person interview to determine eligibility. Eligible, volunteers were between the ages of 18 and 50 and had experienced a “concussion” or non-complicated mTBI within the preceding 18 months, but no sooner than 4 weeks prior to their initial assessment. Before participation, all individuals were required to provide written documentation by a medical or other relevant professional (e.g., physician, nurse, emergency medical technician, coach, physical trainer, police officer, security guard) who either witnessed or was involved in the immediate response

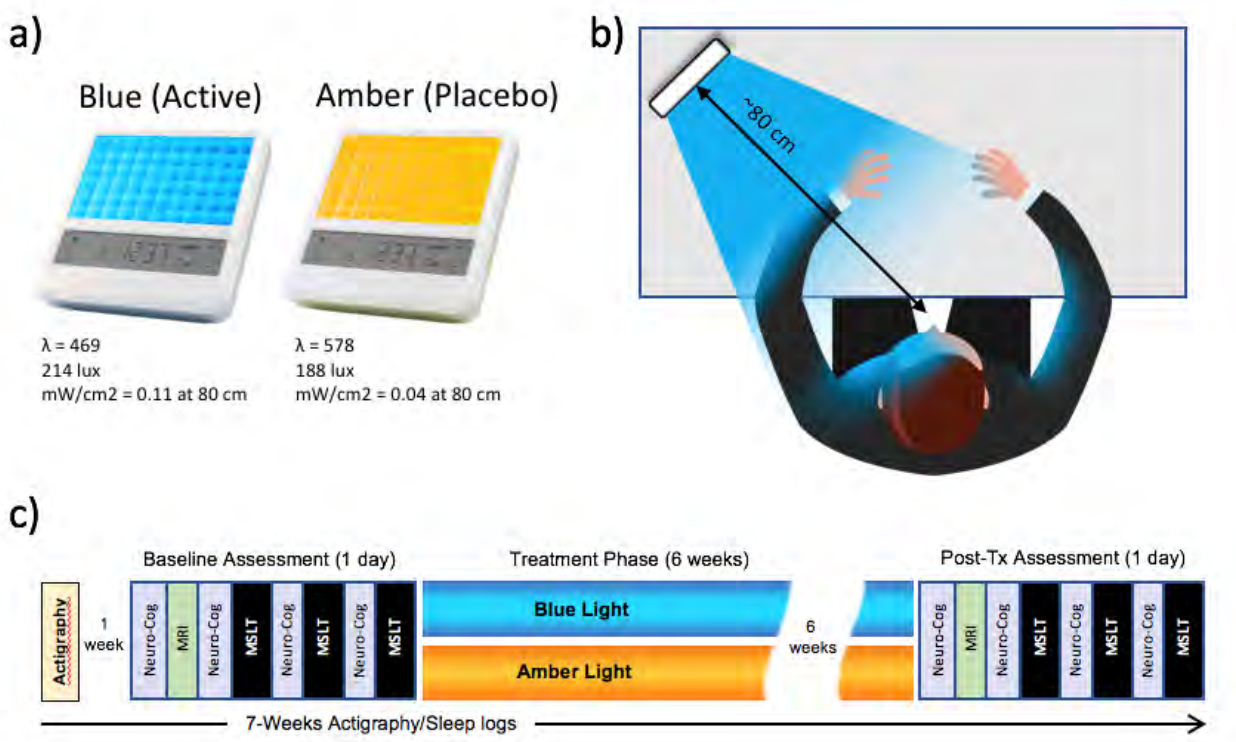


Figure 33. **Light therapy conditions and experimental design.** (**a**) Participants received either a blue (active condition) or amber (placebo condition) light box fitted with light-emitting diodes. **(b)** The participant was instructed to place the device at arm's length on a table at an approximately 45-degree angle and bathe their face with the light for 30-minutes each morning. **(c)** The study lasted for 7-weeks. The figure shows that the participant wore an actigraph sleep monitor for the entire study period. After one week of baseline actigraphy, the participant completed a full day of neurocognitive assessments, magnetic resonance imaging (MRI) scans, and multiple sleep latency tests (MSLTs). Participants were then randomized to one of the two light treatment conditions (blue versus amber), during which time they used the lightbox each morning. At the end of 6-weeks, participants returned to complete another day-long assesses session with the same measures collected at baseline.

to the injury. Eligible, volunteers were required to meet the definition of an mTBI as specified by the VA/DoD practice guidelines (Group, 2009), which define an mTBI as a traumatically induced structural injury and/or physiological disruption caused by an external force (e.g., head impact, blast wave) leading to an alteration in mental status (e.g., confusion, disorientation, retrograde or anterograde amnesia), consciousness (i.e., loss of consciousness less than 30 minutes; alteration of consciousness up to 24 hours), or post-traumatic amnesia up to 24 hours, and/or a Glasgow Coma Scale ≥ 13. For this study, all participants were also required to have reported the onset of significant sleep-related problems that emerged or worsened following the injury. Only primary English speakers (i.e., those who began speaking English as their primary language in the home by 3 years of age), and those who were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) were included. Potential volunteers were also excluded for any history of neurological, mood, or psychotic disorder that was present before the index traumatic injury, as well as abnormal visual acuity not correctable by contact lenses, metal within the body, pregnancy, or other contraindications for MRI. Other exclusionary criteria included current or anticipated shift work, intent to leave the time zone during the course of the study, use of contraindicated medications (i.e., sleep medications;

medications that affect neuroimaging), or use of illicit substances, including recent or long-term marijuana use, or excessive alcohol use (as defined by CDC criteria). Prior to enrollment, all participants completed written informed consent, and were compensated for their time in the study. The protocol for this experiment was approved by the Institutional Review Boards (IRB) of Partners Health Care, McLean Hospital, and the U.S. Army Human Use Protections Office.

Primary endpoints for this study, collected at baseline and post-treatment, included 1) actigraphically measured sleep (minutes per night), 2) actigraphically measured circadian phase shift (i.e., shift in sleep onset time, wake time, and midpoint of the sleep period), and 3) subjective sleepiness, and 4) objective sleepiness. Secondary endpoints included 1) cognitive performance (i.e., psychomotor vigilance, neuropsychological performance, and executive functioning), 2) brain volumetrics, 3) functional connectivity, and 4) white matter axonal integrity. Each of these was assessed at the baseline week or visit and again during the final week or follow-up visit. A total of 38 participants met full criteria for initial enrollment in the study. However, due to participant non-compliance (*n* = 2), disqualifying psychopathology (*n* = 1), and claustrophobia upon entering the scanner (*n* = 1), 34 participants were ultimately randomized to one of the treatment groups (Figure 34). Two participants in the BLUE condition failed to complete required study procedures during the course of treatment, yielding complete data for most outcome measures from 32 participants (15 male; 17 female) ranging in age from 18 to 48 years (*M* = 23.27; *SD* = 7.14). Of these participants, *n* = 16 (50%) received the active BLUE light condition and *n* = 16 (50%) received the placebo AMBER placebo light condition. Table 1 presents the demographic data for the samples.

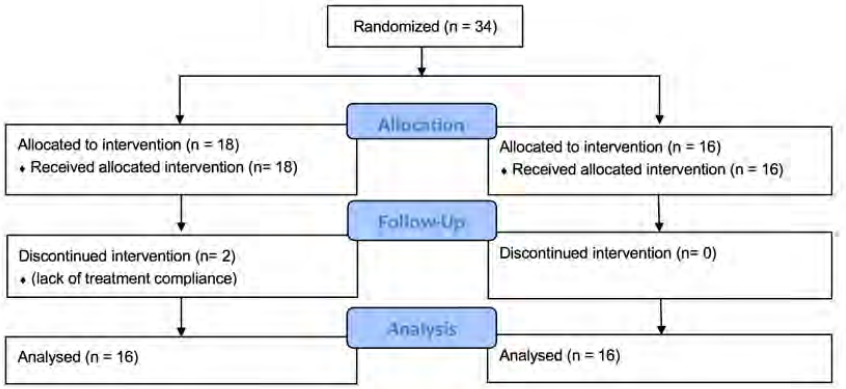


Figure 34. Participant flow diagram. The figure shows that 34 participants were randomly assigned to either the active blue light condition or placebo amber light condition. Two participants from the blue group were excluded due to non-compliance, yielding 16 participants per group in the final analysis.

General Procedure. Over seven weeks, participants completed three laboratory visits, including two full-day neurocognitive assessments plus neuroimaging scans, and were randomly assigned to complete a 6-week at-home light treatment regimen with either daily BLUE or AMBER light therapy each morning.

Visit 1: Intake. Upon arrival, each eligible participant completed the informed consent process followed by the Neurobehavioral Symptom Inventory (NSI) (King et al., 2012), and the MINI International Neuropsychological Interview (MINI) (Sheehan et al., 1998) to screen for psychopathology. Each participant was then fitted with an actigraphic sleep monitor wristwatch (Actiwatch Spectrum, Philips Respironics, OR, USA) and shown how to log onto a secure web-based sleep diary to complete daily questions about sleep and activity. Participants were

instructed to wear the actigraph watch continuously for the duration of the study and return to the lab for a baseline neurocognitive assessment and MRI scan in one week.

Visit 2: Baseline Neurocognitive Assessment/MRI Scan. After one week of at-home baseline actigraphic sleep assessment, participants returned for a baseline neurocognitive and neuroimaging assessment. Participants arrived at the lab at 8:00 a.m. to complete pre-scan procedures, including a pregnancy test for females and brief practice tasks for the functional portion of the scan. Beginning at 9:00 a.m., participants underwent a 60-minute neuroimaging scan that included standard structural MRI (MPRAGE), resting-state functional MRI, and diffusion tensor imaging (DTI). After leaving the scanner at 10:00 a.m., participants completed a half-hour neurocognitive assessment with the Repeatable Battery of Neuropsychological Status (RBANS). Between 10:30-11:00 a.m., polysomnographic electrodes were applied, and the participant underwent the first of three trials of the Multiple Sleep Latency Test (MSLT) at 11:50 a.m. After the MSLT, a break for lunch occurred, followed by administration of a measure of balance and stance stability at 1:15 p.m. A second MSLT occurred at 1:50 p.m. Multiple sleep and symptom questionnaires were administered, followed by the Tower of London at 3:15 p.m., and a third MSLT at 3:50 p.m. After testing, electrodes were removed and the participant was provided with a light therapy device with a full demonstration on its use, as well as a printed instruction brochure that provided detailed information about the use of the device.

Six-Week Light Therapy. Based on a pre-established computer-generated randomization scheme, participants were provided either a BLUE or AMBER light device (described in greater detail below) in a double-blind manner (i.e., participants were not informed that there were different colors of lights and all study staff with direct participant contact were blind to the color of light device assigned to each participant). Participants were instructed to activate the light device every morning within two hours of awakening, but no later than 11:00 a.m., and use the device continuously for 30 minutes. When using the device, participants were instructed to place the lightbox at approximately arm's length (20-30 inches distance from the face) at a slight angle (20-40 degrees), so that the light would bathe both sides of the face, and were encouraged to avoid looking directly at the diodes to avoid visual discomfort. The device was programmed to turn off automatically after 30 minutes of continuous use. Additionally, participants were instructed to log onto a secure website to complete a sleep and light use diary each morning after the completion of light exposure.

Visit 3: Post-Treatment Neurocognitive Assessment/MRI Scan. Upon completion of the 6-weeks of daily morning light treatment, participants returned to the lab for a final assessment session, which was virtually identical to the baseline session (Visit 2). At the end of the day, participants returned all equipment and were released from the study.

Assessment Measures. The following assessment measures and devices were used:

Personality and Psychodiagnostic Assessment. At Visit 1, a trained technician administered the Mini-International Neuropsychiatric Interview (M.I.N.I.), a psychometrically validated scale for assessing psychopathology (Sheehan et al., 1998), and the VA National

Traumatic Brain Injury Neurobehavioral Symptom Inventory (NSI)(King et al., 2012). At Visit 2, participants completed several self-report assessment scales including the Beck Depression Inventory (BDI-II)(Beck, Steer, & Brown, 1996), Rivermead Postconcussion Symptom Questionaire (RPCSQ) and basic questionnaires regarding sleep history, injury history, caffeine use, and demographics.

Actigraphy. Participants wore an Actiwatch Spectrum (Philips Respironics) wristwatch actigraph to monitor activity and sleep. The device collected wrist activity movement counts and accumulated light exposure every 60 seconds throughout the duration of the study. After each participant's study run, the activity data were downloaded from the watch.

Sleepiness and Subjective Sleep Need Assessment. At each visit, participants completed the Epworth Sleepiness Scale (ESS)(Johns, 1991), a measure of typical daytime sleepiness. Additionally, at seven times during each visit day (8:55 a.m., 10:05 a.m., 11:40 a.m., 1:05 p.m., 1:35 p.m., 2:35 p.m., 3:35 p.m.), participants completed a rapid single-item 7-point Likert assessment of immediate sleepiness with the Stanford Sleepiness Scale (SSS)(Herscovitch & Broughton, 1981). Additionally, as an indicator of perceived sleep need, we also asked participants to indicate "how many hours do you need to sleep to feel your best."

MSLT. Following the MRI procedure, each participant underwent a polysomnography (PSG) hook-up following standard procedures using the 10-20 system. A total of 14 leads were connected (i.e., A1, A2, O1, O2, Cz, C3, C4, F3, F4, LEOG, REOG, P3, Pz, P4). At three times during the assessment session (i.e., 11:50 a.m., 1:50 p.m., 3:50 p.m.), participants were escorted to a private, infrared video-monitored, sleep chamber to complete the multiple sleep latency test (MSLT). The participant laid supine on a bed and was connected to a Nihon Kohden Polysmith system (software version 11.0), with an amplifier (JE-912AK) and remote headbox (JE-915A). After standard biocalibration, the participant was instructed to lie quietly and try to relax. The lights were then turned off. PSG recording continued for 20 minutes and was monitored continuously by a trained technician in real time. The procedure was terminated after 20 minutes or was ended early if there were three consecutive 30-second epochs of sleep stage N1 or one continuous epoch of any other sleep stage. Each recording was then independently scored by a trained and certified polysomnographic technician to determine the number of minutes of wakefulness before entering into stage N1 or deeper sleep. A score of 20 indicated no sleep was measured.

Psychomotor Vigilance Test (PVT). At three times during the course of each assessment session (11:30 a.m., 1:25 p.m., 3:25 p.m.), participants completed a 10-minute assessment of attention and vigilance with the psychomotor vigilance test (PVT)(Dinges & Powell, 1985) on a desktop computer. During the task, participants were required to monitor a black screen and press a response key as quickly as possible whenever a target stimulus appeared in the center of the screen. Response time feedback was provided for each response. Each stimulus was presented in a pseudo-random fashion with an inter-stimulus interval that ranged randomly without replacement from 2 to 10 seconds.

Neurocognitive Assessment. From approximately 10:05-10:35 a.m., participants completed the RBANS, a brief battery of well-normed neuropsychological tests that is commonly used for assessing individuals with traumatic brain injury. The test provides several index scores, including: Immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory, and Total Score. Two alternate forms were counterbalanced across the two groups for each administration. Additionally, at approximately 3:15 p.m., participants completed a 10-trial computerized version of the TOL as a measure of executive functioning (i.e., planning and sequencing ability) (Colorado Assessment Tests, http://www.catstests.com). On each trial, the participant began with a starting "tower" that consisted of three "pegs" of differing lengths, each with an arrangement of three different colored "beads" in various configurations upon the pegs. To solve the puzzle, the examinee must rearrange the beads to match a pre-specified goal pattern as quickly and in as few moves as possible. Dependent variables from this task included the number of moves required to match the goal arrangement, the average total move time, and an index of throughput that accounted for both speed and accuracy (i.e., [(proportion of correct moves)/(average total move time in seconds)] x .60).

Light Exposure Devices. At the conclusion of Visit 2, participants were provided with either a BLUE or AMBER a light therapy device to be used each morning. The devices were manufactured by Philips Electronics (Stamford, CT). All units were identical in design, with the exception of the color wavelength of the LEDs. Each device consisted of a 13.5 x 14 cm plastic encased table-mounted device with a 10 x 6 array of light emitting diodes (LEDs). Each LED was encased in a 1 x 1 cm cubical projection element covered by a translucent plastic window. For the active BLUE condition, participants were provided with a commercially available Philips goLITE BLU® Energy Light device (Model HF3321/60). The goLITE BLU Energy Light has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm). The AMBER placebo devices were provided on loan by the manufacturer. The AMBER devices were essentially identical in design to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm). Participants were instructed to use the device on its highest setting, and the device was set to deactivate after 30 minutes of continuous use.

Neuroimaging Methods. Data were collected at baseline and post-treatment using a 3.0 T magnetic resonance imaging scanner (Siemens Tim Trio, Erlangen, Germany) using a 32-channel head coil. All scans occurred between 9:00-10:00 a.m.

Structural Neuroimaging. Volumetric data were collected using a T1 weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) that consisted of 176 sagittal slices (256x256 matrix) with a slice thickness of 1 mm and a voxel size of 1 x 1 x 1 mm^3. T1 weighted structural images were preprocessed using the Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat/) in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were realigned to the anterior-posterior commissure axis and then segmented using the longitudinal pipeline into gray matter, white matter, and cerebrospinal fluid using VBM12, a fully automated algorithm in SPM12. Segmented images were used to create a custom DARTEL template and then the

images were normalized to Montreal Neurological Institute (MNI) space. Smoothing of normalized images was performed with a 10mm full width at half maximum (FWHM) isotropic Gaussian kernel.

Functional Neuroimaging. Resting-state functional MRI images were acquired for 6 minutes using a gradient echo T2*-weighted sequence (TR/TE/flip angle=2 sec/30ms/90°) and a 224 mm FOV. The resting functional images were collected in the same plane with 34 coronal slices and a voxel size of 3.5 x 3.5 x 3.5 mm^3, in an interleaved excitation order, with foot-to-head phase encoding. At the beginning of each scan, four images were acquired and discarded to allow for T1-equilibrium effects. Head movement was restricted using expandable foam cushions, and subjects were asked to remain awake with eyes open while lying still during the scans. Participants were simply instructed to allow their mind to wander during the scan. Resting-state fMRI data were preprocessed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were slice-time corrected, co-registered to their anatomical images, realigned and resliced to 2 x 2 x 2 mm^3 isotropic voxels, unwarped to correct for field inhomogeneity, normalized to the standard three-dimensional space of the Montreal Neurological Institute (MNI), and spatially smoothed using a 6mm isotropic Gaussian kernel. Outliers from motion and global signal intensity were identified using the *ART* toolbox https://www.nitrc.org/projects/artifact_detect/. Images with movement from a preceding image exceeding 0.5mm or a global mean intensity greater than 3 standard deviations were regressed out of the first level general linear models.

Diffusion Tensor Imaging (DTI). DTI scans were acquired using a Siemens Tim Trio 3T scanner (Erlangen, Germany) at McLean Hospital Imaging Center. Diffusion-weighted imaging (DWI) data were acquired along 72 directions with a b-value of 1000 s/mm^2 and following parameters: voxel size = 1.75 x 1.75 x 3.5 mm^3, TR = 6340 ms, TE = 99 ms, flip angle = 90 degrees and 40 axial slices with thickness = 3.5 mm, encompassing the whole brain. A set of 8 images with no diffusion weighting (b0 images) was also acquired. Using dcm2nii toolbox (part of MRIcron(Rorden, Karnath, & Bonilha, 2007)), we converted DWI data from DICOM into NIFTI format. A b-value and b-vector file was generated during this step. The raw data were imported into the DSI Studio (http://dsi-studio.labsolver.org) and converted into SRC format. Each SRC file underwent standard eddy current and subject movement correction, followed by a thorough examination using quality control (QC) procedure to ensure the quality and integrity of data. Neighboring DWI correlation (NDC) values for the current data set were greater than 0.95. No outlier in NDC values (greater than 3 median absolute deviation) was identified.

Data Analysis. Data analysis followed a sequential process. First sleep and performance measures were compared between pre- and post-treatment. Second, we compared gray matter volume (GMV) in the brain between pre- and post-treatment using voxel-based morphometry (VBM). As discussed in detail below, two separate clusters within the left and right thalamus demonstrated significant increases in volume following treatment with BLUE light. Third, the resulting significant GMV clusters were used as seed regions of interest (ROIs) in a subsequent resting state functional connectivity (rsFC) analysis. Significant functional connectivity values between the seed ROIs and associated cortical clusters (ROIs) were extracted for further

analysis. Fourth, the functional connectivity data were also analyzed using Granger causality (GC) analysis to determine the directional nature of the connectivity patterns. Areas which were not found to be structurally connected were not analyzed using GC. Lastly, the seed and target ROIs resulting from the rsFC analysis were implemented as endpoint regions in a fiber tractography analysis using the diffusion tensor imaging scan data. Once fiber tracts were defined for each individual, standard DTI metrics of fiber pathway integrity were extracted and compared between pre-and post-treatment for each light condition. The resulting metrics from each region were extracted for further analysis with relevant behavioral outcome metrics.

Actigraphic Sleep Analysis. Actigraphic data were downloaded and then processed and scored in Actiware® 6 (Philips Respironics) according to standardized procedures. For the present analysis, we averaged the minutes of sleep obtained for each overnight sleep opportunity for the first six nights of the baseline week (i.e., between Visit 1 and 2) and the final six nights preceding the post-treatment visit (Visit 3). For each participant, sleep onset time, wake time, sleep duration, sleep efficiency, and wake after sleep onset (WASO) was calculated. A 2 between (light color: blue vs amber) x 2 within (time: baseline vs post-treatment) mixed analysis of variance (ANOVA) was conducted on each of these variables separately. For all behavioral analyses, we controlled for a set of variables likely to affect sleep, including concussion severity (RPCSQ and occurrence of loss of consciousness (LOC) from the most recent concussion), depression (BDI), and participant age. As appropriate, for select sleep measures, change metrics were also examined as dichotomous outcome variables (i.e., improvement vs. no-improvement) to allow determination of odds ratios (OR).

Cognitive/Behavioral Performance Analysis. To assess the effects of light treatment group on cognitive and behavioral measures, data from self-report questionnaires (e.g., ESS) and cognitive metrics (e.g., TOL) were computed as a change from baseline. These change scores were then compared using one-way ANCOVA, controlling for RPCSQ, LOC, BDI, and age. As appropriate, for select behavioral measures, change metrics were also examined as dichotomous outcome variables (i.e., improvement vs. no-improvement) to allow determination of odds ratios (OR).

GMV Statistical Analysis. Statistical analyses were conducted in several stages. First, processed GMV data from CAT12 were analyzed in SPM12. A 2 between (blue vs. amber) x 2 within (baseline vs. post-treatment) mixed analysis of variance (ANOVA) was conducted within SPM12 using the flexible factorial option, controlling for age, intracranial volume, and the number of days the light device was used (according to online sleep logs). Maps were cluster corrected for family-wise error (FWE, $p < .05$) at the whole brain level. Resulting clusters were then compared from pre-to post-treatment using paired t-tests in SPM12 for the BLUE light group, with age, intracranial volume, and the number of total days in the study during which participants reported using the light device entered as nuisance covariates. To increase precision, separate search territories were placed for the left and right thalamus using the automated anatomic labeling atlas (AAL; (Tzourio-Mazoyer et al., 2002a)). We used a cluster-extent based thresholding, following the recommended approach suggested by Woo, Krishnan, and Wager (Woo et al., 2014), applying a primary significance threshold of $p < 0.001$,

uncorrected, as the default lower limit. Based on this primary height threshold, SPM12 provided the critical cluster size for cluster-extent correction with family-wise error (FWE) maintained at $p < .05$ for the search territory. Between group t-tests were conducted for the BLUE group and resulting significant clusters were used a regions of interest (ROIs) that were then compared for the AMBER group to constrain for multiple comparisons. Using the Region Extraction Tool (REX), the mean GMV estimates were extracted for each cluster for the BLUE and AMBER groups separately and exported to IBM SPSS Statistics 25 for further analyses.

We were interested in the associations between the change metrics for each neuroimaging parameter and several cognitive/behavioral outcome variables. Here, the volumetric change values for each cluster were extracted for each individual for correlation with cognitive/behavioral measures of interest. A hierarchical multiple regression procedure was employed, including covariates for age, intracranial volume, and the number of days the light was used (as determined from online sleep logs) in the first block of the analysis, followed by the specific change values for GMV in the second block. After controlling for covariates, the partial correlation coefficient calculated between GMV change and the cognitive/behavioral metrics.

Functional Connectivity Analysis. A single subject was removed from each group from subsequent fMRI analyses, as more than 20% of their scans were identified as outliers. An independent samples T-test indicated no significant difference between groups in the number of outliers identified and incorporated into subsequent first level models at baseline ($p = .09$) and post-treatment ($p = .54$).

Here, we used the two GMV clusters identified in the previous analysis (i.e., left pulvinar (LPul) and right pulvinar (RPul)) as seed regions for resting state functional connectivity (rsFC) analyses. Functional connectivity analyses were performed with a seed-to-voxel driven approach within the CONN toolbox V17.f (Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessed structural and resting state data had physiological and other noise sources identified as nuisance covariates using a component-based noise correction method (CompCor). The first acquisition image, images identified as outliers, nuisance covariates, as well as white matter and cerebrospinal fluid masks, were regressed out of the first level general linear models. The BOLD time series was then band pass filtered at 0.01-0.1 Hz. Individual subject seed-to-voxel whole-brain connectivity maps were created for the LPul and RPul seeds with the mean time series from each seed used as a predictor in a multiple regression General Linear Model (GLM). The resulting individual bivariate correlation coefficients were Fisher transformed into Z-scores for subsequent second level analyses.

1) Seed-to-Voxel Analysis---Two analyses were performed at the second level to create statistical parametric maps (SPMs) representing associated changes in functional connectivity for each seed region. Repeated measures two-way ANCOVAs were used to investigate the main effect on functional connectivity associated with BLT, with mean-centered age and mean-centered days light used as covariates within the models. SPMs for each seed were defined with a cluster-forming threshold (voxel-level uncorrected $P < .001$) and a cluster-

level extent threshold (Family Wise Error (FWE) corrected P < .05), using a positive contrast, to identify clusters of voxels associated with significant increases in connectivity to the seed region. No clusters were identified using the RPul seed, and three clusters were identified using the LPul seed. A mask was created for each cluster identified containing voxels that correlated with the LPul seed, in order to further investigate Regions of Interest (ROIs) that contained voxels associated with significant change for the treatment group.

2) Seed-ROI Analysis ---To determine the extent of connectivity change observed for either treatment group, the BOLD time-series was extracted from each cluster identified in the seed-to-voxel analyses. Seed-to-ROI within group connectivity analyses were performed using paired T-tests with the identified ROIs (i.e. Left Parietal Cortex: LParC, Left Agranular Frontal Area: LAFA, and the Right Parietal Cortex: RParC), and the LPul seed. Mean-centered age and mean-centered days light used were included in the models as covariates and results were corrected for multiple comparisons (p < .05, seed-level FDR-correction).

The functional connectivity values for each connection were extracted for each individual for further correlation with cognitive/behavioral measures of interest. We applied hierarchical multiple regression procedures, including covariates for age and the number of days the light was used (as determined from online sleep logs) in the first block of the analysis, followed by the specific functional connectivity parameter of interest in the second block. After controlling for covariates, the partial correlation was determined for the parameters of interest.

Directed functional connectivity (DFC) analysis: Granger causality (GC). Raw time-series data were band pass filtered using the Butterworth filter design using higher cutoff frequency of 0.0028 Hz (f_1) and a lower cutoff frequency of 0.1 Hz (f_2). Higher cutoff frequency was determined from time-series length (n = 180 time-points) and repetition time (TR = 2 s) as following:

$$f_1 = \frac{1}{n * TR} = 0.0028 \text{ Hz}$$

The lower cutoff frequency of 0.1 Hz was selected because low frequency (< 0.1 Hz) BOLD fluctuations often show strong correlations at rest (Cordes et al., 2001). The ensemble means from the time-series for each node were removed to make the zero-mean process for GC analysis. Moreover, these steps helped to remove slow trends and physiological noise associated with respiratory and cardiac activities.
A spectral interdependency method (Dhamala, 2013) was used to estimate the DFC between ROIs by quantifying the inter-relationships between their corresponding oscillatory mechanisms as a function of frequency (f) of oscillations. Directional influences between two regions, say a and b, are estimated from a spectral density matrix (S). Matrix S is constructed parametrically from the time-series of systems a and b using autoregressive (AR) modeling as following:

$$GC_{a\to b} = \ln \frac{S_{bb}(f)}{\tilde{H}_{aa}(f)\sum_{aa}\tilde{H}^{*}_{aa}(f)}$$

$$GC_{b\to a} = \ln \frac{S_{aa}(f)}{\tilde{H}_{bb}(f)\sum_{bb}\tilde{H}^{*}_{bb}(f)}$$

Here, $\tilde{H}_{aa} = H_{aa} + \frac{\sum_{ab}}{\sum_{aa}} H_{ab}$ and $\tilde{H}_{bb} = H_{bb} + \frac{\sum_{ab}}{\sum_{bb}} H_{ba}$ represent new transfer function matrices for a and b respectively in terms of noise covariance matrix, Σ and transfer function matrix H. Here, * denotes matrix adjoint. Mathematical details of these estimations are documented previously (Dhamala, 2013).

GC measures can be computed by either parametric or non-parametric methods (Dhamala, Rangarajan, & Ding, 2008a, 2008b). In this study, we used the parametric approach. The optimal model order for parametric approach was calculated by comparing power spectra from the parametric and non-parametric approaches (Dhamala et al., 2008a). Different model orders from 1 to 10 were tested, and the model order, which yielded the lowest power difference, was selected. The threshold level for statistically significant directed functional connection was estimated from surrogated data by using permutation test (n = 1000) and a gamma function under a null hypothesis of no interdependence at the significance level of $p < 10^{-4}$ (Blair & Karniski, 1993; Brovelli et al., 2004) ($p = 10^{-4}/16$, corrected for multiple comparisons). Previously, the GC technique has been shown to have consistent results with the dynamic causal modeling technique, in terms of directional connectivity from resting-state fMRI data (Bajaj, Adhikari, Friston, & Dhamala, 2016).

For the present analyses, the range of GC metrics was extracted for each individual and correlated with cognitive/behavioral measures of interest. Using hierarchical multiple regression procedures, covariates including age, intracranial volume, and the number of days the light was used were entered at a first block, followed by the specific GC range parameter of interest at the second block, and the partial correlation was determined for the parameters of interest.

Anatomical Connectivity Analysis: DTI. Diffusion MRI connectometry (Yeh, Badre, & Verstynen, 2016) was performed to compare longitudinal pair-wise scans between pre and post-treatment conditions for both amber-light treatment (ALT) and blue-light treatment (BLT) groups. The connectometry approach, which is implemented in DSI Studio, uses a permutation test to perform the longitudinal pairwise comparison between white-matter pathways. Tracts, which showed significant longitudinal differences along axonal fiber directions, were identified using a deterministic tractography algorithm (Yeh, Verstynen, Wang, Fernandez-Miranda, & Tseng, 2013). Group averages of local connectome were quantified in terms of their differences in density and diffusivity measurements of water diffusion, *including* fractional anisotropy (FA) as well as isotropic (ISO) diffusion. Here, FA is one of the most common *diffusivity* measures, which is defined for each voxel and represents how fast water diffuses, whereas ISO is a *density* measure and represents how much water diffuses in an isotropic fashion. Both FA and ISO components were estimated using the Q-space diffeormophic reconstruction (QSDR) (Yeh

& Tseng, 2011) approach implemented in DSI Studio. QSDR is a model-free approach, which calculates the distribution of water diffusion using a high-resolution standard brain atlas constructed from 90-diffusion spectrum imaging datasets in the ICBM-152 space. Automated registration to standard template space was used for each subject. All the regions of interest (ROIs) were transformed into MNI space in order to perform diffusion MRI connectometry in QSDR-space. A seed-count of 5000 sub-voxels for each region (LPul, LParC and LAFA) was used for connectometry analysis. All the ROIs were dilated to 3 mm to extend to white matter. Tracts with differences in FA and ISO diffusion were identified for all the connections, which showed significant involvement in functional connectivity analysis i.e., between LPul and LParC and between LPul and LAFA. To limit the tracts between LPul and LAFA, LPul was used as a seed region as well as an end region and LAFA was used as an end region. A lower T-value threshold of 0.5 was used to identify tracts which were more sensitive to light treatment. Track pruning was conducted using 10 iterations, and tract length threshold was 30 voxels. A total of 10000 permutations and false discovery rate (FDR) of 0.05 were used to obtain the null distribution of the tract length. Subject-wise differences for the tracts that showed differences (at FDR between 0 and 0.2) in either FA or ISO diffusion measures were extracted for further correlation analysis with behavioral parameters. Using hierarchical multiple regression procedures, covariates including age, intracranial volume, and the number of days the light was used (as determined from online sleep logs) were entered at a first block, followed by the specific ISO diffusion parameter of interest at the second block, and the partial correlation was determined for the parameters of interest.

PILOT STUDY RESULTS

Baseline Metrics. As evident in Table 1, light condition groups were similar on key variables at baseline, including sex, age, years of education, number of previous concussions, months since injury, concussion severity, depression, functional outcomes of sleep, chronotype, and days of compliance with light treatment (determined from daily time-stamped website diary completion). Half of participants (n = 16) reported only one concussion, while half reported more than one lifetime concussion (range 1 to 7 total). Of those reporting more than one concussion, the modal response (i.e., endorsed by 5 participants) was 2 head injuries.

Actigraphic Sleep. BLUE light produced a significant phase advance in sleep onset and offset times relative to AMBER light. After accounting for covariates (baseline concussion symptoms, loss of consciousness (LOC) from the most recent concussion, depression (BDI), age), there was a significant light-condition x time interaction, $F(1, 21) = 6.16$, $p = .022$ (Figure 35a). Over the course of treatment, planned comparisons showed that participants in the BLUE condition were phase advanced in sleep onset times, generally falling asleep 57.5 minutes earlier in the final week of the study compared to baseline ($p = .004$), while those in the AMBER condition fell asleep 13.8 minutes later compared to baseline ($p = .508$). Overall, 80% of participants in the BLUE condition showed some evidence of earlier sleep onset, while 58.3% of those in the AMBER group did ($\chi^2 = 1.50$, $p = .221$). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 13.04 (95% CI: 0.84 to 202.52; p = .066. Further, planned comparisons showed that

participants in the BLUE condition were awakening 55.9 minutes earlier by the final week of treatment compared to baseline (p = .037), whereas the AMBER condition was awakening only 16.1 minutes earlier after treatment (p = .576; see Figure 35b). Overall, 66.7% of participants in the BLUE condition showed some evidence of earlier wake times, while 50% of those in the AMBER group did (χ^2 = 0.77, p = .38). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 3.68 (95% CI: 0.55 to 24.74; p = .18. There were no significant changes in mean total sleep time (TST) per night between pre- and post-treatment assessments, regardless of light-condition (all p-values > .05; see Figure 35c). There was a nonsignificant trending difference between light-condition groups in the extent of circadian phase shift (CPS; i.e., taking the midpoint between sleep onset and offset for each participant) from baseline, $F(1, 21) = 4.18$, p = .054 (see Figure 35d), such that those in the BLUE light condition showed an average circadian phase advance in the midpoint of the sleep period of 60.1 minutes, whereas those in the AMBER light condition shifted earlier by only 1.9 minutes on average. Overall, while 73.3% of participants who received BLUE light showed at least some evidence of phase advancement,

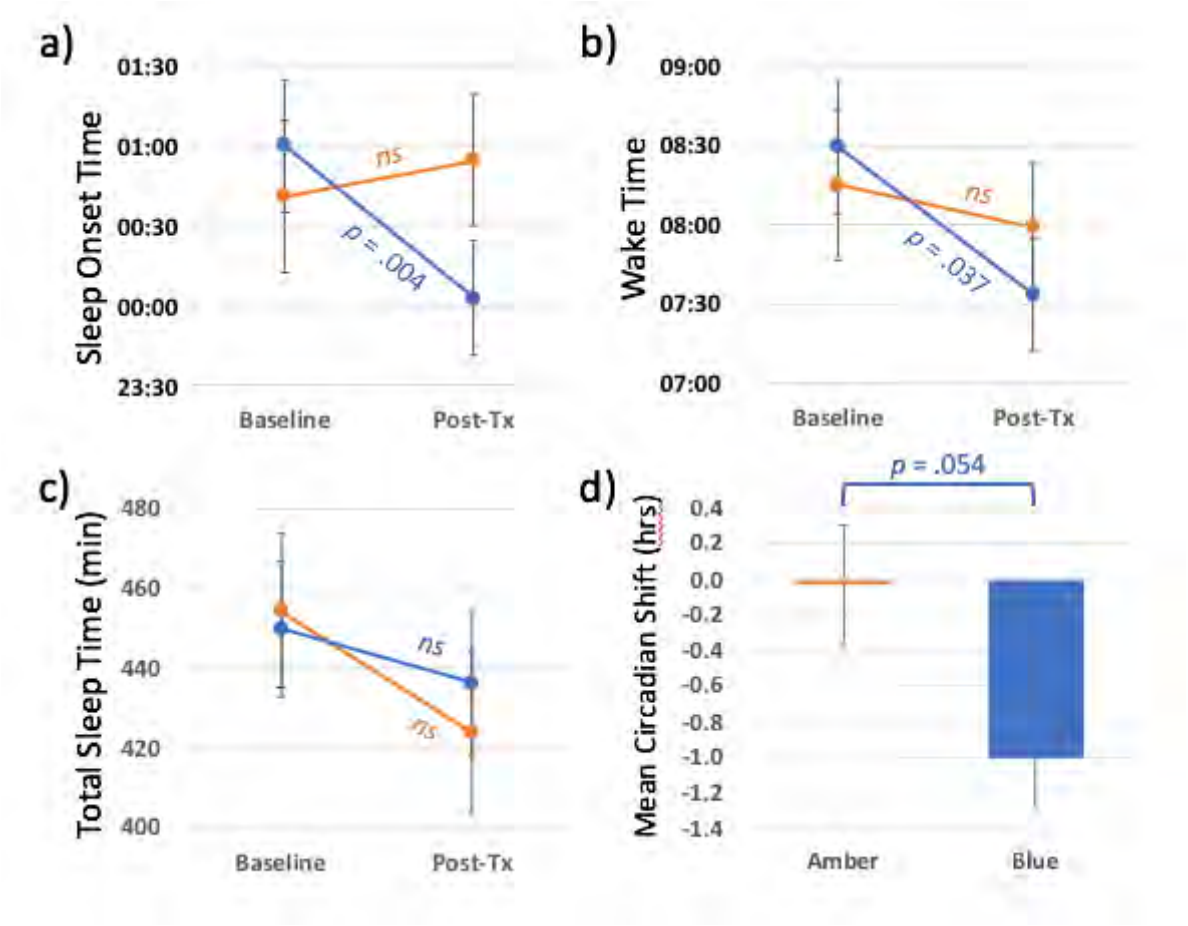


Figure 35. **Effects of light treatment on actigraphic sleep measures.** (**a**) Blue light shifted sleep onset time by 57.5 minutes earlier by the end of treatment, versus no change for the amber group. **(b)** Blue light shifted wake time by 55.9 minutes earlier by the end of treatment, but there was no difference for amber light. **(c)** There was no significant effect of light condition for change in total sleep time (TST) from pre- to post-treatment. **(d)** A comparison of the midpoint of sleep onset and wake time for each light group showed that blue light was associated with a non-significant trend toward a circadian phase advancement in the sleep period of 60.1 minutes by the end of treatment. Error bars represent 1 SE.

58.3% of those in the AMBER group also showed at least some phase advancement (χ^2 = 0.675, p = .411). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 7.34 (95% CI: 0.59 to 90.71; p = .12.

Sleepiness and Subjective Sleep Need. Relative to placebo, the BLUE light intervention led to reduced typical daytime sleepiness $F(1,26) = 5.49$, p = .027 (see Figure 36a). Moreover, we found that 87.5% of the participants in the BLUE light condition showed reduced sleepiness scores from pre- to post-treatment, whereas only 37.5% of those in the AMBER placebo condition showed any measurable reduction in sleepiness over the same timeframe (χ^2 = 8.53, p = .003; see Figure 36b). After controlling for covariates (described above), the odds ratio (OR) for showing any improvement in daytime sleepiness was 25.63 (95% CI: 2.76 to 237.84; p = .004; Nagelkerke R^2 = .446). We also found that the number of hours necessary to subjectively "feel best" was reduced for the BLUE light condition (M = -1.51, SE = 0.47) relative to AMBER (M = .043, SE = 0.47), $F(1,26) = 4.99$, p = .034 (see Figure 36c).

MSLT. As an objective measure of daytime sleepiness/alertness, participants completed a modified version of the MSLT over three time points at baseline and post-treatment. Notably, it was only the second MSLT, occurring in the early afternoon (1:50 p.m.) proximal the "post-lunch dip" (Monk, 2005), that showed a significant light-condition x time interaction, $F(1, 26) = 5.26$, p = .030 (see Figures 36d-f), suggesting that from pre- to post-treatment, participants in the BLUE light condition showed increased latency to fall asleep during the mid-day (i.e., were more alert). There were no significant light-condition x time interactions for the early morning or late afternoon MSLT sessions.

Cognitive/Behavioral Performance. Participants completed multiple cognitive and behavioral tasks at baseline and after 6-weeks of intervention with either the BLUE or AMBER light.

Psychomotor Vigilance. At the first psychomotor vigilance test (PVT), which occurred in the late morning (11:30 a.m.), there was no significant light-condition x time interaction, $F(1, 22) = 0.062$, p = .805 (see Figure 36g), with both groups slowing in reaction time (RT) during the post-treatment session relative to baseline, and no group differences. By the second PVT, in the early afternoon (1:25 p.m.), near the "post-lunch dip", there was a non-significant light-condition x time interaction, $F(1, 22) = 2.985$, p = .098 (see Figure 36h), with post-hoc tests indicating that from pre- to post-treatment, participants in the AMBER light condition showed significant slowing of RT ($p < .005$), while those participants in the BLUE light condition sustained RT from pre- to post-treatment. Finally, by late afternoon (3:25 p.m.), the light-condition x time interaction became non-significant $F(1, 22) = 0.797$, p = .382 (see Figure 36i).

Neuropsychological Performance. Contrary to predictions, light condition had no significant effect on mean performances on a brief neurocognitive performance battery (RBANS), which included immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory, and RBANS Total Score.

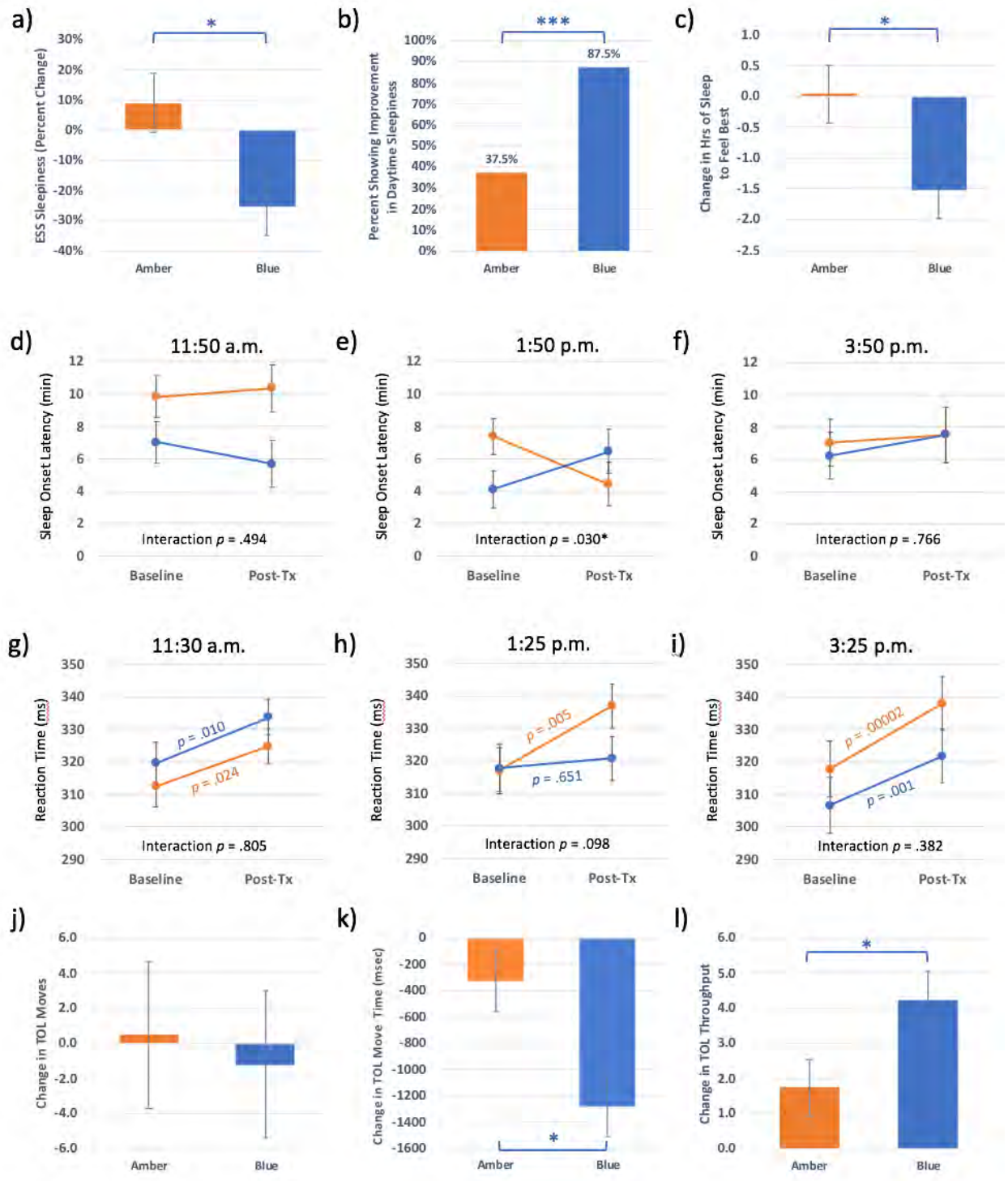


Figure 36. **Effects of light treatment on behavioral variables.** (**a**) Blue light led to a significant reduction in daytime sleepiness scores on the Epworth Sleepiness Scale (ESS), with **(b)** a significantly greater percentage of blue light participants showing some improvement in daytime sleepiness relative to amber participants. **(c)** Blue light was associated with a significant reduction in the number of nightly hours of sleep that participants reported needing to feel their best, relative to the amber group. **(d-f)** Sleep onset latency on the multiple sleep latency test (MSLT) was unaffected by light condition in the late morning (11:50 a.m.) or late afternoon (3:50 p.m.), but showed a significant interaction for the early afternoon "post-lunch dip" period. Similarly, **(g-i)** psychomotor vigilance test reaction time did not differ between groups during the late morning (11:30 a.m.) or late afternoon (3:25 p.m.), but was affected by blue light only in the early afternoon. Although there was **(j)** no effect of light condition on the total number of moves from the Tower of London (TOL) test, **(k)** blue light was associated with a significant improvement in average bead movement times relative to amber light, and **(l)** when speed and accuracy were combined as a metric of "throughput", blue light was associated with significantly more correct moves per minute than the amber placebo group. (*p < .05), **p < .01, ***p < .005).

Executive Functioning. On the Tower of London (TOL), a classic executive function planning task, the light condition did not affect the number of moves required to solve the puzzles between pre- and post-treatment, $F(1,26) = 0.08$, $p = .79$ (see Figure 36j). However, the light-condition did affect the time taken to solve the puzzles, $F(1,26) = 7.45$, $p = .01$ (see Figure 36k). On average, participants who underwent the BLUE wavelength light condition were 1,280 (SE = 234) ms faster in completing each move following treatment, while those in the AMBER placebo condition improved by only 325 (SE = 234) ms per move. When speed and accuracy were combined as a measure of "throughput," there was a significant effect of light condition, $F(1,26) = 4.26$, $p = .049$. As shown in Figure 36l, participants in the BLUE light condition showed an increase in the number of correct bead placements of 4.23 (SE = 0.83) per minute, whereas those in the AMBER condition increased by only 1.73 (SE = 0.83) per minute after treatment. Overall, most participants showed at least some improvement in TOL performance, regardless of condition, with 93.8% of participants in the BLUE group and 81.3% of participants in the AMBER group showing greater throughput after 6-weeks ($\chi^2 = 1.143$, $p = .285$). After accounting for covariates (described above), the odds ratio (OR) for showing any improvement in throughput with BLUE light compared to AMBER was 6.50 (95% CI: 0.41 to 102.15; $p = .183$.

Gray Matter Volume (GMV). To examine morphometric volume changes in the brain, the anatomical brain images obtained during the MRI scan were analyzed in SPM12 with a 2 between (BLUE vs. AMBER) x 2 within (baseline vs. post-treatment) mixed analysis of covariance (ANCOVA), controlling for age, intracranial volume, and the number of days the light device was used. The ANCOVA yielded a large bilateral cluster (807 voxels, $p_{FWE} < .05$; MNI: x = 0, y = -21, z = 3) reflecting a significant light dependent change in volume from pre- to post-treatment. This region was constrained to the pulvinar regions of the left (LPul) and right (RPul) thalamus (Figure 37a). Given the significant interaction, we examined the effects of each light condition individually. As shown in Figure 37b, a pre- to post-treatment *t*-test for those receiving the BLUE light condition showed that this effect was driven primarily by an increase in thalamic GMV (bilateral) ($p_{FWE} < .05$), but this was not evident for the AMBER light condition.

Multiple regression was used to determine the partial correlations between changes in pulvinar volume and performance metrics. As shown in Figure 38a-c, after controlling for age, intracranial volume, and the number of days of light device use, greater volume increases in the pulvinar region of the left thalamus were associated with faster bead pickup time, faster total move time on the TOL, and with a slight increase in subjective ratings of sleepiness at post-treatment, measured using the SSS. Right thalamic volume changes were not associated with any measured changes in cognitive/behavioral scores.

Functional Connectivity. Building on the GMV findings above, we used the two previously identified thalamic clusters (i.e., LPul and RPul) as seed regions in a seed-to-voxel and seed-to-ROI resting state functional connectivity (rsFC) analysis. Repeated measures two-way ANCOVAs were used to investigate the main effect of light-condition on rsFC from pre- to post-treatment.

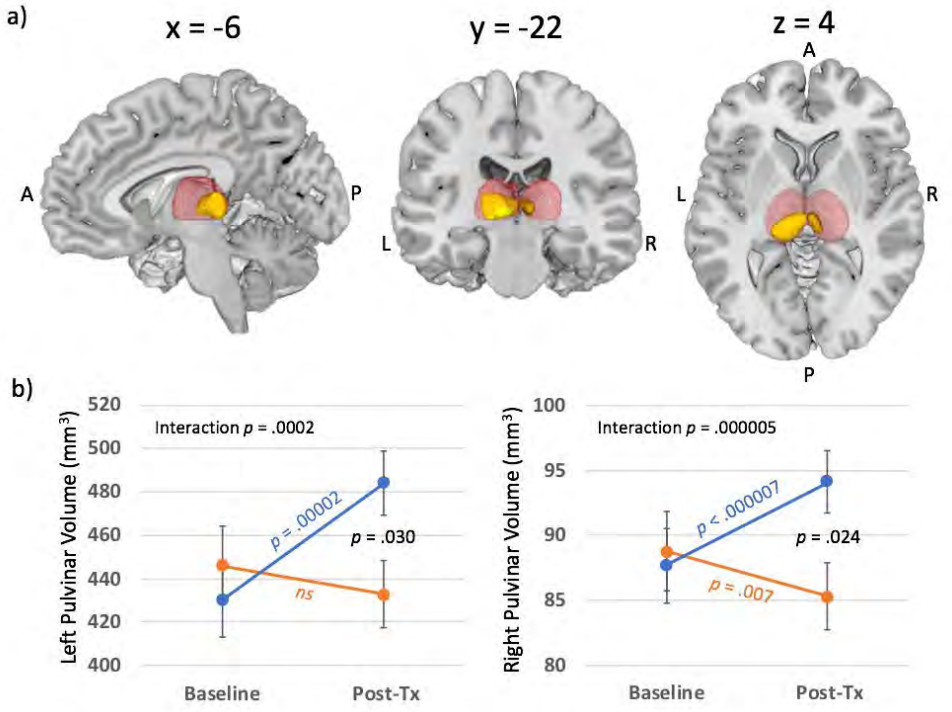


Figure 37. **Voxel-based morphometry results for blue versus amber light treatment.** Results of a whole brain voxel-based morphometry (VBM) analysis comparing baseline and post-treatment changes for those receiving the blue light condition. (**a**) The figure shows the sagittal (left) coronal (middle) and axial (right) orientations. This analysis showed significant increases in gray matter volume (GMV) within the left (567 voxels; MNI: x = -3, y = -22, z = 3) and right (119 voxels; MNI: x = 3, y = -22, z = 3) posterior thalamic volume for those receiving the BLUE light intervention ($p_{FWE} < .05$). (**b**) Extracted volumes from each of these clusters are plotted in the figures for visualization for the left and the right thalamic regions for the BLUE and AMBER groups separately. The location of the left and right thalami are represented by the red wire mesh areas of the figure. It is clear that BLUE light was associated with significant increases in the volume of both the left and right posterior regions, but this was not evident for the same regions in the AMBER group.

Seed-to-Voxel Analysis. Relative to the AMBER light condition, individuals in the BLUE light condition showed increased rsFC from pre- to post-treatment between the LPul seed and voxels comprising three separate areas (Figure 39a), including a region in the left parietal cortex (LParC; β = .34, p = .001), the right parietal cortex (RParC; β = .31, p < .001), and left agranular frontal area (LAFA; β = .34, p < .001). In contrast, the RPul seed region did not show any significant increase in connectivity with other voxel clusters in the brain.

Region of Interest (ROI)-to-ROI Analysis. Within each light-condition, we examined the ROI-to-ROI connectivity. Consistent with the seed-to-voxel analysis, mean rsFC was significantly increased for the BLUE light condition over the course of treatment between the LPul and the three ROIs, including the LParC, $t(25) = 2.38$, p = .03, RParC, $t(25) = 2.26$, p = .03, and LAFA, $t(25) = 2.33$, p = .03). For the AMBER light condition, significant decreases in connectivity over the course of treatment between the LPul and ROIs were found for all three ROIs, including the LParC, $t(25) = -3.58$, p = .002, RParC, $t(25) = -3.65$, p = .001, and LAFA, $t(25) = -4.16$, p < .001 (9b).

As shown in Figure 38d-g, after controlling for standard covariates, increased rsFC between LPul and LParC ROIs from pre- to post-treatment was associated with a significant

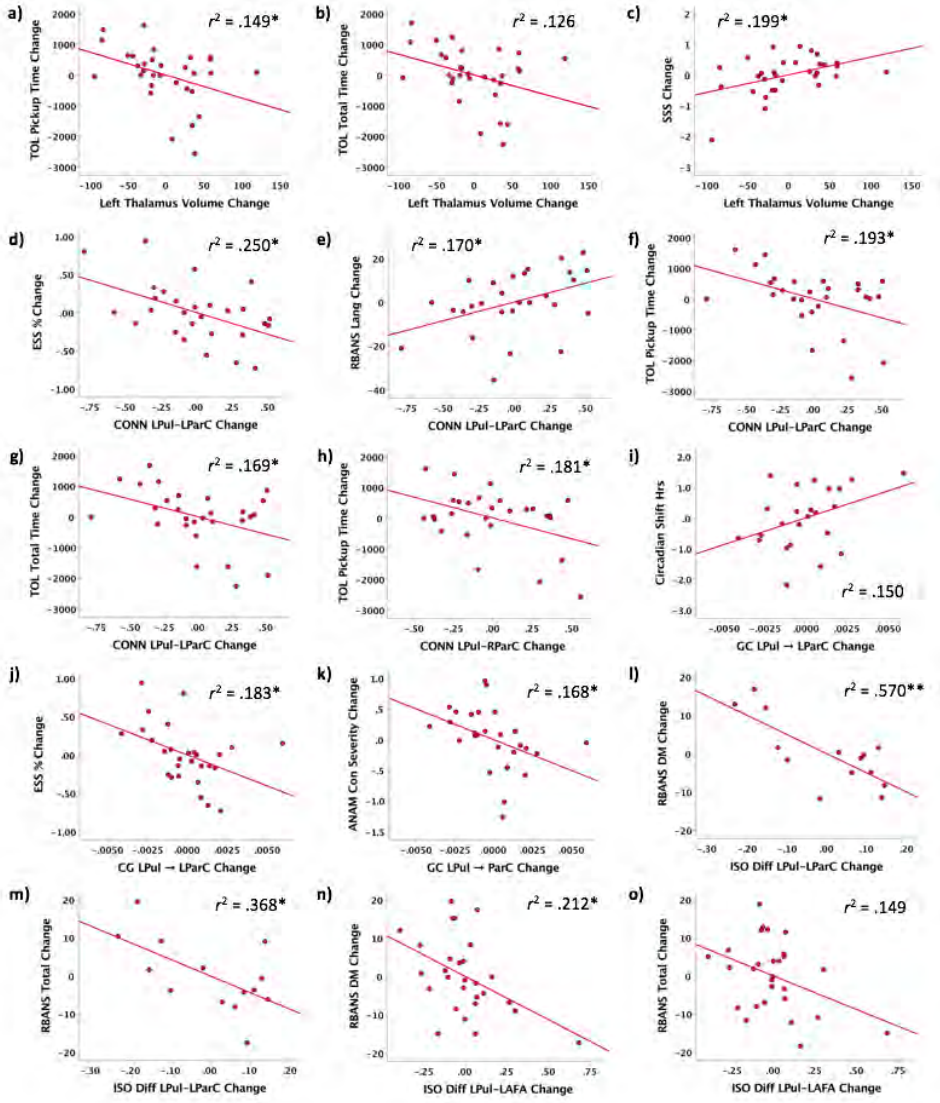


Figure 38. **Association of changes in behavioral measures with changes in voxel-based morphometry, directed connectivity strength, and isotropic diffusion (ISO).** Greater increases in the volume of the left pulvinar region of the thalamus was associated with **(a)** faster pickup speed, **(b)** a trend toward faster total move time on the Tower of London (TOL), and **(c)** slight increases in subjective sleepiness on the Stanford Sleepiness Scale (SSS). Changes in functional connectivity strength from pre- to post-treatment for the Left Pulvinar (LPul) and Left Parietal Cortex (LParC) were associated with **(d)** decreases in daytime sleepiness on the Epworth Sleepiness Scale (ESS), **(e)** improvements in language processing on the Repeatable Battery for Neuropsychological Assessment (RBANS), **(f)** faster average bead pickup time on the TOL, **(g)** faster total move time on the TOL. Similarly, increased functional connectivity between the LPul and Right Parietal Cortex (RParC) was associated with **(h)** faster total move time on the TOL. We found a significant positive association between changes in directed connectivity strength (LPul to LParC) and **(i)** changes in circadian shifts, and significant negative associations with **(j)** changes in daytime sleepiness, and **(k)** scores on the concussion severity scale. We also found a significant negative association between changes in ISO for fibers connecting LPul and LParC and **(l)** changes in delayed memory scores, as well as **(m)** total scores on RBANS battery. ISO for fibers connecting LPul and LAFA also showed a significant negative association with **(n)** changes in delayed memory scores and **(o)** total scores on RBANS battery.

reduction in daytime sleepiness on the ESS (r (23) = -.50, p = .011), increased scores on RBANS Language (r (23) = .418, p = .038), TOL average bead pickup time (r (23) = -.439, p = .028), and TOL Average total move time (r (23) = -.411, p = .041). Similarly, increased rsFC

between the LPul and RParC was also associated with faster bead pickup time on the TOL (*r* (23) = -.425, *p* = .034; Figure 38h).

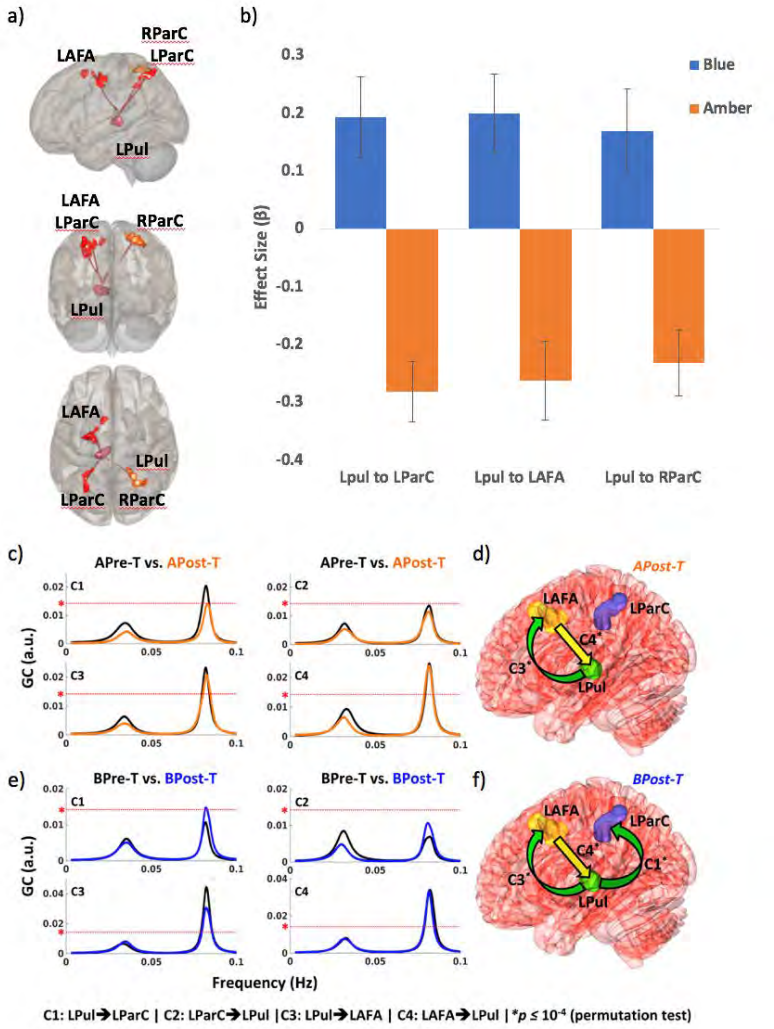


Figure 39. **Functional Connectivity (FC) and Granger causality measures. (a)** The extracted volumes from the VBM analysis were used to investigate the main effect on FC associated with the observed structural changes in the left thalamic (LPul) and right thalamic (RPul) regions. Individual subject seed-to-voxel whole brain connectivity maps identified three clusters of voxels associated with significant increases in connectivity to the LPul. The extracted clusters (i.e. Left Parietal Cortex: LParC, Left Agranular Frontal Area: LAFA, and the Right Parietal Cortex: RParC), are plotted in the figures for visualization with the strength of the correlation represented by the color of the line. **(b)** The resting-state correlations for FC between the LPul and ROIs were extracted as beta weights for each participant and the correlation is plotted for the BLUE and AMBER groups separately with error bars representing the within-group standard errors. **(c-f)** Next we show that the peaks from GC-frequency spectra are at frequency < 0.1 Hz for the directed connectivity from the LPul to LParC (C1), LParC to LPul (C2), LPul to LAFA (C3), and LAFA to LPul (C4) for both ALT group **(c-d)** (Pre-treatment: APre-T and Post-treatment: APost-T), and BLT group **(e-f)** (Pre-treatment: BPre-T and Post-treatment: BPost-T). Dotted lines represent the threshold value of GC estimated from the permutation test at p £10^{-4}. Overall, GC measures between LPul and LAFA (C3 and C4) for APost-T **(e)** and between LPul and LAFA (C3 and C4) as well as from LPul to LParC (C1) for BPost-T **(f)** showed significant directional influence.

Granger causality (GC). To determine if the rsFC connectivity change was “bottom-up” (i.e., increased thalamocortical connectivity) or “top-down” (i.e., increased corticothalamic connectivity), we next employed GC to determine the directional influence between the previously identified areas of interest. The previous analysis revealed that FC was only evident for the left pulvinar connections (i.e., LPul—LParC, LPul—LAFA, and LPul—RParC). However, we did not find structural connectivity between LPul and RParC for any subject/condition, therefore four connections (C1: LPul to LParC, C2: LParC to LPul, C3: LPul to LAFA, and C4: LAFA to LPul) were further interrogated using GC.

GC-frequency spectra for all four directional connections (C1, C2, C3, and C4) were computed. The estimated threshold level of GC strength used to identify significant connections was 0.0142 at $p < 10^{-4}$ (permutation method; corrected for multiple comparisons). In Figures 7c-f, it is evident that GC-frequency spectra for all four connections and for all four conditions (AMBER:

APre-T (Amber-light pre-treatment), APost-T (Amber-light post-treatment); BLUE: BPre-T (Blue-light pre-treatment) and BPost-T (Blue-light post-treatment)) had peaks at frequency < 0.1 Hz, and showing the connectivity patterns for APost-T (39d) and BPost-T (39f). Within the AMBER group, we found that the C1 connection exceeded threshold only at baseline (APre-T), but that connection did not exceed the threshold at APost-T (39c). By contrast, in the BLUE group, this same connection did not reach the threshold at BPre-T, but exceeded the threshold at BPost-T (39e-f). Connection C2 did not exceed the threshold for either BLUE or AMBER conditions (39c and 7e). In addition, two connections (C3 and C4) exceeded the threshold for connectivity at pre- and post-treatment for both the AMBER and BLUE groups, suggesting that these connections were not meaningfully affected by light condition. In sum, the findings suggest that connection C1 (LPul to LParC) was significantly affected by light condition, showing a decrease in directed bottom-up connectivity in the AMBER group and an increase in this bottom-up connectivity within the BLUE group. Other connections either remained below the threshold or were essentially unchanged by light condition.

As in the previous analyses, we also examined the cognitive/behavioral correlates associated with changes in causal flow. As shown in Figure 38i-k, after controlling for age, intracranial volume, and the number of days of light device use, increased causal influence of LPul on LParC from pre- to post-treatment was not significantly associated with change in circadian phase (r (19) = .387, p = .083), but was associated with a significant reduction in typical daytime sleepiness on the ESS (r (23) = -.427, p = .033), and a significant reduction in concussion severity scores on the ANAM (r (23) = -.409, p = .042).

Anatomical Connectivity: We next examined whether the connectivity changes reported above would be associated with corresponding changes within axonal tracts connecting the identified regions.

We found that there were no tracts with significant differences between pre- and post-treatment for fractional anisotropy (FA) (FDR > 0.05) in either AMBER or BLUE light conditions (Figure

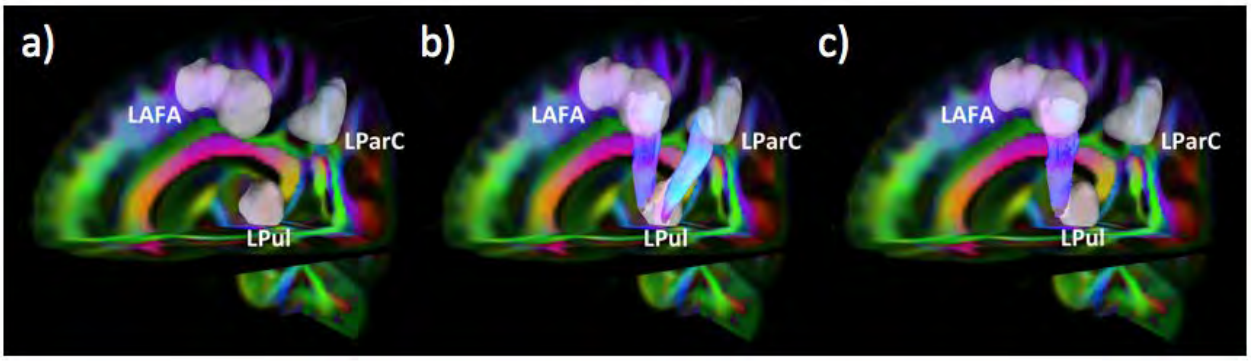


Figure 40. **Diffusion connectometry analysis for amber-light treatment (ALT) and blue-light treatment (BLT) groups.** We found that there were no tracts with significant differences between pre- and post-treatment conditions for fractional anisotropy (FA) (FDR > 0.05) in either ALT or BLT group **(a)**. However, we found tracts connecting LPul and LParC with significant reduction in isotropic diffusion (ISO) following treatment for BLT group **(b)** (FDR < 0.05), but not for ALT group (FDR > 0.05). Also, there were tracts connecting LPul and LAFA with reduced ISO following treatment for BLT group (FDR = 0.11) **(c)** and a significant increase in ISO following treatment for ALT group (FDR < 0.05) **(c)**. Here, identified tracts are color-coded in transverse (right-left: red), longitudinal (anterior-posterior: green) and horizontal (foot-head: blue) directions and overlaid on color-coded FA image.

40a). However, we found tracts connecting LPul and LParC with a significant reduction in isotropic diffusion (ISO) (a measure of white matter disintegrity) following treatment for the BLUE (Figure 40b) (FDR < 0.05), but not for the AMBER light condition (FDR > 0.05). Furthermore, we found that tracts connecting LPul and LAFA showing reduced ISO diffusion following treatment for the BLUE light condition at a less stringent threshold (FDR = 0.11) (Figure 8b) and a significant increase in ISO following treatment for AMBER light condition (FDR < 0.05) (Figure 40c).

We examined the cognitive/behavioral correlates of changes in ISO diffusion within specific white matter tracts discussed above. For the BLUE light condition, subject-wise differences for the tracts connecting LPul and LParC, and LPul and LAFA, were extracted. For the AMBER light condition, subject-wise differences for the tracts connecting LPul and LAFA were extracted. As shown in Figure 38l-o, only changes in RBANS measures showed significant associations with changes in white matter integrity. Specifically, after controlling for age, intracranial volume, and the number of days the light device was used, decreases in ISO diffusion from pre- to post-treatment for the BLUE light condition were associated with improved visual construction (RBANS VC) performance (r (9) = -.714, p = .014), improved delayed memory (RBANS DM) performance (r (9) = -.755, p = .007), and improved total neuropsychological (RBANS Total) performance (r (9) = -.607, p = .048). For the sample as a whole, decreases in ISO diffusion between LPul and LAFA were associated with improved delayed memory (RBANS DM) performance (r (23) = -.460, p = .021), and a trend toward greater total neuropsychological (RBANS Total) performance (r (23) = -.386, p = .057).

DISCUSSION OF PILOT STUDY OUTCOMES

In our pilot six-week randomized placebo-controlled trial of daily light exposure, we found that 30-minutes of morning blue-wavelength light was more effective than amber-wavelength placebo light at shifting sleep-wake periods, reducing subjective and objective sleepiness, and improving cognitive performance among participants recovering from mTBI. Moreover, compared to amber light, the blue light intervention was associated with increases in gray matter volume within the posterior thalamus and greater structural and functional thalamocortical connectivity, as well as multiple associations between improvements in cognitive performance and the observed physiological changes. These findings are consistent with the hypothesized role of morning blue-wavelength light in phase advancing the circadian rhythm of sleep and alertness, and the postulated role of sleep in accelerating neural repair processes. Together, these findings pointed to the ipRGC-SCN-mediated circadian system as a critical contributor to brain repair processes and suggest a potential target mechanism for intervention to facilitate recovery following brain injury. That pilot study served as the basis for the continuation study conducted in the present project and reported earlier.

Overall, our findings are consistent with well-established evidence that blue light exposure affects the timing of sleep-wake cycles through stimulation of the retinohypothalamic system (Geerdink, Walbeek, Beersma, Hommes, & Gordijn, 2016), as we found that the BLUE light condition showed a trend toward phase-advancement of the midpoint of participants' sleep

periods by just over one hour by the end of treatment, with no meaningful change observed for the AMBER light condition. Notably, this alteration in sleep timing was not associated with a measurable change in total sleep time based on actigraphy. While light treatment has shown robust effects for shifting sleep timing (Geerdink et al., 2016; Rosa et al., 2018; Tahkamo, Partonen, & Pesonen, 2018), prior research demonstrates mixed outcomes in terms of modifying total sleep time (TST) or subjective perception of time spent asleep (Figueiro et al., 2014; Richardson et al., 2018; Saxvig et al., 2014; Wu et al., 2018). It should be borne in mind, however, that our primary measure of TST was based entirely on wrist-actigraphy, which has a satisfactory accuracy level (>80%) (Marino et al., 2013), but may not be sensitive enough to detect the subtler effects of light treatment on sleep architecture.

Recent work demonstrates that daily morning blue light therapy improves subjective fatigue and daytime sleepiness in patients with TBI (Sinclair et al., 2014). Our results extend these earlier findings, as our BLUE light condition led to a significant decline in subjective daytime sleepiness and a reduction in self-perceived sleep requirement relative to the AMBER placebo condition. Thus, even though BLUE light did not lead to an increase in total sleep time after treatment, participants treated with BLUE light reported a reduced tendency to “doze” off throughout the day, as well as a decrease in the total time asleep necessary to feel their best. Moreover, BLUE light use was also associated with objectively greater daytime alertness, as evidenced by extended latencies to fall asleep during the early afternoon post-lunch dip, compared to the placebo condition, when measured using polysomnography. The blue-wavelength light intervention was also associated with sustained psychomotor vigilance performance in the early afternoon. Thus, the treatment is associated with improvements in both subjective and objective daytime alertness for individuals recovering from mTBI during times when drowsiness is particularly likely to occur.

When directly comparing the groups on neurocognitive performance, we found a clear superiority in blue-wavelength treatment compared to a placebo light treatment on performance during the TOL, a classic test of visual planning and sequencing ability. Relative to AMBER light, daily exposure to BLUE light in the morning was associated with a significant improvement in the completion speed of each move. Moreover, participants in the BLUE light condition also made more correct moves per unit of time, suggesting greater efficiency in planning and execution when compared to those in the placebo group. To our knowledge, this is the first study to examine the effects of daily blue-wavelength light exposure on executive function tasks that incorporate planning and sequencing ability. Further research will be necessary to determine the extent and nature of neurocognitive changes produced by daily exposure to blue light in the morning.

While prior research suggests an association between regular exposure to blue light in the early waking hours and reduced fatigue and sleepiness in patients with TBI (Sinclair et al., 2014), the underlying neurobiological mechanisms contributing to these effects have remained unclear. Recently, Clark and colleagues demonstrated that fatigue following mTBI was explicitly associated with reduced thalamic volume (Clark et al., 2018). We found that the BLUE light intervention was associated with a significant increase in GMV of the mediodorsal and pulvinar

regions of the thalamus bilaterally compared to the AMBER light condition. Some studies suggest that the thalamus is particularly vulnerable to the disruptive effects of mTBI (Bolzenius et al., 2018; Naess-Schmidt et al., 2017), perhaps due to its centralized location and extensive anatomical/functional connectivity. Furthermore, increases in mean thalamic volume correlate with the recovery of cognitive performance in individuals with mTBI (Munivenkatappa, Devi, Shukla, & Rajeswaran, 2016). Sleep loss is associated with decreased thalamic volumes, suggesting a potential role for sleep in modulating the volume of the thalamus (Dai et al., 2018; Liu, Kong, Liu, Zhou, & Wu, 2014). Our findings suggest that alterations in circadian rhythms or improvements in sleep secondary to daily blue light exposure may contribute to the observed structural changes and associated performance outcomes in this study.

The BLUE light condition was associated with increased functional connectivity between the left thalamus and cortical regions in the frontal and parietal cortex, relative to the AMBER condition, and this change correlated with improvements in daytime sleepiness, language performance, and executive functioning. This effect is consistent with prior research showing negative correlations in thalamocortical functional connectivity and fatigue in patients with mTBI (Nordin et al., 2016). Compared to non-injured controls, patients with mTBI have decreased functional connectivity between the thalamus and cortical regions including the dorsal attention network and the frontoparietal control network (Banks et al., 2016). Moreover, these patterns of disrupted connectivity tend to attenuate throughout recovery, with positive associations between symptom improvement and increases in connectivity across these networks (Banks et al., 2016). Our findings suggest that daily morning exposure to blue-wavelength light may help facilitate the dynamic relationship between the restoration of connectivity with cognitive and symptom recovery.

Finally, we examined whether the increases in the structural connectivity of axonal pathways secondary to the intervention were associated with changes in neurocognitive performance. Prior research in patients with mTBI demonstrates reductions in white matter anisotropy between the left thalamus and prefrontal regions in patients with mTBI (Aoki & Inokuchi, 2016). Our findings suggest that blue light treatment may facilitate the reversal of some of these deficits, as we found increased structural integrity in axonal tracts connecting the left thalamus to the left prefrontal and left parietal cortex after blue light treatment. Moreover, the magnitude of increases in the structural integrity of these pathways correlated with improved neuropsychological performances, particularly those involving visual construction and delayed memory abilities. We propose that the post-treatment decreases in isotropic diffusion for these tracts may reflect increased myelination, due to the proliferation of oligodendrocyte precursor cells that have been previously shown to be enhanced by sleep (Bellesi et al., 2013). Future research will be necessary to verify this assertion. We plan to combine the samples from the two projects into a single analysis in the coming months.

OVERALL CONCLUSIONS

Our original pilot study suggested that morning blue-wavelength light might be an effective adjunctive treatment for improving sleep and circadian rhythm disruption among individuals

recovering from mTBI. The preliminary findings suggested that morning blue light treatment for 6-weeks was associated with significant improvements in sleep timing (earlier sleep onset and wake times) and improved neurocognitive functioning, and that these improvements correlated with changes in brain structure and function. The USAMRDC funded a continuation of this study to allow us to obtain an additional 30+ participants to have adequate power to demonstrate effects. This second study has demonstrated similar outcomes to the pilot work, particularly showing reliable improvements in daytime sleepiness and meaningful changes in brain structure and function in people recovering from mTBI. We have also examined the effects of a single exposure to blue-wavelength light in healthy normal individuals and find that such exposure can enhance acute cognitive performance and brain functioning. Thus, we conclude that blue light has effects on at least two systems in the brain, including 1) a circadian resetting system via the suprachiasmatic nucleus, and 2) a separate acute alerting system, presumably via stimulation of the locus coeruleus. Overall, these findings strongly support the potential usefulness of blue-wavelength light in the treatment of sleep-related issues and recovery from mTBI, and potentially as a method for increasing alertness in healthy normal individuals. These outcomes have direct relevance to enhancing the medical readiness of the force and toward identifying novel methods to sustain warfighter performance. Further research into this potentially useful approach is warranted.

- **What opportunities for training and professional development has the project provided?**

  While the primary goal of this project is not to provide training and professional development, many such experiences have occurred for our team members. The present project has supported:

  2 members of our lab presented research findings and attended lectures at the Military Health Systems Research Symposium, Orlando, FL, August 18-22, 2019

  2 members of our lab presented research findings and attended lectures at the Annual Meeting of The Associated Professional Sleep Societies, San Antonio, TX, June 9-12, 2019.

  1 postdoc attended the DIPY Workshop, Bloomington, IN, March 8-12, 2019

  2 members of our lab presented research findings and lectures at the International Neuropsychological Society, New York, NY, February 14-17, 2018.

  2 members of our lab presented research findings and attended lectures at the Military Health Systems Research Symposium, Orlando, FL, August 20-23, 2018.

  1 member of our lab presented research findings and attended lectures at the Organization for Human Brain Mapping, Singapore, Malaysia, June, 17-21, 2018

  2 members of our lab presented research findings and attended lectures at the Annual Meeting of The Associated Professional Sleep Societies, Baltimore, MD, June 3-6,

2018.

1 member of our lab presented research findings and attended lectures at the Society for Biological Psychiatry, New York, NY, May 10-12, 2018.

1 member of our lab attended a grant writing workshop for early-career researchers at the 16th Annual Lessons for Success, Rockville, MD, April 23-25, 2018.

1 member of our lab presented research findings and attended lectures at the Anxiety and Depression Association of America, Washington DC, April 5-8, 2018.
2 members of our lab presented research findings and attended lectures at International Neuropsychological Society, Washington, DC, February 14-17, 2018.

1 member of our lab presented research findings and attended lectures at the Big Sky Athletic Training and Sports Medicine Conference, Big Sky, MT, February 4-7, 2018.

1 postdoc attended the Applied Workshop on the New SCID-5, Mastering the Diagnostic Interview, University of Michigan.

1 postdoc attended the Computational Psychiatry Course, University of Zurich, Zurich Switzerland, August 28-September 2, 2017.

1 postdoc attended the Neurometrika SPM Workshop, Philadelphia, PA, July 13-24, 2017.

1 postdoc attended the BrainSuite Workshop, Vancouver, CA, June 24, 2017.

1 postdoc attended the FSL Workshop, Vancouver, CA, June 19-23, 2017.

1 member of our lab attended lectures and presented research findings at the Organization for Human Brain Mapping, Vancouver, CA, June 25-29, 2017.

2 members of our lab attended lectures and presented research findings at the Military Health Systems Research Symposium, Orlando, FL, August 26-30, 2017.

3 members of our lab attended lectures and presented research findings at the Associated Professional Sleep Societies Meeting, Boston, MA, June 3-7, 2017

1 member of our lab attended lectures and presented research findings at the Society of Biological Psychiatry Meeting, San Diego, CA, May 18-20, 2017

1 member of our lab attended lectures and presented research findings at the International Neuropsychological Society Meeting, New Orleans, LA, February 1-4, 2017

1 member of our lab attended lectures and presented research findings at the meeting of the Society for Psychophysiological Research, Minneapolis, MN, September 21-25, 2016.

1 member of our lab attended lectures and presented research findings at the Military Health Systems Research Symposium, Orlando, FL, August 15-18, 2016.

2 postdocs attended the NIH Grant Writing Workshop at the University of Arizona (August 2016), Tucson, AZ.

4 members of our lab attended lectures and presented research findings at the Associated Professional Sleep Societies Meeting, Denver, CO, June 11-15, 2016

1 member of our lab attended a workshop entitled: Actigraphy and Figness/Sleep trackers in Adults and Children: Fundamentals and applications, at the Associated Professional Sleep Societies Meeting, Denver, CO, June 11-15, 2016

3 members of our lab attended lectures and presented research findings at the Society of Biological Psychiatry Meeting, Atlanta, GA, May 12-14, 2016

1 postdoc and 1 graduate student attended the CONN Functional Connectivity Workshop (April 2016), in Boston, MA.

4 members of our lab attended lectures and presented research findings at the International Neuropsychological Society Meeting, Boston, MA, February 3-6, 2016

1 postdoc attended the Mind Research Network Functional MRI Training Workshop (Jan 2016) in Albuquerque, NM.

5 college undergraduate students obtained training in research methods during a summer training program in our lab this year, 4 who were sponsored by the University of Arizona and the other by the National Institutes of Health MARC Undergraduate Student Training in Academic Research (U-STAR) Award.

2 undergraduate students were supervised for their Senior Honors Thesis' in our lab.

1 graduate student was supervised for his Master's Thesis in our lab.

Multiple members of our lab have attended regular training in MRI analysis methods and safety as part of an ongoing training series offered at the University of Arizona.

All members of our lab receive regular one-on-one instruction and supervision in the administration and scoring of neuro-psychological assessments, psycho-diagnostic testing, electrode placement, and patient interviewing to ensure best data collection practices.

Over 20 members of our lab have undergone regular in-house training in the use of various brain-imaging software, including SPM12, Matlab, FSL, Freesurfer, TracVis, MRIcron and others.

Over 15 members of our lab have undergone basic training modules in ethical conduct, statistical analysis, and neuroanatomy.

- **How were the results disseminated to communities of interest?**

  During the study we have focused on disseminating knowledge of the impact of mild traumatic brain injury and sleep health to academic and clinical communities of interest. We have presented our work at a variety of conference venues, both military and civilian, to share knowledge with other researchers.

- **What do you plan to do during the next reporting period to accomplish the goals and objectives?**

  Nothing to report

4. **IMPACT**
   - **Effect on the development of the principal discipline(s) of the project**
     Nothing to report.

   - **Effect on other disciplines**
     Nothing to report.

   - **Effect on technology transfer**
     Nothing to report.

   - **Effect on society beyond science and technology**
     Nothing to report.

5. **CHANGES/PROBLEMS:**
   - **Changes in approach and reasons for change**
     Nothing to report.

   - **Actual or anticipated problems or delays and actions or plans to resolve them**
     Nothing to report.

     Changes that had a significant impact on expenditures
     Nothing to report.

     Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
     Nothing to report.

6. **PRODUCTS**

Publications/Presentations:

We have had 13 peer reviewed papers published (or in the process of being published) and 54 conference abstract/talk/poster presentations submitted or completed that were supported in part by this project:

Manuscripts (reverse chronological order)

1. Bajaj, S., Raikes, A.C., Razi, A., Miller, M. A., and Killgore, WDS. Blue-light therapy strengthens effective connectivity within default-mode network following mTBI. (under review)

2. Bajaj, S., Dailey, N., Raikes, A.C., Vanuk, J. R., Weber, M., Rosso, I. M., Rauch, S. L., & Killgore, WDS. Effect of blue light therapy on brain structure and simple reaction time following mild traumatic brain injury (in revision)

3. Raikes, AC, Bajaj S, Dailey, NS, Vanuk, JR, Alkozei, A, Killgore WDS. Altered large scale resting-state functional connectivity is associated with symptom presentation following mild traumatic brain injury. *Journal of Neurotrauma* (in revision)

4. Raikes, AC, Dailey, NS, Shane, BR, Forbeck B, Alkozei, A, Killgore WDS. Daily morning blue light therapy improves daytime sleepiness, sleep quality, and quality of life following a mild traumatic brain injury. *Journal of Head Trauma Rehabilitation* (in revision)

5. Raikes AC, Killgore W.D.S. Potential for the development of light therapies in mild traumatic brain injury. *Concussion*, *3*(3). doi: 10.2217/cnc-2018-0006

6. Raikes AC, Satterfield BC, Killgore W.D.S. Evidence of Actigraphic and Subjective Sleep Disruption Following Mild Traumatic Brain Injury. *Sleep Medicine*. 2018. doi:10.1016/j.sleep.2018.09.018

7. Bajaj, S., Dailey, N. et. al. Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury. Hum. Brain Mapp., 2018, 39(5): 1886-97.

8. Killgore W.D.S, Kent HC, Knight SA, Alkozei A. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. *NeuroReport*. 2018;29(6):488. doi:10.1097/WNR.0000000000001002

9. Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore W.D.S. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLOS ONE*. 2017;12(9):e0184884. doi:10.1371/journal.pone.0184884

10. Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore W.D.S. Blue light therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. Front. Neurol., 2017, 8:616.

11. Alkozei A, Smith R, Pisner DA, et al. Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. *Sleep*. 2016;39(9):1671-1680. doi:10.5665/sleep.6090

12. Alkozei A, Smith R, Killgore W.D.S. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neuroscience Letters*. 2016;616:5-10. doi:10.1016/j.neulet.2016.01.034

13. Killgore W.D.S. Lighting the Way to Better Sleep and Health. *Journal of Sleep Disorders: Treatment and Care*. 2016:*05*(01). doi: 10.4172/2325-9639.1000e104

Abstracts/Talks/Posters (reverse chronological order)

Raikes, A.C., Dailey, N.S., Alkozei, A., Vanuk, J.R., Grandner, M.A., Killgore W.D.S. Daytime sleepiness, depression, and post-concussive symptoms improve following prescribed morning exposure to blue light. Submitted for presentation. SLEEP; 2020

Raikes, A.C., Dailey, N.S., Vanuk, J.R., Alkozei, A., Grandner, M.A., Killgore, W.D.S. Improved daytime sleepiness following daily morning blue light therapy is associated with altered resting-state network connectivity. Submitted for presentation. SLEEP; 2020

Raikes, A.C., Alkozei., A., Vanuk, J.R., Bajaj, S., Satterfield, B.C., Killgore W.D.S., Blue light therapy reduces daytime sleepiness as well as depressive and somatic post-concussive symptoms following mild traumatic brain injury. Accepted for oral presentation and the *Nelson Butters Outstanding Research* Award. INS 2020

Raikes, A.C., Bajaj, S., Dailey N.S., Vanuk, J.R., Alkozei, A., Killgore W.D.S. Vestibular and emotional symptoms are associated with altered large-scale network resting-state functional connectivity after mild traumatic brain injury. Accepted for poster presentation. INS 2020.

Raikes, A.C., Satterfield, B.C, Bajaj S, Grandner, M.A., Killgore, W.D.S. Daily Administered Blue Light Therapy Reduces Daytime Sleepiness and Improves Somatic Symptoms Following Mild Traumatic Brain Injury. Military Health Systems Research Symposium; August 18-22, 2019, Orlando, FL

Bajaj, S, Dailey, N.S., Raikes, A.C., Vanuk, J.R., Weber, M., Rosso, I.M., Rauch, S.L., Killgore, W.D.S. – Impact of Blue-Wavelength Light Therapy on Cortical Volume and Simple Reaction Time Following Mild TBI. Military Health Systems Research Symposium; August 18-22, 2019, Orlando, FL

Bajaj, S., Raikes, A. C, Razi, A., Killgore, W. D. S - Blue-wavelength Light Strengthens the Default Mode Network following Mild TBI: A DCM-DTI Study; Organization for Human Brain Mapping (OHBM) Annual Meeting; June 9-13, 2019; Rome, Italy

Bajaj, S., Dailey, N. S., Raikes, A. C., Vanuk, J. R, Weber, M., Rosso, I.M., Rauch, S.L., Killgore, W.D.S - Effect of Blue Light Therapy on Cortical Volume and Reaction Time following Mild TBI; Organization for Human Brain Mapping (OHBM) Annual Meeting, June 9-13, 2019, Rome, Italy

Raikes, A.C., Grandner, M.A., & Killgore, W.D.S. – Daily Blue Light Therapy Reduces Daytime Sleepiness and Post-concussion Symptoms After Mild Traumatic Brain Injury. SLEEP Annual Meeting; June 8-12, 2019; San Antonio, Texas.

Bajaj, S., Dailey, N. S., Raikes, A. C., Vanuk, J. R., Grandner, M. A., Weber, M., Rosso, I.M., Rauch, S.L., Killgore, W.D.S. - Impact of light therapy on brain structure and simple reaction time following mild traumatic brain injury; SLEEP; June 8-12, 2019, San Antonio, Texas

Raikes, A.C., Grandner, M.A., & Killgore, W.D.S. – Daily Blue Light Therapy Reduces Persistent Post-Mild Traumatic Brain Injury Daytime Sleepiness and Post-concussion. Rocky Mountain Athletic Trainers' Association Clinical Symposium; Apr 11-14, 2019; Phoenix, Arizona

Raikes AC, Killgore W.D.S. Anterior Cingulate Gyrus Volume Predicts Changes in Post-mTBI Daytime Sleepiness Following Blue Wavelength Light Therapy. Poster presented at the: 47th Annual Meeting of the International Neuropsychological Society; February 20-23, 2019; New York City, New York.

Bajaj, S., Raikes, A., Dailey, N. S., Vanuk, J. R., Satterfield, B., Alkozei, A., Weber, M., Rosso. I.M, Rauch, S.L., Grandner, M.A., Killgore, W.D.S. Effect of blue light therapy on cortical structure, sleep and anxiety symptoms following mild traumatic brain injury; SLEEP; June 2-6, 2018; Baltimore, Maryland

Raikes AC, Dailey NS, Killgore W.D.S. Neural & Neurocognitive Correlates of Responsiveness to Blue Light Therapy Following Mild Traumatic Brain Injury. Poster presented at the: American Speech and Hearing Association Annual Meeting; November 15-17, 2018; Boston, MA.

Raikes AC, Killgore W.D.S. Blue light therapy improves self-reported sleep quality in individuals with a recent mild traumatic brain injury. Poster presented at the: Military Health System Research Symposium; August 20-23, 2018; Orlando, FL.

Killgore W.D.S. Executive functioning in individuals with mild traumatic brain injury is enhanced by daily morning blue light therapy. Presented at the: Military Health Systems Research Symposium; August 20-23, 2018; Orlando, FL.

Bajaj S, Raikes AC, Dailey NS, et al. Effect of blue light therapy on cortical volume, sleep, and anxiety symptoms following mild traumatic brain injury. Presented at the: Organization for Human Brain Mapping (OHBM) Annual Meeting; June 17-21, 2018; Singapore.

Bajaj S, Raikes A, Dailey NS, et al. Impact of blue light therapy on cortical structure, sleep, and anxiety symptoms following mild traumatic brain injury. Presented at the: 32nd Annual Meeting of the Associated Professional Sleep Societies; June 2-6, 2018; Baltimore, MD.

Alkozei A, Kent HC, Knight SA, Killgore W.D.S. Changes in Morning Salivary Melatonin Correlate with Prefrontal Responses During Working Memory Performance. Presented at the: 32nd Annual Meeting of the Associated Professional Sleep Societies; June 2-6, 2018; Baltimore, MD.

Killgore W.D.S, Kent HC, Knight SA, Alkozei A. Changes in Morning Salivary Melatonin Correlate with Prefrontal Responses During Working Memory Performance. Presented at the: 73rd Annual Meeting of the Society for Biological Psychiatry; May 10-12, 2018; New York City, NY.

Shane, BR, Vanuk, JR, Bajaj, S, Millan, M, Killgore, WD. Behavioral and Brain Imaging Changes in Patients Receiving Bright Light Therapy Following a Mild Traumatic Brain Injury. Platform presentation at the American Academy of Neurology Conference, Los Angeles, CA, April 21-27, 2018.

Bajaj S, Dailey NS, Vanuk JR, Raikes AC, Weber M, Rosso IM, Rauch SL, Singh A, Killgore W.D.S. Impact of blue light therapy on cortical volume, sleep and anxiety symptoms following mild traumatic brain injury. Anxiety and Depression Association of America; April 5-8, 2018; Washington, D.C.

Alkozei A, Smith R, Dailey NS, Bajaj S, Knight SA, Killgore W.D.S. Exposure to Blue Wavelength Light During Memory Consolidation Improves Long-Delay Verbal Memory Performance. Presented at the: 46th Annual Meeting of the International Neuropsychological Society; February 14-17, 2018; New York City, NY.

Bajaj S, Raikes AC, Dailey NS, et al. Changes in cortical structure, sleep, and anxiety symptoms following blue-wavelength light therapy in individuals with mild traumatic brain injury. Poster presented at the: Big Sky Athletic Training & Sports Medicine Conference; February 4-8, 2018; Big Sky, MT.

Bajaj, S., Alkozei A, Dailey, NS, Killgore, W.D.S. Short wavelength light therapy following mild traumatic brain injury: Can we normalize the abnormal diffusion and quantity of water within brain? Military Health Systems Research Symposium; August 27-30, 2017; Kissimmee, FL,

Alkozei A, Smith R, Killgore W.D.S. Increases in prefrontal activation after exposure to blue versus amber wavelength light during cognitive load. Poster presented at the: University of Arizona Junior Investigator Poster Forum; November 17, 2017; Tucson, AZ.

Killgore W.D.S, Vanuk JR, Bajaj S. Blue wavelength light therapy increases axonal myelination in mild traumatic brain injury. Presented at the: Military Health Systems Research Meeting; August 27-30, 2017; Kissimmee, FL.

Bajaj S, Rosso IM, Rauch SL, Killgore W.D.S. Impact of bright light therapy on structural abnormalities following mild traumatic brain injury. Presented at the: Organization for Human Brain Mapping (OHBM) Annual Meeting; June 25-29, 2017; Vancouver, British Columbia, Canada.

Bajaj, S., Alkozei, A., Killgore, W.D.S. Dynamics of brain's cortical measures following a mild traumatic brain injury. Organization for Human Brain Mapping (OHBM) Annual Meeting; June 25-29, 2017; Vancouver, British Columbia, Canada

Vanuk JR, Shane BR, Millan M, Bajaj S, Grandner MA, Killgore W.D.S. Short-wavelength light therapy as a way of improving sleep, cognition, and functional connectivity following mild traumatic brain injury. Presented at the: 31st Annual Meeting of the Associated Professional Sleep Societies; June 3-7, 2017; Boston, MA.

Bajaj S, Alkozei A, Grandner MA, Killgore W.D.S. Effect of bright light therapy on brain and behavioral abnormalities following a mild traumatic brain injury. Presented at the: 31st Annual Meeting of the Associated Professional Sleep Societies; June 3-7, 2017; Boston, MA.

Killgore, W.D.S., Shane, B.R., Vanuk, J.R., Franco, J., Castellanos, A., Millan, M., Grandner, M.A., & Bajaj, S. Short wavelength light therapy facilitates recovery from mild traumatic brain injury. Oral platform presentation at the SLEEP 2017 Annual Meeting, Boson, MA, June 3-7, 2017.

Bajaj S, Alkozei A, Grandner MA, Killgore W.D.S Effect of Bright Light Therapy on Brain and Behavioral Abnormalities following a mild Traumatic Brain Injury, SLEEP 2017 Annual Meeting, Boson, MA, June 3-7, 2017.

Vanuk JR, Millan M, Shane BR, Bajaj S, Killgore W.D.S. Blue light therapy following a mild traumatic brain injury improves MPFC-amygdala functional connectivity and mood. Presented at the: 72nd Annual Meeting of the Society for Biological Psychiatry; May 18-20, 2017; San Diego, CA.

Killgore W.D.S., Shane BR, Vanuk JR, Franco J, Castellanos A, Millan M, Grandner MA, Bajaj S. Light therapy facilitates thalamo-cortical brain recovery from mild traumatic brain injury. Presented at the: 72nd Annual Meeting of the Society for Biological Psychiatry; May 18-20, 2017; San Diego, CA.

Bajaj S, Alkozei A, Killgore W.D.S. Effect of bright light therapy on white matter abnormalities following a mild traumatic brain injury. Presented at the: 72nd Annual Meeting of the Society for Biological Psychiatry; May 18-20, 2017; San Diego, CA.

Franco J, Millan M, Shane BR, Casellanos A, Killgore W.D.S. Blue wavelength light therapy increases thalamic grey matter volume following mild traumatic brain injury. Presented at the: 45th Annual Meeting of the International Neuropsychological Society; February 1-4, 2017; New Orleans, LA.

Shane BR, Vanuk JR, Bajaj S, Millan M, Killgore W.D.S. Multimodal brain imaging in patients receiving bright light therapy following a mild traumatic brain injury. Presented at the: Western Medical Research Conference; January 26-28, 2017; Carmel, CA.

Vanuk JR, Allen J, Killgore W.D.S. Heart rate variability during light exposure and subsequent network connectivity patterns. Presented at the: Annual Meeting of the Society for Psychophysiological Research; September 21-25, 2016; Minneapolis, MN.

Killgore W.D.S, Vanuk JR, Pisner D, Penetar DM, Weber M. Short wavelength light therapy facilitates recovery from mild traumatic brain injury. Presented at the: Military Health System Research Symposium; August 15-18, 2016; Orlando, FL.

Weber M, Grandner MA, Killgore W.D.S. Blue wavelength light therapy reduces daytime sleepiness following mild traumatic brain injury. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Vanuk JR, Alkozei A, Smith R, Pisner D, Markowski SM, Shane BR, Fridman A, Knight SA, Grandner MA, Killgore W.D.S. Changes in heart rate variability due to light exposure predict frontoparietal connectivity. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Vanuk JR, Alkozei A, Knight SA, Fridman A, Markowski SM, Pisner D, Shane BR, Grandner MA, Killgore W.D.S. The effects of light exposure on heart rate variability predict

sleepiness and vigilance. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Killgore W.D.S, Weber M, Grandner MA, Penetar DM. The effects of light exposure on heart rate variability predict sleepiness and vigilance. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Alkozei A, Pisner D, Markowski SM, et al. Exposure to blue wavelength light is associated with increased dorsolateral prefrontal cortex responses and increases in response times during a working memory task. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Alkozei A, Markowski SM, Pisner D, et al. Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli. Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Killgore W.D.S., Weber M, Palmer W, Penetar DM. Blue wavelength light therapy improves balance following mild traumatic brain injury. Presented at the: 71st Annual Meeting of the Society for Biological Psychiatry; May 12-14, 2016; Atlanta, GA.

Alkozei A, Pisner D, Markowski SM, Vanuk JR, Fridman A, Shane BR, Knight SA, Killgore W.D.S. Increases in prefrontal activation after exposure to blue versus amber wavelength light during cognitive load. Presented at the: 71st Annual Scientific Convention of the Society for Biological Psychiatry; May 12-14, 2016; Atlanta, GA.

Alkozei A, Markowski SM, Pisner D, et al. Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli. Presented at the: 71st Annual Scientific Convention of the Society for Biological Psychiatry; May 12-14, 2016; Atlanta, GA.

Killgore W.D.S, Weber M, Penetar DM. Blue wavelength light therapy improves balance following mild traumatic brain injury. Presented at the: 44th Annual Meeting of the International Neuropsychological Society; February 3-6, 2016; Boston, MA.

Killgore W.D.S, Weber M. Blue wavelength light therapy reduces daytime sleepiness following mild traumatic brain injury. Presented at the: 44th Annual Meeting of the International Neuropsychological Society; February 3-6, 2016; Boston, MA.

Alkozei A, Killgore W.D.S. Exposure to blue wavelength light suppresses anterior cingulate cortex activation in response to uncertainty during anticipation of negative or positive stimuli. Presented at the: 44th Annual Meeting of the International Neuropsychological Society; February 3-6, 2016; Boston, MA.

Alkozei A, Killgore W.D.S. Exposure to blue wavelength light is associated with increased dorsolateral prefrontal cortex responses during a working memory task. Presented at the: 44th Annual Meeting of the International Neuropsychological Society; February 3-6, 2016; Boston, MA.

Shane BR, Alkozei A, Vanuk JR, Weber M, Killgore W.D.S. The effect of bright light therapy for improving sleep among individuals with mild traumatic brain injury. Presented at the: 70th

Annual Meeting of the Society of Biological Psychiatry; May 14-16, 2015; Toronto, Ontario, Canada.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name: William D. “Scott” Killgore, Ph.D.
Project Role: PI
Nearest person month worked: 14
Contribution to Project: Oversees all aspects of project progress and orchestrates data analysis and publication efforts.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Michael Miller
Project Role: Research Specialist
Nearest person month worked: 6
Contribution to Project: Mr. Miller oversees the administrative needs of the study and study staff, in addition to providing scientific and regulatory support. Mr. Miller performs periodic quality control checks.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Alex Hishaw, M.D.
Project Role: Medical Monitor
Researcher Identifier:
Nearest person month worked: 0
Contribution to Project: Dr. Hishaw provides medical consultations as needed in support of the study.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Adam Raikes, Ph.D.
Project Role: Postdoctoral Fellow
Researcher Identifier:
Nearest person month worked: 6

Contribution to Project: Dr. Raikes performs data analysis and oversees neuroimaging processing and data analyses for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Brittany Forbeck
Project Role: Research Technician
Researcher Identifier:
Nearest person month worked: 7
Contribution to Project: Ms. Forbeck provides support with data collection and recruitment activities
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Anna Alkozei, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 13
Contribution to Project: Dr. Alkozei performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Ryan Smith, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 10
Contribution to Project: Dr. Smith performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Sara Knight
Project Role: Lab Manager
Nearest person month worked: 11
Contribution to Project: Ms. Knight oversaw the administrative needs of the study and study staff, in addition to providing regulatory support and performing periodic quality control checks.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056

USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Matthew Allbright
Project Role: Research Technician
Nearest person month worked: 8
Contribution to Project: Mr. Allbright oversees the technical aspects of the project and assists in database export, storage, and management.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Sarah (Markowski) Berryhill
Project Role: Research Technician
Nearest person month worked: 9
Contribution to Project: Mrs. Berryhill provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Alyssa Dormer
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Ms. Dormer provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Ian Anlap
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Anlap provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Simon Esbit
Project Role: Research Technician
Nearest person month worked: 17
Contribution to Project: Mr. Esbit provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Cameron Barnes
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Barnes provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Ayla Bullock
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Ms. Bullock provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Sara Cloonan
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Ms. Cloonan provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Rebecca Woods-Lubbert
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Ms. Woods-Lubbert provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Johnny Vanuk
Project Role: Graduate Student
Nearest person month worked: 8
Contribution to Project: Mr. Vanuk performs data analysis and oversees neuroimaging processing and data analyses for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Aleksandra Klimova
Project Role: Research Technician
Nearest person month worked: 3
Contribution to Project: Ms. Kilmova provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Trevor Grant
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Grant provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Joseph Yee II
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Yee provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Janice Hayhoe
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Hayhoe provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Molly-Marie Richards
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Ms. Richards provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Bradley Shane
Project Role: Research Technician
Nearest person month worked: 4
Contribution to Project: Mr. Shane provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Courtney Smith

Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Ms. Smith provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Yinya Huang
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Ms. Huang provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Andrew Fridman
Project Role: Research Technician
Nearest person month worked: 12
Contribution to Project: Mr. Fridman provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Miyla McIntosh
Project Role: Research Technician
Nearest person month worked: 7
Contribution to Project: Ms. McIntosh provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Melissa Millan
Project Role: Research Technician
Nearest person month worked: 5
Contribution to Project: Ms. Millan oversees project progress and manages the day-to-day needs of the project.
Funding support: USAMRAA W81XWH-14-1-0570

USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: William Palmer
Project Role: Research Technician
Nearest person month worked: 7
Contribution to Project: Mr. Palmer provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Derek Pisner
Project Role: Research Technician
Nearest person month worked: 8
Contribution to Project: Mr. Pisner previously oversaw project progress and managed the day-to-day needs of the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Prabhjyot Singh
Project Role: Research Technician
Nearest person month worked: 5
Contribution to Project: Mr. Singh previously assisted with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Natalie Dailey, Ph.D., CCC-SLP
Project Role: Postdoctoral Fellow
Nearest person month worked: 5
Contribution to Project: Dr. Dailey performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Sahil Bajaj, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 5
Contribution to Project: Dr. Bajaj performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570

USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Skye Challenger
Project Role: Research Technician
Nearest person month worked: 4
Contribution to Project: Ms. Challenger provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Melissa Gottschlich
Project Role: Research Technician
Nearest person month worked: 3
Contribution to Project: Ms. Gottschlich oversees project needs and manages day-to-day aspects
of project operations.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Simone Hyman
Project Role: Research Technician
Nearest person month worked: 4
Contribution to Project: Ms. Hyman provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Jacqueline Marquez
Project Role: Research Technician
Nearest person month worked: 7
Contribution to Project: Ms. Marquez provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Anna Sanova

Project Role: Research Technician
24
Nearest person month worked: 8
Contribution to Project: Ms. Sanova provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Anmol Singh
Project Role: Research Technician
Nearest person month worked: 6
Contribution to Project: Mr. Singh provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Matthew Thurston
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Thurston provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Wing Ka Angela Yung
Project Role: Research Technician
Nearest person month worked: 5
Contribution to Project: Ms. Yung provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Brieann Satterfield, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 2
Contribution to Project: Dr. Satterfield performs data analysis and processing for the project.

Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Garrett Paul Baker
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Baker provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Renata Botello
Project Role: Research Technician
Nearest person month worked: 3
Contribution to Project: Ms. Botello provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Anna Burns
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Burns provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Miriam Chinkers
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Chinkers provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571

USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: James Eric Joshua Del Toro
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Del Toro provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Kyle Lafollette
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Lafollette provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Michael Phillip Lazar
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Lazar provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Meltem Ozcan
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Ms. Ozcan provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Kristin Caleigh Shepard

Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Shepard provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Jeffrey Skalamera
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Skalamera provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Michael James Strong
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Strong provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Sydney Wilkerson
Project Role: Research Technician
Nearest person month worked: 0
Contribution to Project: Mrs. Wilkerson provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Nothing to report

- **What other organizations were involved as partners?**
  Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Please see updated Quad Chart attached in Appendix.

REFERENCES CITED

Alkozei, A., Smith, R., Dailey, N.S., Bajaj, S., & Killgore, W.D.S. (2017). Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS One, 12*(9), e0184884.

Alkozei, A., Smith, R., & Killgore, W.D. (2016). Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neurosci Lett, 616*, 5-10.

Alkozei, A., Smith, R., Pisner, D.A., Vanuk, J.R., Berryhill, S.M., Fridman, A., . . . Killgore, W.D. (2016). Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. *Sleep, 39*(9), 1671-1680.

Alsalaheen, B., Stockdale, K., Pechumer, D., Broglio, S.P., & Marchetti, G.F. (2017). A Comparative Meta-Analysis of the Effects of Concussion on a Computerized Neurocognitive Test and Self-Reported Symptoms. *J Athl Train, 52*(9), 834-846.

Aoki, Y., & Inokuchi, R. (2016). A voxel-based meta-analysis of diffusion tensor imaging in mild traumatic brain injury. *Neurosci Biobehav Rev, 66*, 119-126.

Arbour, C., Khoury, S., Lavigne, G.J., Gagnon, K., Poirier, G., Montplaisir, J.Y., . . . Gosselin, N. (2015). Are NREM sleep characteristics associated to subjective sleep complaints after mild traumatic brain injury? *Sleep Med, 16*(4), 534-539.

Aston-Jones, G., Chen, S., Zhu, Y., & Oshinsky, M.L. (2001). A neural circuit for circadian regulation of arousal. *Nature neuroscience, 4*(7), 732-738.

Aupperle, R.L., Allard, C.B., Simmons, A.N., Flagan, T., Thorp, S.R., Norman, S.B., . . . Stein, M.B. (2013). Neural responses during emotional processing before and after cognitive trauma therapy for battered women. *Psychiatry Research: Neuroimaging, 214*(1), 48-55.

Bajaj, S., Adhikari, B.M., Friston, K.J., & Dhamala, M. (2016). Bridging the Gap: Dynamic Causal Modeling and Granger Causality Analysis of Resting State Functional Magnetic Resonance Imaging. *Brain Connect, 6*(8), 652-661.

Bajaj, S., Vanuk, J.R., Smith, R., Dailey, N.S., & Killgore, W.D.S. (2017). Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. *Front Neurol, 8*, 616.

Banks, S.D., Coronado, R.A., Clemons, L.R., Abraham, C.M., Pruthi, S., Conrad, B.N., . . . Archer, K.R. (2016). Thalamic Functional Connectivity in Mild Traumatic Brain Injury: Longitudinal Associations With Patient-Reported Outcomes and Neuropsychological Tests. *Arch Phys Med Rehabil, 97*(8), 1254-1261.

Baumann, C.R., Werth, E., Stocker, R., Ludwig, S., & Bassetti, C.L. (2007). Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain, 130*(Pt 7), 1873-1883.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *BDI-II: Beck Depression Inventory Manual* (2nd ed.). San Antonio, TX: Psychological Corporation.

Beetar, J.T., Guilmette, T.J., & Sparadeo, F.R. (1996). Sleep and pain complaints in symptomatic traumatic brain injury and neurologic populations. *Arch Phys Med Rehabil, 77*(12), 1298-1302.
Bellesi, M., Pfister-Genskow, M., Maret, S., Keles, S., Tononi, G., & Cirelli, C. (2013). Effects of sleep and wake on oligodendrocytes and their precursors. *J Neurosci, 33*(36), 14288-14300.
Berson, D.M., Dunn, F.A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science, 295*(5557), 1070-1073.
Blair, R.C., & Karniski, W. (1993). An alternative method for significance testing of waveform difference potentials. *Psychophysiology, 30*(5), 518-524.
Bloomfield, I.L., Espie, C.A., & Evans, J.J. (2010). Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? *J Int Neuropsychol Soc, 16*(1), 17-25.
Bolzenius, J.D., Wade, B.S.C., Velez, C.S., Drennon, A.M., Cooper, D.B., Kennedy, J.E., . . . Tate, D.F. (2018). Relationships Between Subcortical Shape Measures and Subjective Symptom Reporting in US Service Members With Mild Traumatic Brain Injury. *J Head Trauma Rehabil, 33*(2), 113-122.
Brainard, G.C., Sliney, D., Hanifin, J.P., Glickman, G., Byrne, B., Greeson, J.M., . . . Rollag, M.D. (2008). Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms, 23*(5), 379-386.
Brovelli, A., Ding, M., Ledberg, A., Chen, Y., Nakamura, R., & Bressler, S.L. (2004). Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. *Proc Natl Acad Sci U S A, 101*(26), 9849-9854.
Bush, G., & Shin, L.M. (2006). The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. *Nat Protoc, 1*(1), 308-313.
Bush, G., Shin, L.M., Holmes, J., Rosen, B.R., & Vogt, B.A. (2003). The Multi-Source Interference Task: validation study with fMRI in individual subjects. *Molecular psychiatry, 8*(1), 60-70.
Cajochen, C., Krauchi, K., & Wirz-Justice, A. (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol, 15*(4), 432-437.
Castriotta, R.J., Wilde, M.C., Lai, J.M., Atanasov, S., Masel, B.E., & Kuna, S.T. (2007). Prevalence and consequences of sleep disorders in traumatic brain injury. *J Clin Sleep Med, 3*(4), 349-356.
Chellappa, S.L., Steiner, R., Blattner, P., Oelhafen, P., Gotz, T., & Cajochen, C. (2011). Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS One, 6*(1), e16429.
Clark, A.L., Sorg, S.F., Holiday, K., Bigler, E.D., Bangen, K.J., Evangelista, N.D., . . . Delano-Wood, L. (2018). Fatigue Is Associated With Global and Regional Thalamic Morphometry in Veterans With a History of Mild Traumatic Brain Injury. *J Head Trauma Rehabil, 33*(6), 382-392.
Clewett, D.V., Huang, R., Velasco, R., Lee, T.H., & Mather, M. (2018). Locus Coeruleus Activity Strengthens Prioritized Memories Under Arousal. *J Neurosci, 38*(6), 1558-1574.
Cole, R.J., Kripke, D.F., Gruen, W., Mullaney, D.J., & Gillin, J.C. (1992). Automatic sleep/wake identification from wrist activity. *Sleep, 15*(5), 461-469.
Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., . . . Meyerand, M.E. (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *AJNR Am J Neuroradiol, 22*(7), 1326-1333.
Dacey, D.M., Liao, H.W., Peterson, B.B., Robinson, F.R., Smith, V.C., Pokorny, J., . . . Gamlin, P.D. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature, 433*(7027), 749-754.

Dai, X.J., Jiang, J., Zhang, Z., Nie, X., Liu, B.X., Pei, L., . . . Zhan, Y. (2018). Plasticity and Susceptibility of Brain Morphometry Alterations to Insufficient Sleep. *Front Psychiatry, 9*, 266.

Deng, Y., Wang, X., Wang, Y., & Zhou, C. (2018). Neural correlates of interference resolution in the multi-source interference task: a meta-analysis of functional neuroimaging studies. *Behav Brain Funct, 14*(1), 8.

Dewan, K., Benloucif, S., Reid, K., Wolfe, L.F., & Zee, P.C. (2011). Light-induced changes of the circadian clock of humans: increasing duration is more effective than increasing light intensity. *Sleep, 34*(5), 593-599.

Dhamala, M. (2013). Spectral interdependency methods. In D. Jaeger & R. Jung (Eds.), *Encyclopedia of Computational Neuroscience*. New York, NY: Springer New York.

Dhamala, M., Rangarajan, G., & Ding, M. (2008a). Analyzing information flow in brain networks with nonparametric Granger causality. *Neuroimage, 41*(2), 354-362.

Dhamala, M., Rangarajan, G., & Ding, M. (2008b). Estimating Granger causality from fourier and wavelet transforms of time series data. *Phys Rev Lett, 100*(1), 018701.

Dichter, G.S., Felder, J.N., Petty, C., Bizzell, J., Ernst, M., & Smoski, M.J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological psychiatry, 66*(9), 886-897.

Dikmen, S., McLean, A., & Temkin, N. (1986). Neuropsychological and psychosocial consequences of minor head injury. *J Neurol Neurosurg Psychiatry, 49*(11), 1227-1232.

Dinges, D.F., & Powell, J.W. (1985). Microcomputer analyses of performance on a portable, simple, visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers, 17*, 652-655.

Farrell-Carnahan, L., Barnett, S., Lamberty, G., Hammond, F.M., Kretzmer, T.S., Franke, L.M., . . . Nakase-Richardson, R. (2015). Insomnia symptoms and behavioural health symptoms in veterans 1 year after traumatic brain injury. *Brain Inj, 29*(12), 1400-1408.

Figueiro, M.G., Plitnick, B.A., Lok, A., Jones, G.E., Higgins, P., Hornick, T.R., & Rea, M.S. (2014). Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. *Clin Interv Aging, 9*, 1527-1537.

Florin-Lechner, S.M., Druhan, J.P., Aston-Jones, G., & Valentino, R.J. (1996). Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. *Brain research, 742*(1), 89-97.

Galea, O.A., Cottrell, M.A., Treleaven, J.M., & O'Leary, S.P. (2018). Sensorimotor and Physiological Indicators of Impairment in Mild Traumatic Brain Injury: A Meta-Analysis. *Neurorehabil Neural Repair, 32*(2), 115-128.

Geerdink, M., Walbeek, T.J., Beersma, D.G., Hommes, V., & Gordijn, M.C. (2016). Short Blue Light Pulses (30 Min) in the Morning Support a Sleep-Advancing Protocol in a Home Setting. *J Biol Rhythms, 31*(5), 483-497.

Gevins, A., & Cutillo, B. (1993). Neuroelectric evidence for distributed processing in human working memory. *Electroencephalography and Clinical Neurophysiology, 87*, 128-143.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., . . . Van Essen, D.C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature, 536*(7615), 171-178.

Glennon, E., Carcea, I., Martins, A.R.O., Multani, J., Shehu, I., Svirsky, M.A., & Froemke, R.C. (2019). Locus coeruleus activation accelerates perceptual learning. *Brain Res, 1709*, 39-49.

Group, M.o.C.m.W. (2009). VA/DoD clinical practice guidelines for maagement of concussion/mild traumatic brain injury. *Journal of Rehabilitation Research and Development, 46*(6), CP1-68.

Gruber, S.A., Dahlgren, M.K., Sagar, K.A., Gonenc, A., & Killgore, W.D.S. (2012). Age of onset of marijuana use impacts inhibitory processing. *Neuroscience letters, 511*(2), 89-94.
Hattar, S., Liao, H.W., Takao, M., Berson, D.M., & Yau, K.W. (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science, 295*(5557), 1065-1070.
Heaton, K.J., Maule, A.L., Maruta, J., Kryskow, E.M., & Ghajar, J. (2014). Attention and visual tracking degradation during acute sleep deprivation in a military sample. *Aviat Space Environ Med, 85*(5), 497-503.
Herscovitch, J., & Broughton, R. (1981). Sensitivity of the stanford sleepiness scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. *Sleep, 4*(1), 83-91.
Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C., & Castro, C.A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med, 358*(5), 453-463.
Indovina, I., Riccelli, R., Chiarella, G., Petrolo, C., Augimeri, A., Giofre, L., . . . Passamonti, L. (2015). Role of the Insula and Vestibular System in Patients with Chronic Subjective Dizziness: An fMRI Study Using Sound-Evoked Vestibular Stimulation. *Front Behav Neurosci, 9*, 334.
Izumi, Y., & Zorumski, C.F. (1999). Norepinephrine promotes long-term potentiation in the adult rat hippocampus in vitro. *Synapse, 31*(3), 196-202.
Johns, M.W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep, 14*(6), 540-545.
Katsuki, H., Izumi, Y., & Zorumski, C.F. (1997). Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region. *Journal of Neurophysiology, 77*(6), 3013-3020.
Kaufman, Y., Tzischinsky, O., Epstein, R., Etzioni, A., Lavie, P., & Pillar, G. (2001). Long-term sleep disturbances in adolescents after minor head injury. *Pediatr Neurol, 24*(2), 129-134.
Killgore, W.D.S., Vanuk, J.R., Shane, B.R., Weber, M., & Bajaj, S. (2019). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. *Neurobiol Dis, 134*, 104679.
King, P.R., Donnelly, K.T., Donnelly, J.P., Dunnam, M., Warner, G., Kittleson, C.J., . . . Meier, S.T. (2012). Psychometric study of the Neurobehavioral Symptom Inventory. *J Rehabil Res Dev, 49*(6), 879-888.
Lacadie, C.M., Fulbright, R.K., Rajeevan, N., Constable, R.T., & Papademetris, X. (2008). More accurate Talairach coordinates for neuroimaging using non-linear registration. *Neuroimage, 42*(2), 717-725.
Lack, L.C., Gradisar, M., Van Someren, E.J., Wright, H.R., & Lushington, K. (2008). The relationship between insomnia and body temperatures. *Sleep Med Rev, 12*(4), 307-317.
Lack, L.C., & Wright, H.R. (2007). Treating chronobiological components of chronic insomnia. *Sleep Med, 8*(6), 637-644.
Langlois, J.A., Rutland-Brown, W., & Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil, 21*(5), 375-378.
Lee, B.-T., Cho, S.W., Khang, H.S., Lee, B.-C., Choi, I.-G., Lyoo, I.K., & Ham, B.-J. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(7), 1487-1492.
Lee, J.O., Lee, E.S., Kim, J.S., Lee, Y.B., Jeong, Y., Choi, B.S., . . . Staab, J.P. (2018). Altered brain function in persistent postural perceptual dizziness: A study on resting state functional connectivity. *Hum Brain Mapp, 39*(8), 3340-3353.

Liu, C., Kong, X.Z., Liu, X., Zhou, R., & Wu, B. (2014). Long-term total sleep deprivation reduces thalamic gray matter volume in healthy men. *Neuroreport, 25*(5), 320-323.
Makley, M.J., English, J.B., Drubach, D.A., Kreuz, A.J., Celnik, P.A., & Tarwater, P.M. (2008). Prevalence of sleep disturbance in closed head injury patients in a rehabilitation unit. *Neurorehabil Neural Repair, 22*(4), 341-347.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., & Burdette, J.H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19*(3), 1233-1239.
Manley, G., Gardner, A.J., Schneider, K.J., Guskiewicz, K.M., Bailes, J., Cantu, R.C., . . . Iverson, G.L. (2017). A systematic review of potential long-term effects of sport-related concussion. *Br J Sports Med, 51*(12), 969-977.
Mantua, J., Grillakis, A., Mahfouz, S.H., Taylor, M.R., Brager, A.J., Yarnell, A.M., . . . Simonelli, G. (2018). A systematic review and meta-analysis of sleep architecture and chronic traumatic brain injury. *Sleep Med Rev, 41*, 61-77.
Mantua, J., Henry, O.S., Garskovas, N.F., & Spencer, R.M.C. (2017). Mild Traumatic Brain Injury Chronically Impairs Sleep- and Wake-Dependent Emotional Processing. *Sleep, 40*(6).
Marino, M., Li, Y., Rueschman, M.N., Winkelman, J.W., Ellenbogen, J.M., Solet, J.M., . . . Buxton, O.M. (2013). Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep, 36*(11), 1747-1755.
Mathias, J.L., & Alvaro, P.K. (2012). Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. *Sleep Med, 13*(7), 898-905.
Matthews, S.C., Strigo, I.A., Simmons, A.N., O'Connell, R.M., Reinhardt, L.E., & Moseley, S.A. (2011). A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. *Neuroimage, 54 Suppl 1*, S69-75.
McCrory, P., Meeuwisse, W., Dvorak, J., Aubry, M., Bailes, J., Broglio, S., . . . Vos, P.E. (2017). Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med, 51*(11), 838-847.
McCuddy, W.T., Espana, L.Y., Nelson, L.D., Birn, R.M., Mayer, A.R., & Meier, T.B. (2018). Association of acute depressive symptoms and functional connectivity of emotional processing regions following sport-related concussion. *Neuroimage Clin, 19*, 434-442.
Monk, T.H. (2005). The post-lunch dip in performance. *Clin Sports Med, 24*(2), e15-23, xi-xii.
Munivenkatappa, A., Devi, B.I., Shukla, D.P., & Rajeswaran, J. (2016). Role of the thalamus in natural recovery of cognitive impairment in patients with mild traumatic brain injury. *Brain Inj, 30*(4), 388-392.
Naess-Schmidt, E.T., Blicher, J.U., Eskildsen, S.F., Tietze, A., Hansen, B., Stubbs, P.W., . . . Nielsen, J.F. (2017). Microstructural changes in the thalamus after mild traumatic brain injury: A longitudinal diffusion and mean kurtosis tensor MRI study. *Brain Inj, 31*(2), 230-236.
Neubauer, A.C., & Fink, A. (2009). Intelligence and neural efficiency. *Neurosci Biobehav Rev, 33*(7), 1004-1023.
Nitschke, J.B., Sarinopoulos, I., Oathes, D.J., Johnstone, T., Whalen, P.J., Davidson, R.J., & Kalin, N.H. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response.
Nordin, L.E., Moller, M.C., Julin, P., Bartfai, A., Hashim, F., & Li, T.Q. (2016). Post mTBI fatigue is associated with abnormal brain functional connectivity. *Sci Rep, 6*, 21183.
Oldfield, R.C. (1971). The assessment of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97-111.
Orff, H.J., Ayalon, L., & Drummond, S.P. (2009). Traumatic brain injury and sleep disturbance: a review of current research. *J Head Trauma Rehabil, 24*(3), 155-165.

Ouellet, M.C., Beaulieu-Bonneau, S., & Morin, C.M. (2006). Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J Head Trauma Rehabil, 21*(3), 199-212.
Owen, A.M., McMillan, K.M., Laird, A.R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human brain mapping, 25*(1), 46-59.
Parcell, D.L., Ponsford, J.L., Redman, J.R., & Rajaratnam, S.M. (2008). Poor sleep quality and changes in objectively recorded sleep after traumatic brain injury: a preliminary study. *Arch Phys Med Rehabil, 89*(5), 843-850.
Patrick, Y., Lee, A., Raha, O., Pillai, K., Gupta, S., Sethi, S., . . . Moss, J. (2017). Effects of sleep deprivation on cognitive and physical performance in university students. *Sleep Biol Rhythms, 15*(3), 217-225.
Phipps-Nelson, J., Redman, J.R., Dijk, D.J., & Rajaratnam, S.M. (2003). Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep, 26*(6), 695-700.
Phipps-Nelson, J., Redman, J.R., Schlangen, L.J., & Rajaratnam, S.M. (2009). Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiol Int, 26*(5), 891-912.
Poldrack, R.A. (2015). Is "efficiency" a useful concept in cognitive neuroscience? *Dev Cogn Neurosci, 11*, 12-17.
Ponsford, J.L., Ziino, C., Parcell, D.L., Shekleton, J.A., Roper, M., Redman, J.R., . . . Rajaratnam, S.M. (2012). Fatigue and sleep disturbance following traumatic brain injury--their nature, causes, and potential treatments. *The Journal of head trauma rehabilitation, 27*(3), 224-233.
Raikes, A.C., Athey, A., Alfonso-Miller, P., Killgore, W.D.S., & Grandner, M.A. (2019). Insomnia and daytime sleepiness: risk factors for sports-related concussion. *Sleep Med, 58*, 66-74.
Raikes, A.C., Bajaj, S., Dailey, N.S., Smith, R.S., Alkozei, A., Satterfield, B.C., & Killgore, W.D.S. (2018). Diffusion Tensor Imaging (DTI) Correlates of Self-Reported Sleep Quality and Depression Following Mild Traumatic Brain Injury. *Front Neurol, 9*, 468.
Raikes, A.C., & Killgore, W.D. (2018). Potential for the development of light therapies in mild traumatic brain injury. *Concussion, 3*(3), CNC57.
Raikes, A.C., Satterfield, B.C., & Killgore, W.D.S. (2019). Evidence of actigraphic and subjective sleep disruption following mild traumatic brain injury. *Sleep Med, 54*, 62-69.
Raikes, A.C., & Schaefer, S.Y. (2016). Sleep Quantity and Quality during Acute Concussion: A Pilot Study. *Sleep, 39*(12), 2141-2147.
Rao, V., Spiro, J., Vaishnavi, S., Rastogi, P., Mielke, M., Noll, K., . . . Makley, M. (2008). Prevalence and types of sleep disturbances acutely after traumatic brain injury. *Brain Inj, 22*(5), 381-386.
Revell, V.L., & Skene, D.J. (2007). Light-induced melatonin suppression in humans with polychromatic and monochromatic light. *Chronobiol Int, 24*(6), 1125-1137.
Riccelli, R., Passamonti, L., Toschi, N., Nigro, S., Chiarella, G., Petrolo, C., . . . Indovina, I. (2017). Altered Insular and Occipital Responses to Simulated Vertical Self-Motion in Patients with Persistent Postural-Perceptual Dizziness. *Front Neurol, 8*, 529.
Richardson, C., Cain, N., Bartel, K., Micic, G., Maddock, B., & Gradisar, M. (2018). A randomised controlled trial of bright light therapy and morning activity for adolescents and young adults with Delayed Sleep-Wake Phase Disorder. *Sleep Med, 45*, 114-123.
Rorden, C., Karnath, H.O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *J Cogn Neurosci, 19*(7), 1081-1088.

Rosa, J.P.P., Silva, A., Rodrigues, D.F., Simim, M.A., Narciso, F.V., Tufik, S., . . . de Mello, M.T. (2018). Effect of bright light therapy on delayed sleep/wake cycle and reaction time of athletes participating in the Rio 2016 Olympic Games. *Chronobiol Int, 35*(8), 1095-1103.
Saxvig, I.W., Wilhelmsen-Langeland, A., Pallesen, S., Vedaa, O., Nordhus, I.H., & Bjorvatn, B. (2014). A randomized controlled trial with bright light and melatonin for delayed sleep phase disorder: effects on subjective and objective sleep. *Chronobiol Int, 31*(1), 72-86.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.
Shidara, M., & Richmond, B.J. (2002). Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science, 296*(5573), 1709-1711.
Silvetti, M., Alexander, W., Verguts, T., & Brown, J.W. (2014). From conflict management to reward-based decision making: actors and critics in primate medial frontal cortex. *Neuroscience & Biobehavioral Reviews, 46*, 44-57.
Sinclair, K.L., Ponsford, J.L., Taffe, J., Lockley, S.W., & Rajaratnam, S.M. (2014). Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair, 28*(4), 303-313.
Skene, D.J. (2003). Optimization of light and melatonin to phase-shift human circadian rhythms. *J Neuroendocrinol, 15*(4), 438-441.
Smith, M.R., Revell, V.L., & Eastman, C.I. (2008). Phase advancing the human circadian clock with blue-enriched polychromatic light. *Sleep Med*.
Smoski, M.J., Felder, J., Bizzell, J., Green, S.R., Ernst, M., Lynch, T.R., & Dichter, G.S. (2009). fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of affective disorders, 118*(1), 69-78.
Stein, M.B., Simmons, A.N., Feinstein, J.S., & Paulus, M.P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *The American journal of psychiatry, 164*(2), 318-327.
Strain, J., Didehbani, N., Cullum, C.M., Mansinghani, S., Conover, H., Kraut, M.A., . . . Womack, K.B. (2013). Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology, 81*(1), 25-32.
Straube, T., Mentzel, H.-J., & Miltner, W.H. (2007). Waiting for spiders: brain activation during anticipatory anxiety in spider phobics. *Neuroimage, 37*(4), 1427-1436.
Strigo, I.A., Simmons, A.N., Matthews, S.C., Arthur, D., & Paulus, M.P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Archives of General Psychiatry, 65*(11), 1275-1284.
Sufrinko, A.M., Howie, E.K., Elbin, R.J., Collins, M.W., & Kontos, A.P. (2018). A Preliminary Investigation of Accelerometer-Derived Sleep and Physical Activity Following Sport-Related Concussion. *J Head Trauma Rehabil, 33*(5), E64-E74.
Sullivan, K.A., Berndt, S.L., Edmed, S.L., Smith, S.S., & Allan, A.C. (2016). Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. *Appl Neuropsychol Adult, 23*(6), 426-435.
Sullivan, K.A., Blaine, H., Kaye, S.A., Theadom, A., Haden, C., & Smith, S.S. (2018). A Systematic Review of Psychological Interventions for Sleep and Fatigue after Mild Traumatic Brain Injury. *J Neurotrauma, 35*(2), 195-209.
Szabadi, E. (2013). Functional neuroanatomy of the central noradrenergic system. *J Psychopharmacol, 27*(8), 659-693.
Tahkamo, L., Partonen, T., & Pesonen, A.K. (2018). Systematic review of light exposure impact on human circadian rhythm. *Chronobiol Int*, 1-20.

Theadom, A., Cropley, M., Parmar, P., Barker-Collo, S., Starkey, N., Jones, K., . . . Group, B.R. (2015). Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med, 16*(8), 926-932.
Thorne, D.R. (2006). Throughput: a simple performance index with desirable characteristics. *Behav Res Methods, 38*(4), 569-573.
Towns, S.J., Silva, M.A., & Belanger, H.G. (2015). Subjective sleep quality and postconcussion symptoms following mild traumatic brain injury. *Brain Inj, 29*(11), 1337-1341.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002a). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002b). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.
van Maanen, A., Meijer, A.M., van der Heijden, K.B., & Oort, F.J. (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev, 29*, 52-62.
Vandewalle, G., Balteau, E., Phillips, C., Degueldre, C., Moreau, V., Sterpenich, V., . . . Maquet, P. (2006). Daytime light exposure dynamically enhances brain responses. *Curr Biol, 16*(16), 1616-1621.
Vandewalle, G., Gais, S., Schabus, M., Balteau, E., Carrier, J., Darsaud, A., . . . Maquet, P. (2007). Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cereb Cortex, 17*(12), 2788-2795.
Vandewalle, G., Maquet, P., & Dijk, D.J. (2009). Light as a modulator of cognitive brain function. *Trends Cogn Sci, 13*(10), 429-438.
Vandewalle, G., Schmidt, C., Albouy, G., Sterpenich, V., Darsaud, A., Rauchs, G., . . . Dijk, D.J. (2007). Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. *PLoS One, 2*(11), e1247.
Vazey, E.M., Moorman, D.E., & Aston-Jones, G. (2018). Phasic locus coeruleus activity regulates cortical encoding of salience information. *Proc Natl Acad Sci U S A, 115*(40), E9439-E9448.
Verma, A., Anand, V., & Verma, N.P. (2007). Sleep disorders in chronic traumatic brain injury. *J Clin Sleep Med, 3*(4), 357-362.
Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141.
Wickwire, E.M., Schnyer, D.M., Germain, A., Williams, S.G., Lettieri, C.J., McKeon, A.B., . . . Manley, G.T. (2018). Sleep, Sleep Disorders, and Circadian Health following Mild Traumatic Brain Injury in Adults: Review and Research Agenda. *J Neurotrauma, 35*(22), 2615-2631.
Williams, B.R., Lazic, S.E., & Ogilvie, R.D. (2008). Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clin Neurophysiol, 119*(2), 429-438.
Wiseman-Hakes, C., Gosselin, N., Sharma, B., Langer, L., & Gagnon, I. (2019). A Longitudinal Investigation of Sleep and Daytime Wakefulness in Children and Youth With Concussion. *ASN Neuro, 11*, 1759091418822405.
Woo, C.W., Krishnan, A., & Wager, T.D. (2014). Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. *Neuroimage, 91*, 412-419.
Wu, L.M., Amidi, A., Valdimarsdottir, H., Ancoli-Israel, S., Liu, L., Winkel, G., . . . Redd, W.H. (2018). The Effect of Systematic Light Exposure on Sleep in a Mixed Group of Fatigued Cancer Survivors. *J Clin Sleep Med, 14*(1), 31-39.

Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377.
Yeh, F.C., Badre, D., & Verstynen, T. (2016). Connectometry: A statistical approach harnessing the analytical potential of the local connectome. *Neuroimage, 125*, 162-171.
Yeh, F.C., & Tseng, W.Y. (2011). NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage, 58*(1), 91-99.
Yeh, F.C., Verstynen, T.D., Wang, Y., Fernandez-Miranda, J.C., & Tseng, W.Y. (2013). Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS One, 8*(11), e80713.
Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., . . . Buckner, R.L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol, 106*(3), 1125-1165.

APPENDICES
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Bright Light Therapy for Treatment of Sleep Problems Following Mild TBI Study
Tasks and Assessments

Screening Visit
VA National Traumatic Brain Injury Neurobehavioral Symptom Inventory (NSI)
Screen Time Questionnaire (STQ)
Mini-International Neuropsychiatric Interview (MINI)
Edinburgh Handedness Survey (EHS)
Personality Assessment Inventory (PAI)
Wechsler Abbreviated Scale of Intelligence II (WASI II)

Baseline and Post-Treatment Visits
Stanford Sleepiness Scale (SSS)
Multi-Source Interference Task (MSIT)
N-Back Task
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
ANAM4 Battery
Psychomotor Vigilance Test (PVT)
Invincibility Beliefs Index (IBI)
Go/No-Go Task (GNG)
Day of Scan Questionnaire
Morningness-Eveningness Questionnaire (MEQ)
Functional Outcome of Sleep Questionnaire (FOSQ)
Evaluation of Risks Scale (EVAR)
Patient Health Questionnaire (PHQ)
Pittsburgh Sleep Quality Index (PSQI)
Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ)
Beck Depression Inventory (BDI-II)
Balloon Analog Risk Task (BART)
Spielberger State-Trait Anxiety Inventory (STAI)
Tower of London (TOL)
Satisfaction with Life Scale (SWLS)
Buss-Perry Aggression Questionnaire (BPAQ)

Appendix II: Symptom Checklist Included in VA's National Traumatic Brain Injury Evaluation and Treatment Protocol

NEUROBEHAVIORAL SYMPTOM INVENTORY

Please rate the following symptoms with regard to how much they have disturbed you *SINCE YOUR INJURY*.

0 = None- Rarely if ever present; not a problem at all

1 = Mild- Occasionally present, but it does not disrupt activities; I can usually continue what I'm doing; doesn't really concern me.

2 = Moderate- Often present, occasionally disrupts my activities; I can usually continue what I'm doing with some effort; I feel somewhat concerned.

3 = Severe- Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel like I need help.

4 = Very Severe- Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

1. Feeling dizzy:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

2. Loss of balance:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

3. Poor coordination, clumsy:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

4. Headaches:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

5. Nausea:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

6. Vision problems, blurring, trouble seeing:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

7. Sensitivity to light

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

8. Hearing difficulty:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

9. Sensitivity to noise:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

10. Numbness or tingling on parts of my body:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

11. Change in taste and/or smell:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

12. Loss of appetite or increase appetite:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

13. Poor concentration, can't pay attention, easily distracted:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

14. Forgetfulness, can't remember things:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

15. Difficulty making decisions:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

16. Slowed thinking, difficulty getting organized, can't finish things:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

17. Fatigue, loss of energy, getting tired easily:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

18. Difficulty falling or staying asleep:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

19. Feeling anxious or tense:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

20. Feeling depressed or sad:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

21. Irritability, easily annoyed:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

22. Poor frustration tolerance, feeling easily overwhelmed by things:

0	1	2	3	4
NONE	MILD	MODERATE	SEVERE	VERY SEVERE

Subject Number: _____ Date:_____

In a typical week, we would like to know how much and when you are using your TV and Computer. Please place a C (computer) and/or T (television) in each hour time slot to indicate use.

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
12AM							
1AM							
2AM							
3AM							
4AM							
5AM							
6AM							
7AM							
8AM							
9AM							
10AM							
11AM							
12PM							
1PM							
2PM							
3PM							
4PM							
5PM							
6PM							
7PM							
8PM							
9PM							
10PM							
11PM							

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 6.0.0 (January 1, 2009)

			Patient Number:			
			Time Interview Began:			
Interviewer's Name:			***Time Interview Ended:***			
Date of Interview:			***Total Time:***			

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
		Past	☐	296.20-296.26 Single	F32.x	☐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	☐
B	SUICIDALITY	Current (Past Month) ☐ Low ☐ Moderate ☐ High	☐			
C	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	☐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	☐
		Past	☐			
	BIPOLAR I DISORDER	Current	☐	296.0x-296.6x	F30.x-F31.9	☐
		Past	☐	296.0x-296.6x	F30.x-F31.9	☐
	BIPOLAR II DISORDER	Current	☐	296.89	F31.8	☐
		Past	☐	296.89	F31.8	☐
	BIPOLAR DISORDER NOS	Current	☐	296.80	F31.9	☐
		Past	☐	296.80	F31.9	☐
D	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	☐
		Lifetime	☐			
E	AGORAPHOBIA	Current	☐	300.22	F40.00	☐
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	☐	300.23	F40.1	☐
		Non-Generalized	☐	300.23	F40.1	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	☐
I	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	☐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	☐
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
K	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	☐
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9		
	MOOD DISORDER WITH	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/	☐
	PSYCHOTIC FEATURES	Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	☐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		☐ No	☐ Yes ☐Uncertain		
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	301.7	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question G6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:

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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	For the past two weeks, were you depressed or down, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
		➡ IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **A1b** AND **A2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

Over that two week period, when you felt depressed or uninterested:

		Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
	IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes; Past Episode ❒ No ❒ Yes				
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF **YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED YES FOR THAT TIME FRAME?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO	**YES**
MAJOR DEPRESSIVE EPISODE	
CURRENT	❒
PAST	❒
RECURRENT	❒

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

B. SUICIDALITY

				Points
	In the past month did you:			
B1	Suffer any accident? IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in that accident either actively or passively (e.g. not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of this accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Want to harm yourself or to hurt or to injure yourself or have mental images of harming yourself?	NO	YES	2
B5	Think about suicide? IF NO TO B5, SKIP TO B7. OTHERWISE ASK:	NO	YES	6

Frequency		Intensity	
Occasionally	❒	Mild	❒
Often	❒	Moderate	❒
Very often	❒	Severe	❒

	Can you state that you will not act on these impulses during this treatment program?	NO	YES	
B6	Feel unable to control these impulses?	NO	YES	8
B7	Have a suicide plan?	NO	YES	8
B8	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
B9	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
B10	Attempt suicide? IF NO SKIP TO B11: Hope to be rescued / survive ❒ Expected / intended to die ❒	NO	YES	9
	In your lifetime:			
B11	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT B1) CODED **YES**?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B11) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO **YES**

SUICIDALITY CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER .

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO **C1b**: IF **YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO **C2b**: IF **YES** ASK:

b Are you currently feeling persistently irritable? NO YES

➡

IS **C1a** OR **C2a** CODED **YES**? NO YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes Past Episode ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES

		Current Episode		Past Episode	
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RATING CURRENT EPISODE: NO YES NO YES

IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES?
IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?

WHEN RATING PAST EPISODE:
IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES?
IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?

CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.

C4	What is the longest time these symptoms lasted?				
	a) 3 days or less		❒		❒
	b) 4 to 6 days		❒		❒
	c) 7 days or more		❒		❒
C5	Were you hospitalized for these problems?	NO	YES	NO	YES

IF YES, STOP HERE AND CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME.

C6	Did these symptoms cause significant problems at home, at work, socially in your relationships with others, at school or in some other important way?	NO	YES	NO	YES

ARE **C3** SUMMARY AND **C5** AND **C6** CODED **YES** AND EITHER **C4a or b or c** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4c** AND **C6** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO **YES**

MANIC EPISODE

CURRENT ❒
PAST ❒

ARE **C3** SUMMARY **AND C5** AND **C6** CODED **NO** AND EITHER **C4b** OR **C4c** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4b** AND **C6** CODED **YES** AND IS **C5** CODED **NO?**

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO **YES**

HYPOMANIC EPISODE

CURRENT ❒
PAST ❒

ARE **C3** SUMMARY AND **C4a** CODED **YES** AND IS **C5** CODED **NO**? **NO** **YES**

HYPOMANIC SYMPTOMS

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

CURRENT ❒
PAST ❒

C7 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more manic episodes (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more hypomanic EPISODES (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF PAST "HYPOMANIC SYMPTOMS" IS CODED POSITIVE ASK:
Did you have 2 or more episodes of hypomanic SYMPTOMS (**C4a**) in your lifetime
(including the current episode if present)? NO YES

D. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**? IF YES TO D5, SKIP TO D7.	NO	YES *PANIC DISORDER LIFETIME*
D6		IF **D5** = **NO,** ARE ANY D4 ANSWERS CODED **YES**? THEN SKIP TO **E1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*

D7 In the past month, did you have such attacks repeatedly (2 or more), and did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks? NO YES

PANIC DISORDER CURRENT

E. AGORAPHOBIA

E1 Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about? NO YES

IF **E1** = **NO**, CIRCLE **NO** IN **E2**.

E2 Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them? NO YES

AGORAPHOBIA CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

F. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
F2	Is this social fear excessive or unreasonable and does it almost always make you anxious?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them or suffer through them most of the time?	➡ NO	YES
F4	Do these social fears disrupt your normal work, school or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1 In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.)

(DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)

NO YES
↓
SKIP TO **G4**

G2 Did they keep coming back into your mind even when you tried to ignore or get rid of them?

NO YES
↓
SKIP TO **G4**

G3 Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?

NO YES
obsessions

G4 In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?

NO YES
compulsions

➡

IS **G3** OR **G4** CODED **YES**?

NO YES

➡

G5 At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?

NO YES

G6 In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?

NO **YES**

O.C.D. CURRENT

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
H3	During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H4	**In the past month:**			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE **3** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES
H5	**In the past month:**			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE **2** OR MORE **H5** ANSWERS CODED **YES**?	➡ NO	YES

H6	During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?	**NO** **YES** ***POSTTRAUMATIC STRESS DISORDER CURRENT***

I. ALCOHOL DEPENDENCE / ABUSE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

		➡	
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	NO	YES

I2 **In the past 12 months**:

a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? IF **YES** TO ANY, CODE **YES**.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES

ARE **3** OR MORE **I2** ANSWERS CODED **YES**?

***** IF YES, SKIP I3 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO	YES*
ALCOHOL DEPENDENCE **CURRENT**	

I3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

ARE **1** OR MORE **I3** ANSWERS CODED **YES**?

NO	YES
	ALCOHOL ABUSE **CURRENT**

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicoden, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "PeaCe Pill", "Tranq", "Hog"), or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO	YES
	g	If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

***** IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO **YES ***

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **YES**

SUBSTANCE ABUSE
CURRENT

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.
HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.
THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

		Now I am going to ask you about unusual experiences that some people have.			BIZARRE
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES →**K6**
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES →**K6**
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES →**K6**
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, newspapers, books or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES →**K6**
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? INTERVIEWER**:** ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO K6a:** have you heard sounds / voices in the past month?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES →**K8b**

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO YES
↳ **K13**

IF NO TO K11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO K13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **K1**a TO **K7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO K12 AND MOVE TO K13

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

LIFETIME

K12 a ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO K13 AND K14 AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

CURRENT

K13 ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K6b, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS FROM K1b TO K10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM K1a TO K7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

L. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

L1	a	How tall are you?	❑ ft ❑❑ in. ❑❑❑ cm.
	b.	What was your lowest weight in the past 3 months?	❑❑❑ lbs. ❑❑❑ kgs.
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO YES

In the past 3 months:

L2		In spite of this low weight, have you tried not to gain weight?	➡ NO YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO YES
	c	Have you thought that your current low body weight was normal or excessive?	NO YES
L5		ARE 1 OR MORE ITEMS FROM **L4** CODED **YES**?	➡ NO YES
L6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO YES

FOR WOMEN: ARE **L5 AND L6** CODED **YES**?

FOR MEN: IS **L5** CODED **YES**?

NO YES

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

M. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
M3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	YES ↓ Skip to M8
M7	Do these binges occur only when you are under (____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

M8 IS **M5** CODED **YES** AND IS EITHER **M6** OR **M7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **M7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a "worry wart") AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES?**	➡ NO	YES
N4		Do these anxieties and worries disrupt your normal work, school or social functioning or cause you significant distress?	**NO**	**YES**

GENERALIZED ANXIETY DISORDER
CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

O2	**SUMMARY**: HAS AN ORGANIC CAUSE BEEN RULED OUT?	❒ No	❒ Yes	❒ Uncertain

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
		➡	
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO **YES**

ANTISOCIAL PERSONALITY DISORDER
LIFETIME

THIS CONCLUDES THE INTERVIEW

REFERENCES

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry. 1997; 12:232-241.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997; 12: 224-231.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 1998;59(suppl 20):22-33.

Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. European Psychiatry. 1998; 13:26-34.

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A validation study of this instrument was made possible, in part, by grants from SmithKline Beecham and the European Commission.
The authors are grateful to Dr. Pauline Powers for her advice on the modules on Anorexia Nervosa and Bulimia.

MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:

A	Major Depressive Episode
C	(Hypo) manic Episode
K	Psychotic Disorders

MODULE K:

1a	IS **K11b** CODED YES?	NO	YES
1b	IS **K12a** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2 a	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e**?	YES	YES
b	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a**?	YES	YES

c Is a Major Depressive Episode coded YES (current or past)?
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)?
and
is **"**Hypomanic Symptoms" coded NO (current and past)?

Specify:

- If the depressive episode is **current** or **past** or both
- **With Psychotic Features** Current: If 1b or 2a (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) = YES

MAJOR DEPRESSIVE DISORDER

	current	past
MDD	❑	❑

With Psychotic Features

Current	❑
Past	❑

d Is a Manic Episode coded YES (current or past)?

Specify:

- If the Bipolar I Disorder is **current** or **past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES
  and MDE (current and past) = NO
- **With Psychotic Features** Current: If 1b or 2a (current) or 2b (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) or 2b (past) = YES
- If the **most recent episode** is manic, depressed,
  mixed or hypomanic or unspecified (all mutually exclusive)
- **Unspecified** if the Past Manic Episode is coded YES AND
  Current (C3 Summary AND C4a AND C6 AND O2) are coded YES

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Mixed	❑
Hypomanic	❑
Unspecified	❑

e Is Major Depressive Episode coded YES (current or past)?
and
Is Hypomanic Episode coded YES (current or past)?
and
Is Manic Episode coded NO (current and past)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑

f Is MDE coded NO (current and past)
and
Is Manic Episode coded NO (current and past)?
and is either:

1) C7b coded YES for the appropriate time frame?

or

2) C3 Summary coded YES for the appropriate time frame?
and
C4a coded YES for the appropriate time frame?
and
C7c coded YES for the appropriate time frame?

Specify if the Bipolar Disorder NOS is **current** or **past** or both

BIPOLAR DISORDER NOS

	current	past
Bipolar Disorder NOS	❑	❑

M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI. The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Past
	SUBSTANCE INDUCED MOOD DISORDER	Current Past
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)
	MDE WITH CATATONIC FEATURES	Current (2 weeks)
B	DYSTHYMIA	Current (Past 2 years) Past
C	SUICIDALITY	Current (Past Month) Risk: ❑ Low ❑ Medium ❑ High
D	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR DISORDER NOS	Current Past
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current Past
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current Past
	SUBSTANCE INDUCED MANIC EPISODE	Current Past
	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current Past
E	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
F	AGORAPHOBIA	Current
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)
H	SPECIFIC PHOBIA	Current
I	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
J	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
K	ALCOHOL DEPENDENCE	Past 12 Months
	ALCOHOL DEPENDENCE	Lifetime
	ALCOHOL ABUSE	Past 12 Months
	ALCOHOL ABUSE	Lifetime
L	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months
	SUBSTANCE DEPENDENCE (Non-alcohol)	Lifetime
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months

M	PSYCHOTIC DISORDERS	Lifetime
		Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	SCHIZOPHRENIA	Current
		Lifetime
	SCHIZOAFFECTIVE DISORDER	Current
		Lifetime
	SCHIZOPHRENIFORM DISORDER	Current
		Lifetime
	BRIEF PSYCHOTIC DISORDER	Current
		Lifetime
	DELUSIONAL DISORDER	Current
		Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current
		Lifetime
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current
		Lifetime
	PSYCHOTIC DISORDER NOS	Current
		Lifetime
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	MOOD DISORDER NOS	Lifetime
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current
		Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current
		Past
N	ANOREXIA NERVOSA	Current (Past 3 Months)
O	BULIMIA NERVOSA	Current (Past 3 Months)
	BULIMIA NERVOSA PURGING TYPE	Current
	BULIMIA NERVOSA NONPURGING TYPE	Current
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
P	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)
	GENERALIZED ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
Q	ANTISOCIAL PERSONALITY DISORDER	Lifetime
R	SOMATIZATION DISORDER	Lifetime
		Current
S	HYPOCHONDRIASIS	Current
T	BODY DYSMORPHIC DISORDER	Current
U	PAIN DISORDER	Current
V	CONDUCT DISORDER	Past 12 Months
W	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Children/Adolescents)	Past 6 Months
	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Adults)	Lifetime
		Current
X	ADJUSTMENT DISORDERS	Current
Y	PREMENSTRUAL DYSPHORIC DISORDER	Current
Z	MIXED ANXIETY-DEPRESSIVE DISORDER	Current

EDINBURGH HANDEDNESS SURVEY

Subject ID#:_____

Date: _____

Please indicate your preferences in the use of hands in the following activities by putting a + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. If in any case you are really indifference put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which the hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife [without fork]		
7	Spoon		
8	Broom [upper hand]		
9	Striking Match [match]		
10	Opening Box [lid]		

Do not write below this line

L.Q.:_____ DECILE: _____

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Personality Assessment Inventory™ (PAI®)

Leslie C. Morey, PhD



Revised and updated materials help increase the accuracy of personality assessment.

Purpose:	22 nonoverlapping full scales provide a comprehensive assessment of adult psychopathology in ages 18 years and older
Age Range:	Adult Elder Adult
Admin:	Individual or group
Time:	50-60 minutes to administer; 15-20 minutes to score
Qualification:	C
Sample Reports:	N/A
Related Products:	PAI® Professional Report Service PAI® Software Portfolio Personality Assessment Inventory™-Adolescent

With its newly revised Professional Manual, Profile Form Adults-Revised, and Critical Items Form-Revised, the PAI® continues to raise the standard for the assessment of adult psychopathology. This objective inventory of adult personality assesses psychopathological syndromes and provides information relevant for clinical diagnosis, treatment planning, and screening for psychopathology. Since its introduction, the PAI has been heralded as one of the most important innovations in the field of clinical assessment.

PAI® Scales and Subscales

The 344 PAI items constitute 22 nonoverlapping scales covering the constructs most relevant to a broad-based assessment of mental disorders: 4 validity scales, 11 clinical scales, 5 treatment scales, and 2 interpersonal scales. To facilitate interpretation and to cover the full range of complex clinical constructs, 10 scales contain conceptually derived subscales.

The PAI Clinical scales were developed to provide information about critical diagnostic features of 11 important clinical constructs. These 11 scales may be divided into three broad classes of disorders: those within the neurotic spectrum, those within the psychotic spectrum, and those associated with behavior disorder or impulse control problems.

The Treatment scales were developed to provide indicators of potential complications in treatment that would not necessarily be apparent from diagnostic information. These five scales include two indicators of potential for harm to self or others, two measures of the respondent's environmental circumstances, and one indicator of the respondent's motivation for treatment.

The Interpersonal scales were developed to provide an assessment of the respondent's interpersonal style along two dimensions: a warmly affiliative versus a cold rejecting style, and a dominating/controlling versus a meekly submissive style. These axes provide a useful way of conceptualizing many different mental disorders: persons at the extremes of these dimensions may present with a variety of disorders. A number of studies provide evidence that diagnostic groups differ on these dimensions.

The PAI includes a Borderline Features scale and an Antisocial Features scale. Both of these scales specifically assess character pathology. The Borderline Features scale is the only PAI scale that has four subscales, reflecting the factorial complexity of the construct. The Antisocial Features scale includes a total of three facets: one assessing antisocial behaviors, and the other two assessing antisocial traits.

WASI-II Record Form

WECHSLER ABBREVIATED SCALE OF INTELLIGENCE — SECOND EDITION

Calculation of Examinee's Age

Test Date: Year ____ Month ____ Day ____

ID: ____

Sex: ☐ F ☐ M Handedness: ☐ R ☐ L

Test Age: ____

Address/School/Testing Site: ____

Highest Education/Grade: ____

Examiner Name: ____

Total Raw Score to *T* Score Conversion

Subtest	Raw Score	*T* Scores			
Block Design					
Vocabulary					
Matrix Reasoning					
Similarities					
Sum of *T* Scores					
		Verbal Comp.	Perc. Rsng.	Full Scale–4	Full Scale–2

Examinee Visual/Hearing Aids During Testing

Check type of aid examinee needed:	Used	Not Used
☐ Glasses	☐	☐
☐ Prescription Lenses	☐	☐
☐ Assisted Listening Device	☐	☐
☐ Other:	☐	☐

Sum of *T* Scores to Composite Score Conversion

Scale	Sum of *T* Scores	Composite Score	Percentile Rank	Confidence Interval 90% or 95%
Verbal Comp.		VCI			–
Perc. Rsng.		PRI			–
Full Scale–4		FSIQ–4			–
Full Scale–2		FSIQ–2			–

Ranges of Expected Scores

Scores:	Confidence Level 90%	68%
FSIQ–4		
WISC-IV FSIQ	–	–
WAIS-IV FSIQ	–	–

Subtest *T* Score Profile

	Verbal Comprehension		Perceptual Reasoning	
	VC	SI	BD	MR
80				
75				
70				
65				
60				
55				
50				
45				
40				
35				
30				
25				
20				

Composite Score Profile

	VCI	PRI	FSIQ
160			
155			
150			
145			
140			
135			
130			
125			
120			
115			
110			
105			
100			
95			
90			
85			
80			
75			
70			
65			
60			
55			
50			
45			
40			

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3 4 5 6 7 8 9 10 11 12 A B C D E 282563-1 3

Product Number 0158981596

1. Block Design

(Time limit: See item)

Start
Ages 6–8: Item 1
Ages 9–90: Item 3

Reverse
Ages 9–90: Does not obtain a perfect score on *either* Item 3 or Item 4, administer the preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue
After 2 consecutive scores of 0.

Stop
Ages 6–8: After Item 11.

Record & Score
Items 1–4: Score 0, 1, or 2 points.
Items 5–13: Score 0, 4, 5, 6, or 7 points.

	Design	Presentation Method	Time Limit	Completion Time		Constructed Design		Score				
6–8	1. Examinee / Examiner	Model and Picture	30"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	2.	Model and Picture	30"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
9–90	3.	Model and Picture	45"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	4.	Model and Picture	45"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	5.	Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	6.	Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	7.	Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	8.	Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	9.	Picture	120"					0	71–120 4	46–70 5	31–45 6	1–30 7
	10.	Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
	11.	Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
6–8 STOP	12.	Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
	13.	Picture	120"					0	101–120 4	81–100 5	56–80 6	1–55 7

Maximum Raw Score
Ages 6–8: 57
Ages 9–90: 71

Block Design Total Raw Score ____

2. Vocabulary

Start
Ages 6–90:
Item 4

Reverse
Ages 6–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue
After 3 consecutive scores of 0.

Stop
Age 6:
After Item 22.
Ages 7–11:
After Item 25.
Ages 12–14:
After Item 28.

Record & Score
Items 1–3: Score 0 or 1 point.
Items 4–5: Score 0 or 2 points.
Items 6–31: Score 0, 1, or 2 points.
See the Manual for sample responses.

	Item	Response	Score
	1. Fish		0 1
	2. Shovel		0 1
	3. Shell		0 1
6–90	†4. Shirt		0 2
	5. Car		0 2
	6. Lamp		0 1 2
	7. Bird		0 1 2
	8. Tongue		0 1 2
	9. Pet		0 1 2
	10. Lunch		0 1 2
	11. Bell		0 1 2
	12. Calendar		0 1 2
	13. Alligator		0 1 2
	14. Dance		0 1 2

†If the examinee provides a 2-point response that requires feedback or gives an incorrect (0 point) response, provide corrective feedback as instructed in the Manual.

continue

2. Vocabulary *(continued)*

Discontinue after 3 consecutive scores of 0.

	Item	Response	Score
	15. Summer		0 1 2
	16. Reveal		0 1 2
	17. Decade		0 1 2
	18. Entertain		0 1 2
	19. Tradition		0 1 2
	20. Enthusiastic		0 1 2
	21. Improvise		0 1 2
	22. Haste		0 1 2
6 STOP	23. Trend		0 1 2
	24. Impulse		0 1 2
	25. Ruminate		0 1 2
7–11 STOP	26. Mollify		0 1 2
	27. Extirpate		0 1 2
	28. Panacea		0 1 2
12–14 STOP			

continue

2. Vocabulary *(continued)*

Discontinue after **3** consecutive scores of 0.

Item	Response	Score
29. Perfunctory		0 1 2
30. Insipid		0 1 2
31. Pavid		0 1 2

Maximum Raw Score
Age 6: 41
Ages 7–11: 47
Ages 12–14: 53
Ages 15–90: 59

Vocabulary Total Raw Score ____

3. Matrix Reasoning

Start
Ages 6–8: Sample Items A & B, then Item 1
Ages 9–90: Sample Items A & B, then Item 4

Reverse
Ages 9–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in **reverse** order until two consecutive perfect scores are obtained.

Discontinue
After **3** consecutive scores of 0.

Stop
Ages 6–8: After Item 24.

Record & Score
Score **0** or **1** point.
Correct responses are in **color**.

	Item	Response					Score	
6–90	SA.	1	**2**	3	4	5		
	SB.	1	2	**3**	4	5		
6–8	1.	1	**2**	3	4	5	0	1
	2.	**1**	2	3	4	5	0	1
	3.	1	2	**3**	4	5	0	1
9–90	4.	**1**	2	3	4	5	0	1
	5.	1	2	3	4	**5**	0	1
	6.	**1**	2	3	4	5	0	1
	7.	1	2	**3**	4	5	0	1
	8.	1	2	**3**	4	5	0	1
	9.	1	2	3	**4**	5	0	1
	10.	1	**2**	3	4	5	0	1
	11.	1	2	**3**	4	5	0	1
	12.	1	2	3	**4**	5	0	1
	13.	**1**	2	3	4	5	0	1
	14.	1	2	3	**4**	5	0	1
	15.	1	**2**	3	4	5	0	1
	16.	1	2	3	4	**5**	0	1
	17.	1	2	3	**4**	5	0	1
	18.	1	**2**	3	4	5	0	1
	19.	1	2	3	**4**	5	0	1
	20.	1	**2**	3	4	5	0	1
	21.	1	2	**3**	4	5	0	1
	22.	1	2	**3**	4	5	0	1
	23.	**1**	2	3	4	5	0	1
6–8 STOP	24.	1	2	3	**4**	5	0	1
	25.	1	2	3	**4**	5	0	1
	26.	1	**2**	3	4	5	0	1
	27.	1	2	3	4	**5**	0	1
	28.	1	2	3	4	**5**	0	1
	29.	**1**	2	3	4	5	0	1
	30.	1	**2**	3	4	5	0	1

Maximum Raw Score
Ages 6–8: 24
Ages 9–90: 30

Matrix Reasoning Total Raw Score ____

4. Similarities

Start
Ages 6–8: Item 1
Ages 9–90: Item 4

Reverse
Ages 9–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in **reverse** order until two consecutive perfect scores are obtained.

Discontinue
After **3** consecutive scores of 0.

Stop
Ages 6–8: After Item 22.

Record & Score
Items 1–3: Score **0** or **1** point. Correct responses are in **color**.
Items 4–5: Score **0** or **2** points.
Items 6–24: Score **0**, **1**, or **2** points. See Manual for sample responses.

	Picture Item	Response	Score
6–8	†1.	1 2 **3** 4 5	0 1

Picture Item	Response	Score
2.	1 2 3 **4** 5	0 1

Picture Item	Response	Score
3.	1 **2** 3 4 5	0 1

	Verbal Items	Response	Score
9–90	§† 4. Green–Blue		0 2
	§† 5. Square–Triangle		0 2
	6. Cow–Bear		0 1 2
	7. Shirt–Jacket		0 1 2
	8. Pen–Crayon		0 1 2
	9. Hat–Umbrella		0 1 2
	10. Airplane–Bus		0 1 2
	11. Door–Window		0 1 2
	12. Child–Adult		0 1 2

§If the examinee provides a response that suggests he or she does not understand the task, provide the specified prompt in the Manual.

†If the examinee provides a 2-point response that requires feedback or provides an incorrect (0 point) response, provide corrective feedback as instructed in the Manual.

continue

4. Similarities *(continued)*

Discontinue after **3** consecutive scores of 0.

Verbal Items	Response	Score
13. Shoulder–Ankle		0 1 2
14. Love–Hate		0 1 2
15. Smooth–Rough		0 1 2
16. Hand–Flag		0 1 2
17. Wall–Line		0 1 2
18. Heat–Wind		0 1 2
19. More–Less		0 1 2
20. Shadow–Echo		0 1 2
21. Tradition–Habit		0 1 2
22. Peace–War		0 1 2
6–8 STOP 23. Time–Progress		0 1 2
24. Memory–Practice		0 1 2

Maximum Raw Score
Ages 6–8: 41
Ages 9–90: 45

Similarities Total Raw Score ____

WASI®-II

WECHSLER ABBREVIATED SCALE OF INTELLIGENCE®— SECOND EDITION

Examinee Name: Age:

Parent/Guardian Name:

Examiner Name:

Record Form

Behavioral Observations

Referral source/Reason for referral/Presenting complaint(s)

Physical appearance

Language (e.g., first/native language, other language, English fluency, expressive and receptive language ability, articulation)

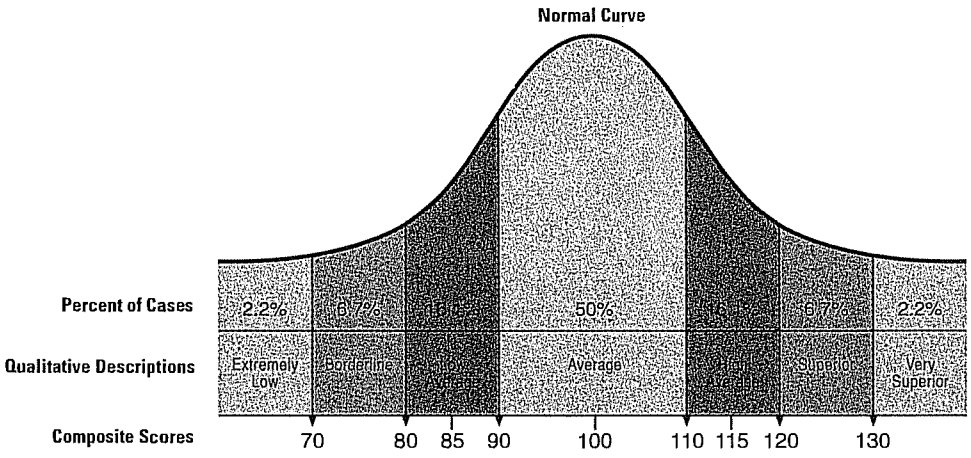
Attention and concentration

Attitude toward testing (e.g., rapport, eager to speak, working habits, interest, motivation, reaction to success/failure)

Affect/Mood

Unusual behaviors/Verbalizations (e.g., perseverations, stereotypic movements, bizarre and atypical verbalizations)

Other notes



PEARSON

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Printed in the United States of America.

Subject: _____ Date: _____ Time: ____:____

SSS #1

Please put an **X** next to the statement that best describes how you feel:

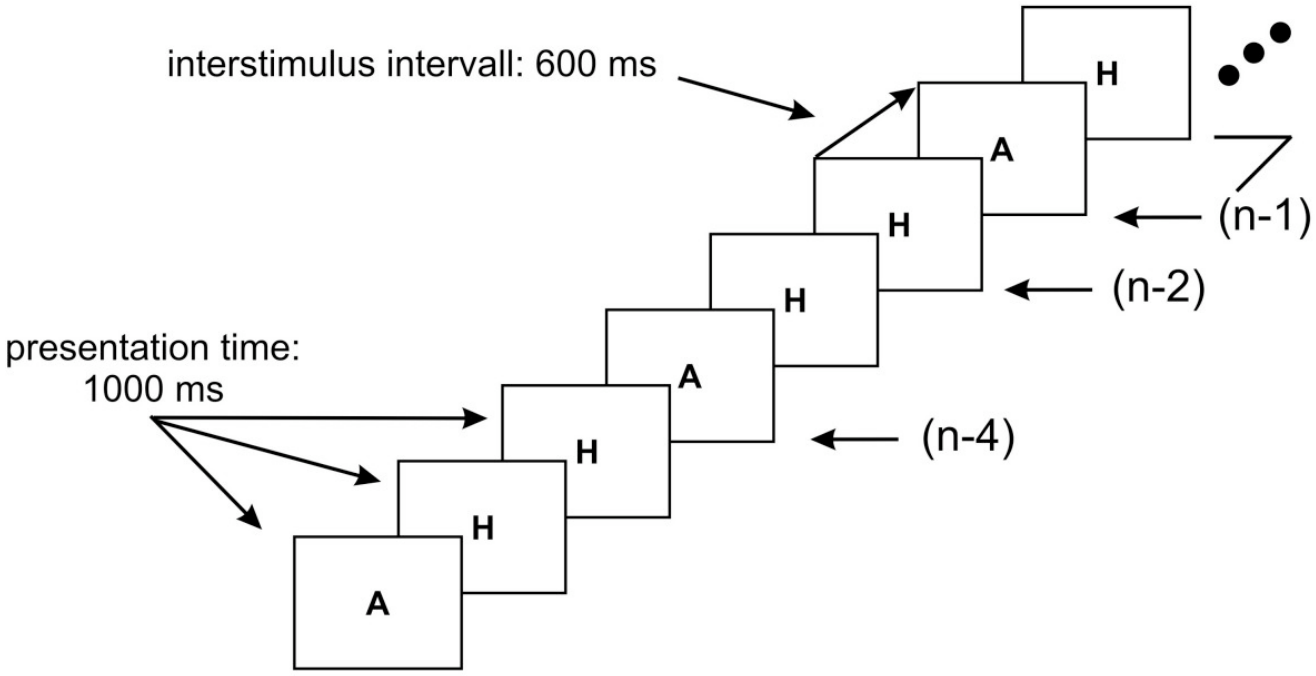
Right now I am:

- ☐ Feeling active, vital, alert or wide awake
- ☐ Functioning at high levels, but not at peak; able to concentrate
- ☐ Awake, but relaxed; responsive but not fully alert
- ☐ Somewhat foggy, let down
- ☐ Foggy; losing interest in remaining awake; slowed down
- ☐ Sleepy, woozy, fighting sleep; prefer to lie down
- ☐ No longer fighting sleep, sleep onset soon; having dream-like thoughts
- ❖ Asleep

Multi-Source Interference Task (MSIT)



N-back task


interstimulus intervall: 600 ms
presentation time:
1000 ms
H
A
H
H
A
H
H
A
(n-1)
(n-2)
(n-4)

RBANS™

Repeatable Battery for the Assessment of Neuropsychological Status

Christopher Randolph

Record Form A

Subject #_____ Age____ Sex____ Education Level _____

Examiner_____ Date of Testing_____ Ethnicity_____

Observations: _____

_____

_____

	Immediate Memory	Visuospatial/ Constructional	Language	Attention	Delayed Memory	Total Scale
Index Score						
Confidence Interval ____%						
Percentile						

Index Score	Percentile Rank	Total Scale Index Score
160	>99.9	160
155	>99.9	155
150	>99.9	150
145	99.9	145
140	99.6	140
135	99	135
130	98	130
125	95	125
120	91	120
115	84	115
110	75	110
105	63	105
100	50	100
95	37	95
90	25	90
85	16	85
80	9	80
75	5	75
70	2	70
65	1	65
60	0.4	60
55	0.1	55
50	<0.1	50
45	<0.1	45
40	<0.1	40

ISBN 015-4166-03-0

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PsychCorp

0154166030

1 List Learning

Trial 1

Say *I am going to read you a list of words. I want you to listen carefully and, when I finish, repeat back as many words as you can. You don't have to say them in the same order that I do—just repeat back as many words as you can remember, in any order. Okay?*

Trials 2–4

Say *I am going to read the list again. When I finish, repeat back as many words as you can, even if you have already said them before. Okay?*

Record responses in order.

Scoring: 1 point for each word correctly recalled on each trial.

List	Trial 1	Trial 2	Trial 3	Trial 4
Market				
Package				
Elbow				
Apple				
Story				
Carpet				
Bubble				
Highway				
Saddle				
Powder				

Number Correct		+		+		+		=	
	Total Trial 1		Total Trial 2		Total Trial 3		Total Trial 4		Total Score Range=0–40

2 Story Memory

Trial 1

Say ***I am going to read you a short story. I'd like you to listen carefully and, when I finish, repeat back as much of the story as you can remember. Try and use the same wording, if you can. Okay?***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Trial 2

Say ***I am going to read that same story again. When I finish, I want you to again repeat back as much of the story as you can remember. Try to repeat it as exactly as you can.***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Scoring: 1 point for *verbatim* recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story	Responses	Trial 1 Score (0 or 1)	Trial 2 Score (0 or 1)	Item Score (0–2)
1. On ***Tuesday,***				
2. ***May***				
3. ***Fourth,***				
4. in ***Cleveland,*** Ohio,				
5. a ***3 alarm***				
6. ***fire*** broke out.				
7. ***Two***				
8. ***hotels***				
9. and a ***restaurant***				
10. were ***destroyed***				
11. before the ***firefighters (firemen)***				
12. were able to ***extinguish it (put it out).***				
			Total Score (Trial 1 + Trial 2) Range=0–24	

3 Figure Copy

Time Limit: 4 minutes

Fold this page back and present the Figure Copy Drawing Page along with the stimulus. Ask the examinee to make an exact copy of the figure. Tell the examinee that he or she is being timed, but that the score is based *only* on the exactness of his or her copy.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

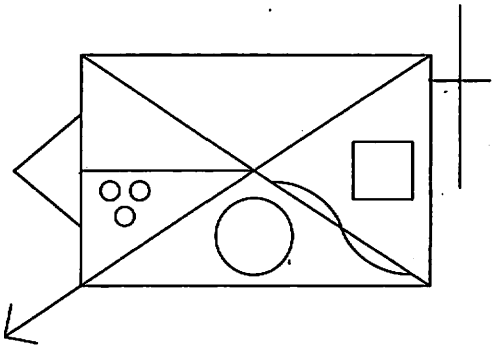


Figure Copy Criteria

(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of staff **Placement:** must protrude from appropriate corner of rectangle such that staff appears to be continuation of diagonal cross
		Total Score Range=0–20		

Figure Copy Drawing Page

(Fold back for use.)

4 Line Orientation

Time Limit: 20 seconds/item

Present the sample item, and say ***These two lines down here*** (indicate) ***match two of the lines on top. Can you tell me the numbers, or point to the lines that they match?*** Correct any errors and make sure the examinee understands the task. Continue with Items 1–10.

Scoring: 1 point for each line correctly identified.

Item	Responses	Correct Responses	Score (0, 1, or 2)
Sample		1, 7	
1.		10, 12	
2.		4, 11	
3.		6, 9	
4.		8, 13	
5.		2, 4	

Item	Responses	Correct Responses	Score (0, 1, or 2)
6.		1, 6	
7.		3, 10	
8.		5, 8	
9.		1, 3	
10.		11, 13	
		Total Score Range=0–20	

5 Picture Naming

Time Limit: 20 seconds/item

Ask the examinee to name each picture. Give the semantic cue only if the picture is obviously misperceived.

Scoring: 1 point for each item that is correctly named spontaneously or following semantic cue.

Item	Semantic Cue	Responses	Score (0 or 1)
1. chair	a piece of furniture		
2. pencil	used for writing		
3. well	you get water from it		
4. giraffe	an animal		
5. sailboat	used on the water (if "boat," query "what kind")		
6. cannon	a weapon, used in war		
7. pliers	a tool		
8. trumpet	a musical instrument ("cornet" okay)		
9. clothespin	used to hold laundry on a line		
10. kite	it's flown in the air		
		Total Score Range=0–10	

6 Semantic Fluency

Time Limit: 60 seconds

Say ***Now I'd like you to tell me the names of all of the different kinds of fruits and vegetables that you can think of. I'll give you one minute to come up with as many as you can. Ready?***

Scoring: 1 point for each correct response.

1. _____	11. _____	21. _____	31. _____
2. _____	12. _____	22. _____	32. _____
3. _____	13. _____	23. _____	33. _____
4. _____	14. _____	24. _____	34. _____
5. _____	15. _____	25. _____	35. _____
6. _____	16. _____	26. _____	36. _____
7. _____	17. _____	27. _____	37. _____
8. _____	18. _____	28. _____	38. _____
9. _____	19. _____	29. _____	39. _____
10. _____	20. _____	30. _____	40. _____

Total Score
Range=0–40 ☐

7 Digit Span

Say ***I am going to say some numbers, and I want you to repeat them after me. Okay?***
Read the numbers at the rate of 1 per second. Only read the second string in each set if the first string was failed. Discontinue after failure of both strings in any set.

Scoring: 2 points for the first string correct, 1 point for the second string correct, and 0 points for both strings failed.

Item First String	String Score (0 or 2)	Second String	String Score (0 or 1)	Item Score (0–2)
1. 4—9		5—3		
2. 8—3—5		2—4—1		
3. 7—2—4—6		1—6—3—8		
4. 5—3—9—2—4		3—8—4—9—1		
5. 6—4—2—9—3—5		9—1—5—3—7—6		
6. 2—8—5—1—9—3—7		5—3—1—7—4—9—2		
7. 8—3—7—9—5—2—4—1		9—5—1—4—2—7—3—8		
8. 1—5—9—2—3—8—7—4—6		5—1—9—7—6—2—3—6—5		

Total Score
Range=0–16 ☐

8 Coding

Time Limit: 90 seconds

Say ***Look at these boxes*** (indicate key). ***For each one of these marks there is a number that goes with it. Down here there are marks, but no numbers. I want you to fill in the number that goes with each mark.***

Demonstrate the first three. Say ***Now I would like you to fill in the rest of these boxes up to the double lines*** (indicate) ***for practice.*** Correct any errors as they are made. Make sure that the examinee understands the task and has correctly completed the sample items before you begin timing.

Say ***Now I would like you to continue to fill in the numbers that match the marks. Go as quickly as you can without skipping any. When you reach the end of the line, go on to the next one. Ready? Go ahead.***

Redirect the examinee to the task if he or she becomes distracted. If the examinee is unable to comprehend the task, the subtest score is 0.

Scoring: 1 point for each item correctly coded within 90 seconds (*do not* score the sample items).

Note: Familiarize yourself with these instructions before administering this subtest.

Total Score Range=0–89	

9 List Recall

Say ***Do you remember the list of words that I read to you in the beginning? Tell me as many of those words as you can remember now.***

Scoring: 1 point for each word correctly recalled.

List (Do not read.)	Response	Score (0 or 1)
Market		
Package		
Elbow		
Apple		
Story		
Carpet		
Bubble		
Highway		
Saddle		
Powder		
	Total Score Range=0–10	

10 List Recognition

Say ***I'm going to read you some words. Some of these words were on that list, and some of them weren't. I want you to tell me which words were on the list.*** For each word, ask ***Was_____ on the list?***

Scoring: 1 point for each word correctly identified. Circle the letter corresponding to examinee's response (y = yes, n = no); bold, capitalized (**Y, N**) letter indicates correct response.

List	Circle One	List	Circle One	List	Circle One	List	Circle One
1. **Apple**	**Y** n	6. sailor	y **N**	11. **Bubble**	**Y** n	16. **Saddle**	**Y** n
2. honey	y **N**	7. velvet	y **N**	12. prairie	y **N**	17. **Powder**	**Y** n
3. **Market**	**Y** n	8. **Carpet**	**Y** n	13. **Highway**	**Y** n	18. angel	y **N**
4. **Story**	**Y** n	9. valley	y **N**	14. oyster	y **N**	19. **Package**	**Y** n
5. fabric	y **N**	10. **Elbow**	**Y** n	15. student	y **N**	20. meadow	y **N**
						Total Score Range=0–20	

11 Story Recall

Say: ***Do you remember that story about a fire that I read to you earlier? Tell me as many details from the story as you can remember now.***

Scoring: 1 point for each verbatim recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story (Do not read.)	Responses	Item Score (0 or 1)
1. On ***Tuesday,***		
2. ***May***		
3. ***Fourth,***		
4. in ***Cleveland,*** Ohio,		
5. a ***3 alarm***		
6. ***fire*** broke out.		
7. ***Two***		
8. ***hotels***		
9. and a ***restaurant***		
10. were ***destroyed***		
11. before the ***firefighters (firemen)***		
12. were able to ***extinguish it (put it out).***		
	Total Score Range=0–12	

12 Figure Recall

Say ***Do you remember that figure that I had you copy? I want you to draw as much of it as you can remember now. If you remember a part, but you're not sure where it goes, put it anywhere. Try to draw as much of it as you can.***

Now, present the Figure Recall Drawing Page.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet.A for complete scoring criteria and scoring examples.

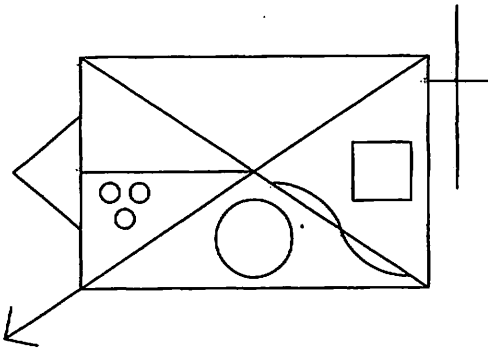


Figure Recall Criteria

(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of staff **Placement:** must protrude from appropriate corner of rectangle such that staff appears to be continuation of diagonal cross
		Total Score Range=0–20		

Figure Recall Drawing Page

(Fold back for use.)

ANAM4™

Automated Neuropsychological Assessment Metrics

Quick Start Guide

Scope of This Document

This is a quick start reference to familiarize a first-time user with the basic concepts and operations of the ANAM4™ software.

Disclaimer

The ANAM4™ testing system does not constitute the practice of medicine or the provision of professional health care advice. The information provided by ANAM4™ software is of a general nature and does not represent medical advice, a diagnosis, or prescription for treatment. You are advised to seek the advice of a qualified medical professional or researcher for interpretation of test results. C-SHOP and the University of Oklahoma are not responsible for any decisions made based on information obtained using ANAM4™ software. Your qualified medical professional has the sole responsibility for establishing diagnosis and suggesting appropriate treatment.

Further Reading

For additional information regarding ANAM4™ or ANAM4™ data files, please refer to the ANAM4™ User Guide.

Revision 3, March 2007
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Requirements

Hardware Requirements

The ANAM4™ system is designed for use on personal computer systems. Minimum hardware requirements include the following:

- **Processor speed:** Pentium 90 MHz microprocessor.
- **Memory:** 32 MB RAM.
- **Storage:** The core ANAM4™ test system requires a minimum of approximately 25MB. Due to data storage requirements and to ensure optimal performance, at least 150MB of free space is highly recommended. A full ANAM4™ installation including ancillary modules (ADEPT™/APR™) requires approximately 50MB of space (130MB if the .NET Framework v2.0 is not already present). Due to data storage requirements and to ensure optimal performance, at least 300MB of free space prior to installation is highly recommended.
- **Response device:** Most standard input devices are supported, including a serial mouse, USB mouse and keyboard, and PS/2 mouse and keyboard. When using laptop computers, most internal keyboards and pointing devices will be adequate for most ANAM4 test modules, but the use of external input devices is highly recommended where practical.

Software Requirements

- **Operating system:** Windows 95/98/2000, NT4.0, or XP. To date, ANAM4™ has not been fully tested on Windows ME or Windows Vista.
- **Windows updates:** Application of all Windows updates. Updates are available at: http://update.microsoft.com
- **Flash animation:** For operating systems older than Windows XP, Adobe Flash Player is required to view the opening logo screen. Flash may be acquired via free download: http://www.adobe.com/go/getflashplayer

  Note: When installing Flash Player via the website, uncheck the accompanying Yahoo toolbar before clicking "Install Now" unless you desire the toolbar.

1 Installing and Running ANAM4™

The ANAM4™ test system consists of a library of tests designed for a broad spectrum of clinical and research applications. This library of computer-based tests was constructed to meet the need for precise measurement of cognitive processing efficiency in a variety of psychological assessment contexts that include neuropsychology, readiness to perform, neurotoxicology, pharmacology, and human factors research.

ANAM4™ will be automatically installed from the installation CD. If the installation does not begin automatically, click Start > Run on the task bar. Type your CD drive letter followed by :\Setup (e.g., D:\Setup or E:\Setup). Finally, click **OK** to proceed with the installation.

The default installation directory is C:\Program Files\C-SHOP\ANAM4.

Upon installation, a desktop icon for ANAM4™ will be created. 

To run ANAM4™, double-click on the ANAM4™ icon located on your desktop, the AnamMenu.exe file located in the C:\Program Files\C-SHOP\ANAM4 directory, or the ANAM4 program listed in start->Programs->ANAM4.

2 Starting ANAM4™

Starting ANAM4™

1. Double-click the ANAM4 icon on your desktop.

ANAM4 Splash Screen

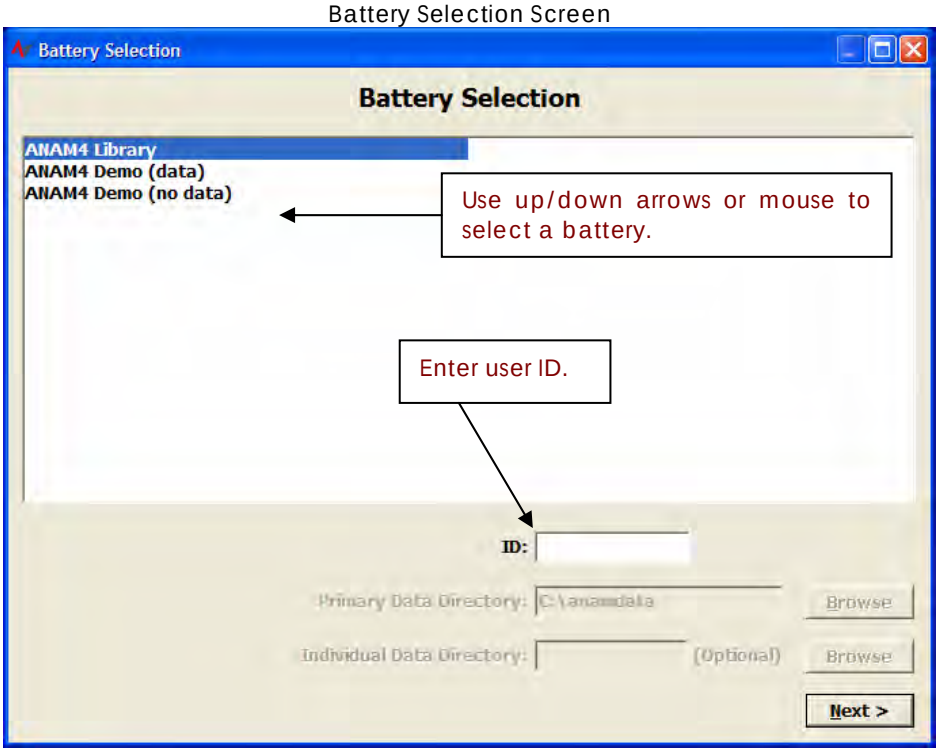


Selecting a Battery and Entering the User ID

The *Battery Selection* screen allows the user to choose a battery, specify an ID number, and specify data directories.

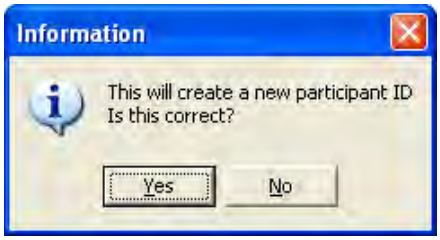
1. Use the up/down cursor keys or mouse to select the desired ANAM4™ battery.

Battery Selection Screen



2. Enter a user ID. The user ID can be any alphanumeric character string.

Note: If a test ID is entered that has never been used on this computer, you will be asked to verify that you are creating a new participant ID. If this is correct, click **Yes**. If the session is a repeat administration for this person (thus, the participant ID has been used previously), you will not receive this prompt.



Changing Data Directories (Folders)

The default data storage directory is C:\anamdata. All data files will be stored in this directory unless specified otherwise.

To change the Primary Data Directory or Individual Data Directory:

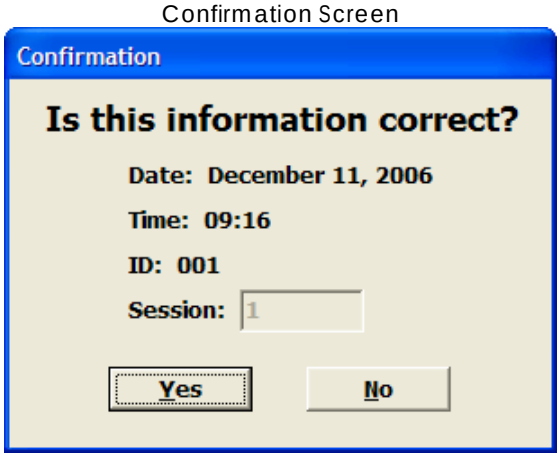
1. Press <**Alt**><**F1**>. This will unlock the *Primary Data Directory* and *Individual Data Directory* fields for modification.
2. Type the path location of the directory for data storage or click **Browse**. If you select Browse, navigate to the directory where you would like to store the ANAM data files.

After confirming all information on the *Battery Selection* screen, Press **Enter** or click **Next** to continue.

Confirming Date, Time, ID, and Session Number

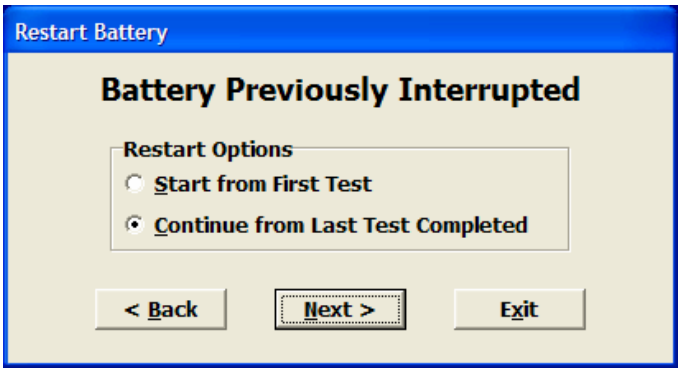
1. Confirm that the Date and Time on your computer are accurately set. If not, click on **No**, close the *Battery Selection* screen that reappears by clicking on the red close button at the upper right corner, correct the Date/Time setting, and restart ANAM4™.
2. Confirm that the correct Session number is about to be run. If you are certain that it needs to be changed, press <**Alt**><**F1**> to unlock the field and enter the desired session number.

Confirmation Screen



Restarting a Previously Cancelled Battery

1. If the specified Session was previously canceled before completion, you may see the following screen asking if you wish to *Start from First Test* or *Continue from Last Test Completed*. You are also allowed to go back to the *Battery Selection* screen.

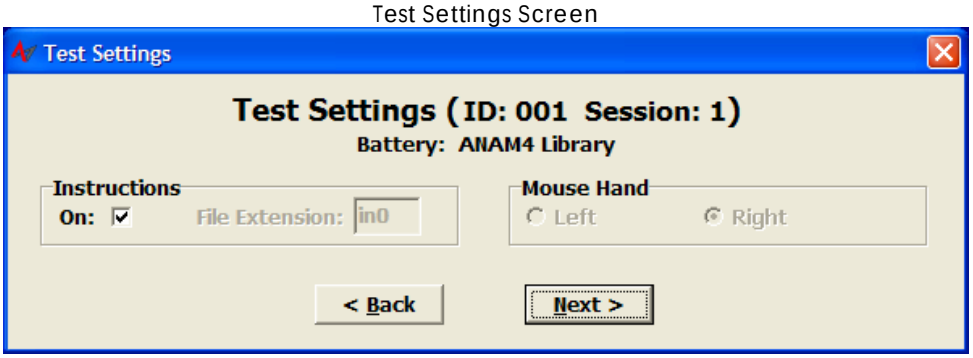


2. Once you have selected the desired option, click on **Next** to continue.

Selecting Test Settings

The *Test Settings* screen allows the user to customize the ANAM4™ test session.

Test Settings Screen



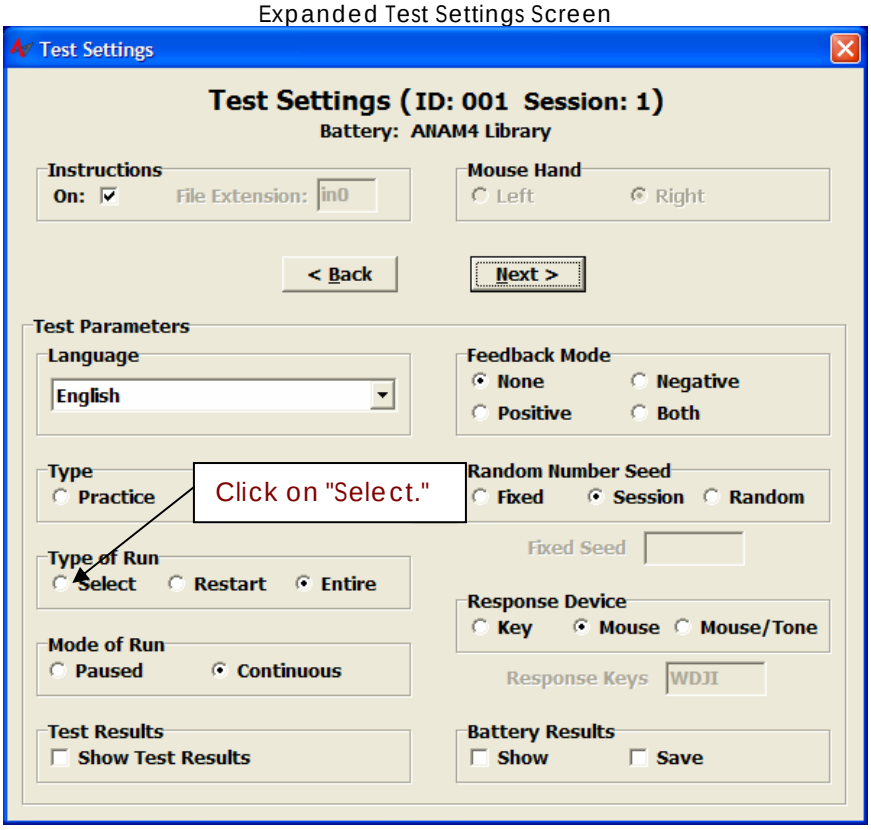
Note: After using the battery a few times for a particular person, you may wish to turn off instructions by deselecting the "Instructions" box. Make sure it is checked **On** the first time through.

1. If you have a participant who uses the computer mouse with the left hand and you wish to obtain responses using the left hand, press <**Alt**><**F1**> to unlock the Mouse Hand setting and select **Left**.
2. If the Test Settings are correct, press **Enter** or click on **Next** to begin the testing.

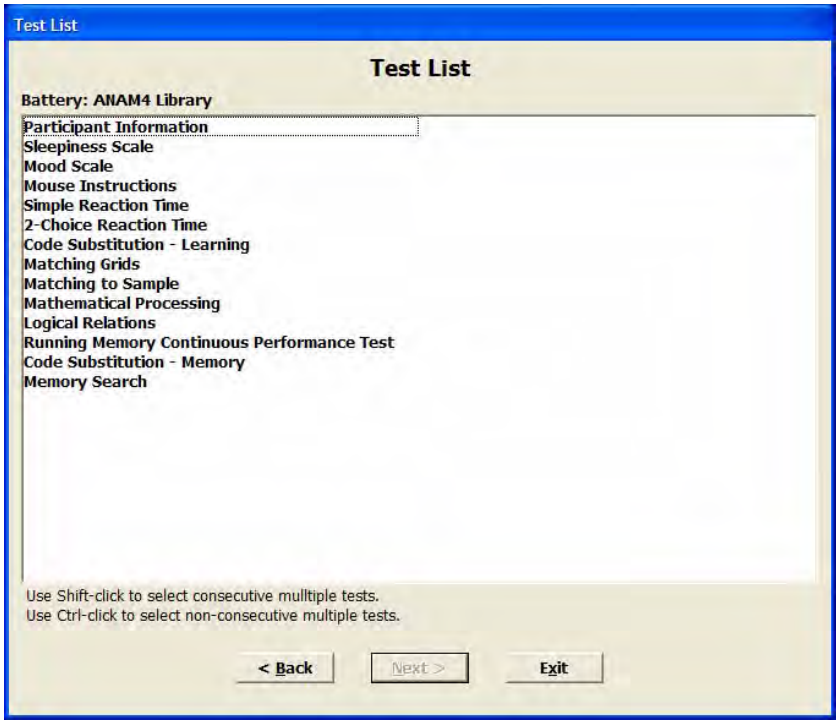
Selecting a Specific Test or Subset of Tests

1. If you wish to select a single test or subset of tests, press <**Alt**><**F2**> and then click on **Select** under Type of Run.

Expanded Test Settings Screen



2. Press **Enter** or click on **Next** to continue. The list of tests within the battery will appear on the next screen.



3. After selecting the desired test or set of tests using the instructions at the bottom of the screen, press **Enter** or click on **Next** to continue.

Proceeding through the Battery

1. Tests will proceed in sequence.

   Note: If instructions are On, the typical sequence for each test is one or more pages of instructions, a screen with the test name, the test itself, and (if selected from the *Test Settings* screen) a feedback screen summarizing individual Test Results.

2. If you wish to abort from any test (end the test without collecting data), press <**Alt**><**F1**> at any time following the instructions screen(s).

   Note: The <**Alt**><**F1**> exit function works ONLY after the display of test instructions is complete.



3. After the test aborts, you will see the above window. If you wish to cancel the rest of the battery, click **Yes**. If you wish to continue with the remaining tests, click **No**.
4. At the conclusion of the battery, you will see a "Thank You" message informing you that the Test Battery is complete.



ANAM4™ Data

Four types of data files are generated following test administration through the ANAM4™ test system as follows:

- Summary Data Files in Text Format (CSV) – summary statistics computed across all items/trials of a given test (without variable labels)
- Raw Data Files in Text Format (CSV) – individual item/trial information (without variable labels)
- Summary Data Files in XML Format – summary statistics computed across all items/trials of a given test (with variable labels)
- Raw Data Files in XML Format – Individual item/trial information (with variable labels).

File Naming

Data filenames are coded in the following manner. The first letter represents the type of file as follows:

- **S** for summary data in text format
- **R** for raw data in text format
- **X** for summary data in XML format
- **Z** for raw data in XML format.

The next sequence of characters corresponds to the participant ID code (of variable length). The ID code is followed by a P or T designating a Practice or Test session, respectively. The final portion of the filename indicates the session number. A three-letter file extension is used to identify the specific test. A list of test extensions can be found in **Chapter 4**.

> Example: ***S32545T01.SRT*** is a summary data file for participant 32545 for Test Session number 1 of the Simple Reaction Time test.

ANAM4™ Data Directories

The default *Primary Data Directory* is C:\anamdata. Data from all completed tests will be saved in this directory. By default, no *Individual Data Directory* is specified. For information on changing the *Primary Data Directory* or *Individual Data Directory*, see **Chapter 2**.



ANAM4™ Tests

ANAM4™ Test Names, Modules, and Extensions

Test Name	Module Name (.exe)	Extension
2-Choice Reaction Time	2choice	.2ch
4-Choice Reaction Time	4choice	.4ch
Code Substitution		
Learning	codesub	.cds
Immediate	codesub	.cdi
Delayed	codesub	.cdd
Demographics	demog	.sub
Digit Reaction Time	digitrt	.drt
Dual Task (Tracking / Memory)	dualtask	.dtn
Grammatical Reasoning	gram	.grm
Logical Relations	logical	.lrs
Manikin	manikin	.mkn
Matching Grids	matching	.mtg
Matching to Sample	mat2samp	.m2s
Mathematical Processing	math	.mth
Memory Search	stern	.stn
Mental State Exam	mse	.mse
Mood Scale	mood	.moo
Procedural Reaction Time	procrt	.pro
Pursuit Tracking	pursuit	.pur
Reaction Time	react	.rct
Relative Judgment	reljudg	.rlj
Running Memory CPT	runcpt	.cpt
Simple Reaction Time	simplert	.srt
Sleepiness Scale	sleepsc	.slp
Spatial Processing - Simultaneous	dspat	.spd
Spatial Processing - Delayed	spat	.spa
Standard CPT	stdcpt	.scp
Stroop Test	stroop	.str
Switching	switch	.swt
Symbolic Reaction Time	symbolrt	.sym
Tapping	tapping	.tpl, .tpr
Tower Puzzle	tower	.atp
Unstable Tracking	track	.trk
Visual Vigilance	visvig	.vis

For More Information

ANAM4™ User Manual
www.c-shop.ou.edu/literature/manual.pdf

Quick Start Guide for the ADEPT™ Software
www.c-shop.ou.edu/literature/ADEPTquickstart.pdf

Quick Start Guide for the APR™ Software
www.c-shop.ou.edu/literature/APRquickstart.pdf

ANAM4™ Technical Literature
www.c-shop.ou.edu

Technical Support
www.c-shop.ou.edu

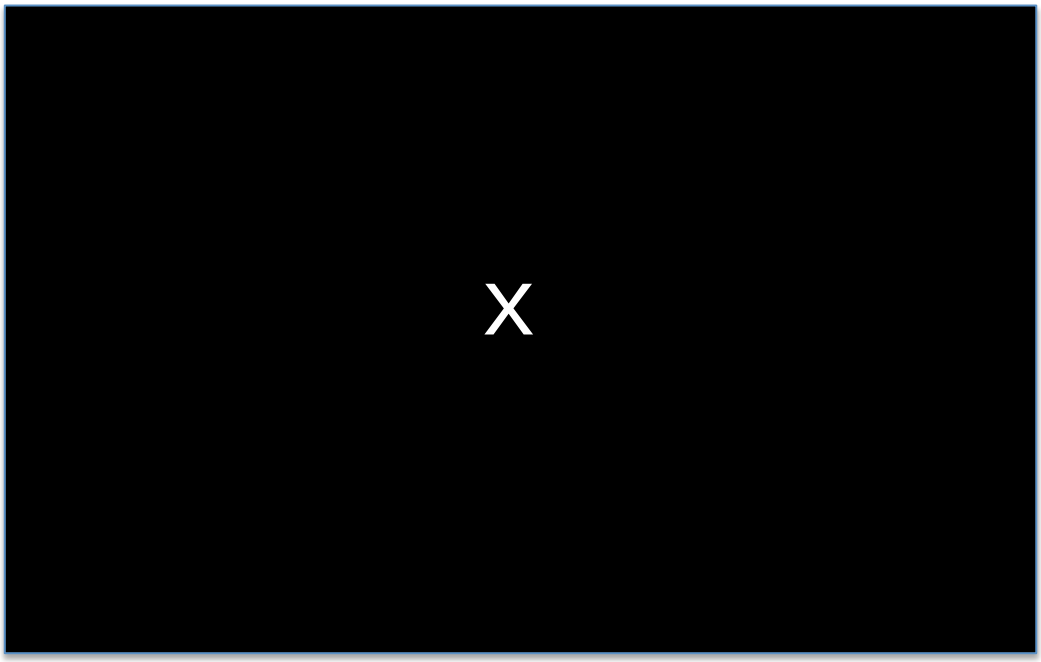


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Psychomotor Vigilance Test

Press the spacebar every time an “x” appears on the screen.



Subject: _____ Date:_____

Read the following scenarios. Each scenario presents a situation and asks a question about the chance or likelihood that you would experience a particular outcome. For each one, think about how likely that outcome would be for YOU in that situation. Do NOT worry about how most people would do in a particular situation—just think about the chance that a particular outcome would happen to YOU in that situation. Circle the percent chance that best represents the probability that the outcome would happen to YOU.

1. You arrive 25 minutes late for a big job interview. What is the probability that YOU will get the job?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

2. If you were to find yourself confronted by a vicious angry dog, what is the probability that YOU could get away unharmed?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

3. Regardless of your moral convictions, if you were to shoplift a pair of $50 sunglasses from a chain drug store, what is the probability that YOU could get away with it without being caught?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

4. While leaving a popular night club, you are attacked by a drunk man in his early 20s wielding a 10 inch knife. During the scuffle, your friend is stabbed, but not fatally. What is the chance that YOU will be killed during the attack?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

5. While on vacation, you meet up with a stranger asking for help. Although the story the stranger tells you is heart wrenching and he seems very sincere, you are aware that he may just be a con-artist trying to scam you. If the stranger truly is a con-artist, what is the probability YOU will end up being scammed out of some of your money?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

6. You awaken one morning realizing that you engaged in unprotected sex with someone you just met. Now that the alcohol has worn off, your partner remorsefully tells you that he/she has suffered for a long time with a very serious sexually transmitted disease. What is the chance that YOU will contract the sexually transmitted disease yourself after this contact?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

7. While on vacation in a far away country, your 3 traveling companions have all contracted a bad case of diarrhea after drinking the water. You realize that you just drank some of the same water about an hour ago. What is the likelihood that YOU will come down with diarrhea too?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

8. While on vacation in the woods, you decide to go hiking in an unfamiliar and thickly wooded area without a map or guide. What is the likelihood that YOU will get lost?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

9. You have been at a nightclub for 4 hours. During that time you have had 7 alcoholic beverages. You are feeling a little "buzzed" but you decide to drive yourself home anyway because it is only about 5 miles away. What is the probability that YOU will make it home without any negative incident?

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

10. While playing golf one afternoon a thunderstorm comes up quickly. There is much wind and occasional lightning is hitting nearby. Because you are winning the game and only have two more holes to play, you decide to continue to the end. What is the likelihood that YOU will be struck by lightning before finishing the game?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

11. While at your job you discover that one of your superiors has been embezzling large amounts of money from your organization. You decide to inform higher management of his illegal behavior. What is the chance that YOUR future career at the company will be harmed by reporting him?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

12. Your company has a strict policy forbidding the removal of computer equipment from the work premises. However, you have a big project due that can only be completed if you "borrow" a company laptop computer over the weekend. What is the probability that YOU could secretly remove the computer for the weekend and return it to work on Monday without ever being caught?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

13. You are a foreigner living in a war-torn country that is filled with violence and frequent sniper attacks. Although it is dark outside and there are many hostile insurgents in the area, you decide to drive alone and unarmed down a 10 mile stretch of empty highway to spend the weekend in the next town. What is the probability that YOU will be killed while making the trip?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

14. While staying at a high rise hotel a bad fire breaks out several floors below yours. After hearing the fire alarm and smelling smoke, you quickly devise a plan of escape. What is the likelihood that YOU would be unable to figure out a way to escape and would die in the fire?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

15. A severe natural disaster has devastated your town, resulting in widespread panic, looting, and deadly violence. The escape routes leading from the town are blocked with gridlock traffic and street gangs are killing at random and using violent means to steal limited necessities and survive. What is the chance that YOU will be able to outmaneuver the looters and escape the town unharmed?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

16. You enter a competition in an arena in which you are particularly talented. What is the chance that YOU will ultimately win the competition?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

17. You are sightseeing off a tall bridge where many individuals have tried to commit suicide by jumping to their deaths in the water below. Approximately half of all jumpers have not survived the long drop into the bay. Unfortunately, you stumble and are accidentally knocked off of the bridge. What is the likelihood that YOU would die in the fall?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

18. Your biggest rival has challenged you in some way. What is the likelihood that YOU will ultimately defeat your rival at whatever he/she has challenged you with?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

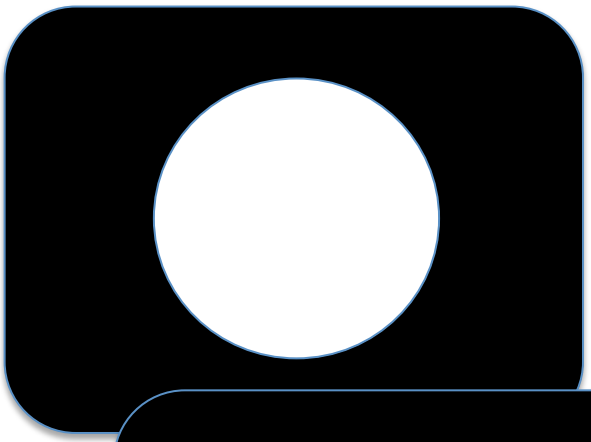
19. A bad automobile accident has just occurred in front of you. In one of the cars, the driver is unconscious and bleeding. You smell gas and notice that smoke is starting to billow out from the car. Afraid that the car may explode at any moment, you work to pull the unconscious driver from the car. What is the chance that YOU will die in the process of saving the driver?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

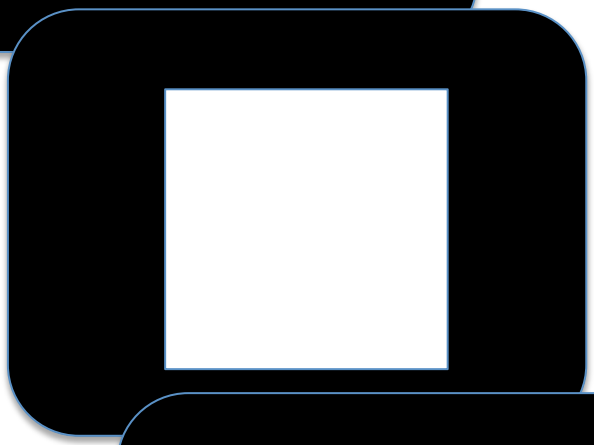
20. While on vacation on a tropical island you decided to rent a small motor boat to do some sightseeing and fishing out along the island coast. After stopping the boat some distance from the shore you lay down to take a brief nap. Upon awakening you realize that you can no longer see the shore and notice that there is a fierce storm coming. What is the likelihood that YOU will die at sea?

    0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

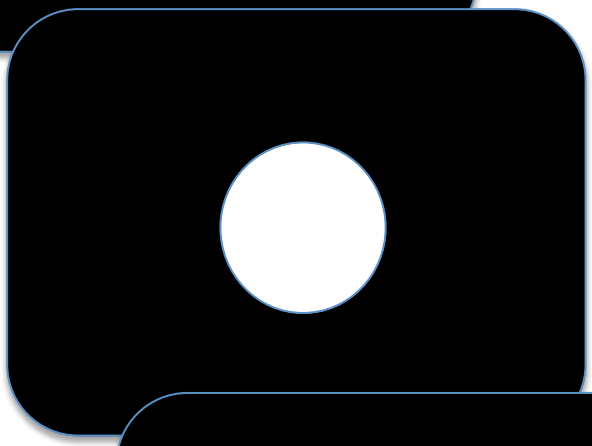
Go/No-Go Task



Go



Go



Go



No Go

Day of Scan Information Questionnaire (DSIQ)

Day of Scan Information Questionnaire (DSIQ)

Subject ID _____

Date _____

Age _____
(Years)

Height _____
(Feet/Inches)

Weight _____
(Pounds)

Sex

◯ Male
◯ Female

Handedness

◯ Right
◯ Left
◯ Both/Neither

What is the highest grade or level of school that you have completed or the highest degree you have obtained?

◯ < 9th
◯ 9th
◯ 10th
◯ 11th
◯ HS Grad
◯ 2yr College
◯ College Grad
◯ Some Grad School
◯ Masters
◯ Doctorate

With what ethnicity do you identify?

◯ White
◯ Hispanic/Latino
◯ Black/African-American
◯ Native-American/American Indian
◯ Asian/Pacific Islander
◯ Other

Do you have any problems with reading?

◯ No ◯ Yes

If yes, please explain

_____

What is your primary language (what do you speak at home most of the time)?

◯ English ◯ Spanish ◯ Other

If other, please specify

_____

Caffeine Use

Did you have any caffeine containing products today?

◯ Yes ◯ No

If yes, how much?

_____

On average, how many cups of caffeinated coffee do you drink per day?

_____

On average, how many cups of caffeinated tea do you drink per day?

_____

On average, how many cans of caffeinated soda do you drink per day?

_____

On average, how many caffeinated sports drinks do you drink per day?

_____

If you drink caffeinated sports drinks, what brand do you drink?

_____

Do you use any other caffeinated products, such as Vivarin?

◯ Yes ◯ No

If yes, what?

_____

How much?

_____

How often?

_____

Nicotine Use

Do you smoke cigarettes?

◯ Yes ◯ No

If YES, about how many cigarettes do you smoke per day?

_____

How long have you been smoking?

_____
(____ years ____ months)

Have you tried to quit?

◯ Yes ◯ No

If YES, how many times?

_____

If NO, did you ever smoke cigarettes in the past?

◯ Yes ◯ No

If YES, how many cigarettes did you smoke per day?

_____

When did you start smoking? _____

When did you quit? _____

Do you use smokeless tobacco, such as dip or chew?

◯ Yes ◯ No

If YES, about how much do you use per day?

_____

If NO, did you ever use smokeless tobacco in the past?

◯ Yes ◯ No

If YES, how much did you use per day?

_____

When did you start using? _____

When did you quit? _____

Do you use any other nicotine-containing products?

◯ Yes ◯ No

If YES, what?

_____

How much?

_____

How often?

_____

Other

Do you take diet pills?

◯ Yes ◯ No

If YES, what brand?

_____

How much?

_____

How often?

_____

Are you currently taking any medications, vitamins, or supplements?

◯ Yes ◯ No

If YES, please list:

_____
(Name: ____ Dosage (per day): ____ (e.g. Ibuprofen, 200 mg))

If YES, please list:

_____
(Name: ____ Dosage (per day): ____)

If YES, please list:

_____
(Name: ____ Dosage (per day): ____)

If YES, please list:

_____
(Name: ____ Dosage (per day): ____)

How many times per month do you drink (alcohol)?

_____

On those occasions, what is the average number of drinks you consume?

_____

On those occasions, what is the largest number of drinks you consume?

_____

How many times in the past year have you used marijuana?

_____

Have you ever used marijuana at other times in your life?

◯ Yes ◯ No

If YES, at what age did you begin smoking marijuana?

_____

On approximately how many occasions have you used marijuana?

_____

Do you use any other street drugs currently or in the past year?

◯ Yes ◯ No

If yes, what?

_____

How much?

_____

How often?

_____

Physical Information

If female, when was your last menstrual period (be as precise as possible)?

_____

(Date of period: _____ or about _____ days ago)

Concussion Information

How many "concussions" have you had in your life?

_____

Did you lose consciousness or get "knocked out" each time?

_____

How long ago was your most recent concussion?

_____

Date it happened _____

Briefly describe the situation that led to your most recent concussion

_____

Did you "see stars" during your last concussion?

◯ Yes ◯ No

Did you lose consciousness during your last concussion?

◯ Yes ◯ No

If YES, for how long were you unconscious?

_____
(Minutes)

Did you notice that your sleep became worse following the concussion?

◯ Yes ◯ No

After your concussion, what sleep problems became more noticeable to you (Select all that apply)?

	Yes	No
I get sleepier during the day	◯	◯
I get drowsier than I used to when trying to concentrate or work	◯	◯
I fall asleep when I should not	◯	◯
It is harder to stay alert during the day	◯	◯
It is harder to fall asleep at night	◯	◯
I fall asleep much later than I used to	◯	◯
I fall asleep much earlier than I used to	◯	◯
I sleep later in the morning than I used to	◯	◯
I wake up much earlier in the morning than I used to	◯	◯
When I do sleep, it is fitful or less restful than it used to be	◯	◯
I wake up off and on throughout the night more than I used to	◯	◯
I have more nightmares than I used to	◯	◯

In the months BEFORE your concussion, at what time did you normally go to bed at night on weeknights (Sun-Thurs)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM ◯ PM

In the months BEFORE your concussion, at what time did you normally go to bed at night on weekends (Fri-Sat)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM ◯ PM

In the months BEFORE your concussion, what time did you typically awaken on weekdays (Mon-Fri)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

In the months BEFORE your concussion, what time did you typically awaken on weekends (Sat-Sun)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM ◯ PM

In the months BEFORE your concussion, how long did it typically take you to fall asleep at night on weeknights (Sun-Thurs)?

_____
(HH:MM)

In the months BEFORE your concussion, how long did it typically take you to fall asleep at night on weekends (Fri-Sat)?

_____
(HH:MM)

Current Sleep Habits

How much sleep did you get last night?

_____
(HH:MM (e.g. 07:30 for 7 hours 30 minutes of sleep))

Since your concussion, how much do you typically sleep on weeknights (Sun-Thurs)?

_____
(HH:MM)

Since your concussion, how much do you typically sleep on weekend nights (Fri-Sat)?

_____
(HH:MM)

Since your concussion, at what time do you normally go to bed at night on weeknights (Sun-Thurs)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

Since your concussion, at what time do you normally go to bed at night on weekends (Fri-Sat)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

Since your concussion, at what time do you typically awaken on weekdays (Mon-Fri)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

Since your concussion, at what time do you typically awaken on weekends (Sat-Sun)?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

Since your concussion, how long does it typically take to fall asleep at night on weeknights (Sun-Thurs)?

_____
(HH:MM (e.g. 00:15 for 15 minutes))

Since your concussion, how long does it typically take you to fall asleep at night on weekends (Fri-Sat)?

_____
(HH:MM)

Since your concussion, at what time of day do you feel sleepiest?

_____
(In standard time HH:MM)

AM or PM?

◯ AM
◯ PM

Since your concussion, at what time of day do you feel most alert?

_____
(In standard time HH:MM)

AM or PM?

◯ AM ◯ PM

Since your concussion, how much time do you need to sleep per night to feel your best?

_____
(HH:MM)

Since your concussion: "If I get less than _____ hours/minutes of sleep, I notice an impairment in my ability to function at work."

_____
(HH:MM)

Since your concussion: "If I get more than _____ hours/minutes of sleep, I notice an impairment in my ability to function at work."

_____
(HH:MM)

Is daytime sleepiness currently a problem for you?

◯ Yes ◯ No

Are you currently doing shift work, that is, working early morning, evening, or night shifts?

◯ Yes ◯ No

Do you ever have trouble falling asleep?

◯ Yes ◯ No

If yes, how often per week, month, or year?

_____
((Designate time period in the next question))

If yes, how often per time period?

◯ Week
◯ Month
◯ Year

If yes, did this start or get worse since your concussion?

◯ Yes ◯ No

Do you ever have trouble staying asleep?

◯ Yes ◯ No

If yes, how often per week, month, or year?

_____
((Designate time period in the next question))

If yes, how often per time period?

◯ Week
◯ Month
◯ Year

If yes, did this start or get worse since your concussion?

◯ Yes ◯ No

Do you take more than two daytime naps per month?

◯ Yes ◯ No

If yes, about how many times per week do you nap?

_____

At what time of day do you normally begin your nap?

_____
(HH:MM)

AM or PM?

◯ AM
◯ PM

At what time of day do you normally wake up from your nap?

_____
(HH:MM)

AM or PM?

◯ AM
◯ PM

Do you consider yourself a light, normal, or heavy sleeper?

◯ Light
◯ Normal
◯ Heavy

Have you ever been diagnosed or treated for sleep apnea or sleep disordered breathing?

◯ Yes ◯ No

I yawn often

◯ 1 (Never) ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 (Always yawning)

When I see or hear someone else yawn, I will yawn too

◯ 1 (Never)
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ 8
◯ 9
◯ 10 (Every time)

Recent Risk of Dozing Off (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in the last two weeks. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 - Would never doze
1 - Slight chance of dozing
2 - Moderate chance of dozing
3 - High chance of dozing

	Would never doze (0)	Slight chance of dozing (1)	Moderate chance of dozing (2)	High chance of dozing (3)
1. Sitting and reading	◯	◯	◯	◯
2. Watching TV	◯	◯	◯	◯
3. Sitting, inactive in a public place (e.g. a theater or meeting)	◯	◯	◯	◯
4. As a passenger in a car for an hour without a break	◯	◯	◯	◯
5. Lying down to rest in the afternoon when circumstances permit	◯	◯	◯	◯
6. Sitting and talking to someone	◯	◯	◯	◯
7. Sitting quietly after a lunch without alcohol	◯	◯	◯	◯

8. In a car, while stopped for a few minutes in traffic	○	○	○	○

Source: Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 1991; 14(6): 540-5.

MEQ

SUBJECT:_____ DATE: _____/_____/_____

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?
   - _____5:00 - 6:30 AM
   - _____6:30 - 7:45 AM
   - _____7:45 - 9:45 AM
   - _____9:45 - 11:00 AM
   - _____11:00 AM - 12:00 PM

2. Considering only your own "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?
   - _____8:00 - 9:00 PM
   - _____9:00 - 10:15 PM
   - _____10:15 PM - 12:30 AM
   - _____12:30 - 1:45 AM
   - _____1:45 - 3:00 AM

3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?
   - _____not at all dependent
   - _____slightly dependent
   - _____fairly dependent
   - _____very dependent

4. Assuming adequate environmental conditions, how easy do you find getting up in the mornings?
   - _____not at all easy
   - _____not very easy
   - _____fairly easy
   - _____very easy

5. How alert do you feel during the first half hour after having woken in the mornings?
   - _____not at all alert
   - _____slightly alert
   - _____fairly alert
   - _____very alert

6. How is your appetite during the first half-hour after having woken in the mornings?
   - _____very poor
   - _____fairly poor
   - _____fairly good
   - _____very good

7. During the first half-hour after having woken in the morning, how tired do you feel?
   - _____very tired
   - _____fairly tired
   - _____fairly refreshed
   - _____very refreshed

8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?

_____seldom or never later
_____less than one hour later
_____1-2 hours later
_____more than two hours later

9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is between 7:00-8:00 AM. Bearing in mind nothing else but your own "feeling best" rhythm how do you think you would perform?
____would be in good form
_____would be in reasonable for
_____would find it difficult
_____would find it very difficult

10. At what time in the evening do you feel tired and as a result in need of sleep?
_____8:00 - 9:00 PM
_____9:00 - 10:15 PM
____10:15 PM - 12:45 AM
____12:45 - 2:00 AM
____2:00 - 3:00 AM

11. You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering only your own "feeling best" rhythm which ONE of the four testing times would you choose?
_____8:00 - 10:00 AM
_____11:00 AM - 1:00 PM
_____3:00 - 5:00 PM
_____7:00 - 9:00 PM

12. If you went to bed at 11:00 PM at what level of tiredness would you be?
_____not at all tired
_____a little tired
_____fairly tired
_____very tired

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?
_____will wake up at usual time and will NOT fall asleep
_____will wake up at usual time and will doze thereafter
_____will wake up at usual time but will fall asleep again
_____will NOT wake up until later than usual

14. One night you have to remain awake between 4:00 - 6:00 AM in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?
_____would NOT go to bed until watch was over
_____would take a nap before and sleep after
_____would take a good sleep before and nap after
_____would take ALL sleep before watch

15. You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own "feeling best" rhythm which ONE of the following times would you choose?
    _____8:00 - 10:00 AM
    _____11:00 AM - 1:00 PM
    _____3:00 - 5:00 PM
    _____7:00 - 9:00 PM

16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 10:00 - 11:00 PM. Bearing in mind nothing else but your own "feeling best" rhythm how well do you think you would perform?
    _____would be in good form
    _____would be in reasonable form
    _____would find it difficult
    _____would find it very difficult

17. Suppose that you can choose your own work hours. Assume that you worked a FIVE-hour day (including breaks) and that your job was interesting and paid by results. During which time period would you want that five consecutive hours to END?
    _____12:00 - 4:00 AM
    _____4:00 - 8:00 AM
    _____8:00 - 9:00 AM
    _____9:00 AM - 2:00 PM
    _____2:00 - 5:00 PM
    _____5:00 PM - 12:00 AM

18. At what time of the day do you think that you reach your "feeling best" peak?
    _____12:00 - 5:00 AM
    _____5:00 - 8:00 AM
    _____8:00 - 10:00 AM
    _____10:00 AM - 5:00 PM
    _____5:00 - 10:00 PM
    _____10:00 PM - 12:00 AM

19. One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be?
    _____definitely a "morning" person
    _____rather more a "morning" than an "evening" type
    _____rather more an "evening" than a "morning" type
    _____definitely an "evening" type

FOSQ

Study ID _____ Date_____

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words “sleepy” or “tired” are used, it means the feeling that you can’t keep your eyes open, your head is droopy, that you want to “nod off”, or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

Please circle one answer for each question. Please try to be as accurate as possible.

0 – I don’t do this activity for other reasons
1 – No difficulty
2 – Yes, a little difficulty
3 – Yes, Moderate difficulty
4 – Yes, Extreme difficulty

1. Do you generally have difficulty concentrating on things you do because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
2. Do you generally have difficulty remembering things because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
3. Do you have difficulty finishing a meal because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
4. Do you have difficulty working on a hobby (for example: sewing, collecting, gardening) because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
5. Do you have difficulty doing work around the house (for example: cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
6. Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
7. Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
8. Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	**0**	**1**	**2**	**3**	**4**
9. Do you have difficulty take care of financial affairs and doing paperwork (for example: writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
10. Do you have difficulty performing employed or volunteer work because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
11. Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**

0 – I don’t do this activity for other reasons

1 – No difficulty
2 – Yes, a little difficulty
3 – Yes, Moderate difficulty
4 – Yes, Extreme difficulty

	0	**1**	**2**	**3**	**4**
12. Do you have difficulty visiting with your family or friends in **your** home because you become sleepy or tired?					
13. Do you have difficulty visiting with your family or friends in **their** homes because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
14. Do you have difficulty doing things for your family or friends because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
15. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
16. Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	**0**	**1**	**2**	**3**	**4**
17. Do you have difficulty watching a movie or videotape because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
18. Do you have difficulty enjoying the theater or a lecture because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
19. Do you have difficulty enjoying a concert because you become sleepy or tired?	**0**	**1**	**2**	**3**	**4**
20. Do you have difficulty watching television because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
21. Do you have difficulty participating in religious services, meetings or a group club because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
22. Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
23. Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
24. Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
25. Do you have difficulty keeping a pace with others your own age because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
26. How would you rate yourself in your general level of activity?		**1**	**2**	**3**	**4**
		1= Very low; 2= Low; 3= Medium; 4= High			
27. Has your intimate or sexual relationship been affected because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
28. Has your desire for intimacy or sex been affected because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
29. Has your ability to become sexually aroused been affected because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**
30. Has your ability to have an orgasm been affected because you are sleepy or tired?	**0**	**1**	**2**	**3**	**4**

VIII. Preferences

1. Please mark the bubble which best describes your feelings **RIGHT NOW**.

I feel like gambling

not at all ○○○○○○○○○○○○○○○○○○○○○○○○○ very much

I am driving and the light turns yellow. I feel like

stopping ○○○○○○○○○○○○○○○○○○○○○○○○○ accelerating

The lights suddenly go out in an unfamiliar stairwell

I don't move ○○○○○○○○○○○○○○○○○○○○○○○○○ I proceed immediately

I feel like

avoiding everyone ○○○○○○○○○○○○○○○○○○○○○○○○○ taking on the world

I feel like diving from a diving board, which is

very high ○○○○○○○○○○○○○○○○○○○○○○○○○ very low

I like

routine ○○○○○○○○○○○○○○○○○○○○○○○○○ adventure

I seek

the thrill of danger ○○○○○○○○○○○○○○○○○○○○○○○○○ tranquillity

I am in a hurry

I take a dangerous shortcut ○○○○○○○○○○○○○○○○○○○○○○○○○ I take a safe detour

I am open to

negotiation ○○○○○○○○○○○○○○○○○○○○○○○○○ confrontation

I prefer to

direct ○○○○○○○○○○○○○○○○○○○○○○○○○ be supervised

I give priority to

reason ○○○○○○○○○○○○○○○○○○○○○○○○○ action

I like to listen to music

at a loud volume ○○○○○○○○○○○○○○○○○○○○○○○○○ very softly

I am sure of myself

not at all ○○○○○○○○○○○○○○○○○○○○○○○○○ completely

I prefer discussions, which are

animated ○○○○○○○○○○○○○○○○○○○○○○○○○ calm

A hostile situation

weakens me ○○○○○○○○○○○○○○○○○○○○○○○○○ reinforces me

A menacing dog approaches

I confront it ○○○○○○○○○○○○○○○○○○○○○○○○○ I run away

Faced with a potentially dangerous event

I take my time ○○○○○○○○○○○○○○○○○○○○○○○○○ I instantly react

Seeing a person who is drowning, I first

dive in ○○○○○○○○○○○○○○○○○○○○○○○○○ call for help

I prefer work that is

well planned ○○○○○○○○○○○○○○○○○○○○○○○○○ not planned

I am right

all the time ○○○○○○○○○○○○○○○○○○○○○○○○○ never

I emphasize

precision ○○○○○○○○○○○○○○○○○○○○○○○○○ speed

I like to drive

very fast ○○○○○○○○○○○○○○○○○○○○○○○○○ very slow

I like to listen to music with a tempo that is

very slow ○○○○○○○○○○○○○○○○○○○○○○○○○ very fast

I like to take risks

not at all ○○○○○○○○○○○○○○○○○○○○○○○○○ a lot

THANK YOU FOR COMPLETING THIS SURVEY!

Please provide any additional comments below or on the back of the survey, if needed.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

SUBJECT #: _____ **DATE:** _____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

TOTAL: _____

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

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A2663B 10-04-2005

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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A2662B 10-04-2005

Session (1 or 2) _____ ID# _____ Date _____ Time _____ AM PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

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Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

Rivermead Post Concussion Symptoms Questionnaire

Modified (Rpq-3 And Rpq-13)[42] Printed With Permission: Modified Scoring System From Eyres 2005 [28]

Subject ID: Date:

After a head injury or accident some people experience symptoms that can cause worry or nuisance. We would like to know if you now suffer any of the symptoms given below. Because many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each symptom listed below please circle the number that most closely represents your answer.

0 = not experienced at all
1 = no more of a problem
2 = a mild problem
3 = a moderate problem
4 = a severe problem

Compared with **before** the accident, do you **now** (i.e., over the last 24 hours) suffer from:

	not experienced	no more of a problem	mild problem	moderate problem	severe problem
Headaches	0	1	2	3	4
Feelings of dizziness	0	1	2	3	4
Nausea and/or vomiting	0	1	2	3	4
Noise sensitivity (easily upset by loud noise)	0	1	2	3	4
Sleep disturbance	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being irritable, easily angered	0	1	2	3	4
Feeling depressed or tearful	0	1	2	3	4
Feeling frustrated or impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor concentration	0	1	2	3	4
Taking longer to think	0	1	2	3	4
Blurred vision	0	1	2	3	4
Light sensitivity (easily upset by bright light)	0	1	2	3	4
Double vision	0	1	2	3	4
Restlessness	0	1	2	3	4
Are you experiencing any other difficulties? Please specify, and rate as above.					
1.	0	1	2	3	4
2.	0	1	2	3	4

Administration only:

RPQ-3 *(total for first three items)*	
RPQ-13 *(total for next 13 items)*	

http://www.maa.nsw.gov.au/default.aspx?MenuID=148

Administration only

Individual item scores reflect the presence and severity of post concussive symptoms. Post concussive symptoms, as measured by the RPQ, may arise for different reasons subsequent to (although not necessarily directly because of) a traumatic brain injury. The symptoms overlap with broader conditions, such as pain, fatigue and mental health conditions such as depression[72].

The questionnaire can be repeated to monitor a patient's progress over time. There may be changes in the severity of symptoms, or the range of symptoms. Typical recovery is reflected in a reduction of symptoms and their severity within three months.

Scoring

The scoring system has been modified from Eyres, 2005[24].

The items are scored in two groups. The first group (RPQ-3) consists of the first three items (headaches, feelings of dizziness and nausea) and the second group (RPQ-13) comprises the next 13 items. The total score for RPQ-3 items is potentially 0–12 and is associated with early symptom clusters of post concussive symptoms. If there is a higher score on the RPQ-3, earlier reassessment and closer monitoring is recommended.

The RPQ-13 score is potentially 0–52, where higher scores reflect greater severity of post concussive symptoms. The RPQ-13 items are associated with a later cluster of symptoms, although the RPQ-3 symptoms of headaches, dizziness and nausea may also be present. The later cluster of symptoms is associated with having a greater impact on participation, psychosocial functioning and lifestyle. Symptoms are likely to resolve within three months. A gradual resumption of usual activities is recommended during this period, appropriate to symptoms. If the symptoms do not resolve within three months, consideration of referral for specialist assessment or treatment services is recommended.

References:

Eyres, S., Carey, A., Gilworth, G., Neumann, V., Tennant, A. (2005). Construct validity and reliability of the Rivermead Post Concussion Symptoms Questionnaire. *Clinical Rehabilitation*, 19, 878-887.

King, N. S., Crawford, S., Wenden, F.J., Moss, N.E.G. Wade, D.T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability *Journal of Neurology*, 242, 587-592.

Potter, S., Leigh, E., Wade, D., Fleminger, S. (2006). The Rivermead Post Concussion Symptoms Questionnaire *Journal of Neurology*, October 1-12.

http://www.maa.nsw.gov.au/default.aspx?MenuID=148

Beck Depression Inventory (BDI-II)

Participant ID

_____

Beck Depression Inventory (BDI-II)

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

◯ I do not feel sad. (0)
◯ I feel sad much of the time. (1)
◯ I am sad all the time. (2)
◯ I am so sad or unhappy that I can't stand it. (3)

2. Pessimism

◯ I am not discouraged about my future. (0)
◯ I feel more discouraged about my future than I used to be. (1)
◯ I do not expect things to work out for me. (2)
◯ I feel my future is hopeless and will only get worse. (3)

3. Past Failure

◯ I do not feel like a failure. (0)
◯ I have failed more than I should have. (1)
◯ As I look back, I see a lot of failures. (2)
◯ I feel I am a total failure as a person. (3)

4. Loss of Pleasure

◯ I get as much pleasure as I ever did from the things I enjoy. (0)
◯ I don't enjoy things as much as I used to. (1)
◯ I get very little pleasure from the things I used to enjoy. (2)
◯ I can't get any pleasure from the things I used to enjoy. (3)

5. Guilty Feelings

◯ I don't feel particularly guilty. (0)
◯ I feel guilty over many things I have done or should have done. (1)
◯ I feel quite guilty most of the time. (2)
◯ I feel guilty all of the time. (3)

6. Punishment Feelings

◯ I don't feel I am being punished. (0)
◯ I feel I may be punished. (1)
◯ I expect to be punished. (2)
◯ I feel I am being punished. (3)

7. Self-Dislike

◯ I feel the same about myself as ever. (0)
◯ I have lost confidence in myself. (1)
◯ I am disappointed in myself. (2)
◯ I dislike myself. (3)

8. Self-Criticalness

◯ I don't criticize or blame myself more than usual. (0)
◯ I am more critical of myself than I used to be. (1)
◯ I criticize myself for all of my faults. (2)
◯ I blame myself for everything bad that happens. (3)

9. Suicidal Thoughts or Wishes

◯ I don't have any thoughts of killing myself. (0)
◯ I have thoughts of killing myself, but I would not carry them out. (1)
◯ I would like to kill myself. (2)
◯ I would kill myself if I had the chance. (3)

10. Crying

◯ I don't cry anymore than I used to. (0)
◯ I cry more than I used to. (1)
◯ I cry over every little things. (2)
◯ I feel like crying, but I can't. (3)

11. Agitation

◯ I am no more restless or wound up than usual. (0)
◯ I feel more restless or wound up than usual. (1)
◯ I feel so restless or agitated that it's hard to stay still. (2)
◯ I am so restless or agitated that I have to keep moving or doing something. (3)

12. Loss of Interest

◯ I have not lost interest in other people or activities. (0)
◯ I am less interested in other people or things than before. (1)
◯ I have lost most of my interest in other people or things. (2)
◯ It's hard to get interested in anything. (3)

13. Indecisiveness

◯ I make decisions about as well as ever. (0)
◯ I find it more difficult to make decisions than usual. (1)
◯ I have much greater difficulty in making decisions than I used to. (2)
◯ I have trouble making any decisions. (3)

14. Worthlessness

◯ I do not feel I am worthless. (0)
◯ I don't consider myself as worthwhile and useful as I used to. (1)
◯ I feel more worthless as compared to other people. (2)
◯ I feel utterly worthless. (3)

15. Loss of Energy

◯ I have as much energy as ever. (0)
◯ I have less energy than I used to have. (1)
◯ I don't have enough energy to do very much. (2)
◯ I don't have enough energy to do anything. (3)

16. Changes in Sleep Pattern.

◯ I have not experienced any change in my sleeping pattern. (0)
◯ I sleep somewhat more than usual. (1a)
◯ I sleep somewhat less than usual. (1b)
◯ I sleep a lot more than usual. (2a)
◯ I sleep a lot less than usual. (2b)
◯ I sleep most of the day. (3a)
◯ I wake up 1-2 hours early and can't get back to sleep. (3b)

17. Irritability

◯ I am no more irritable than usual. (0)
◯ I am more irritable than usual. (1)
◯ I am much more irritable than usual. (2)
◯ I am irritable all the time. (3)

18. Changes in Appetite

◯ I have not experienced any change in my appetite. (0)
◯ My appetite is somewhat less than usual. (1a)
◯ My appetite is somewhat more than usual. (1b)
◯ My appetite is much less than before. (2a)
◯ My appetite is much greater than usual. (2b)
◯ I have no appetite at all. (3a)
◯ I crave food all the time. (3b)

19. Concentration Difficulty

◯ I can concentrate as well as ever. (0)
◯ I can't concentrate as well as usual. (1)
◯ It's hard to keep my mind on anything for very long. (2)
◯ I find I can't concentrate on anything. (3)

20. Tiredness or Fatigue

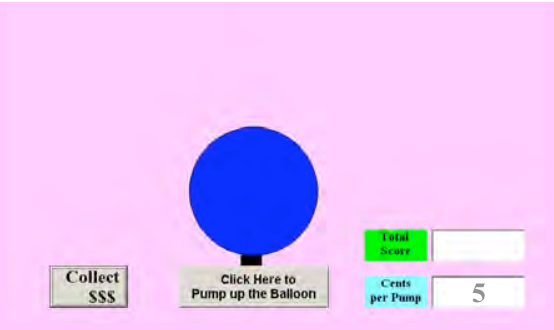
◯ I am no more tired or fatigued than usual. (0)
◯ I get more tired or fatigued more easily than usual. (1)
◯ I am too tired or fatigued to do a lot of the things I used to do. (2)
◯ I am too tired or fatigued to do most of the things I used to do. (3)

21. Loss of Interest in Sex

◯ I have not noticed any recent change in my interest in sex. (0)
◯ I am less interested in sex than I used to be. (1)
◯ I am much less interested in sex now. (2)
◯ I have lost interest in sex completely. (3)

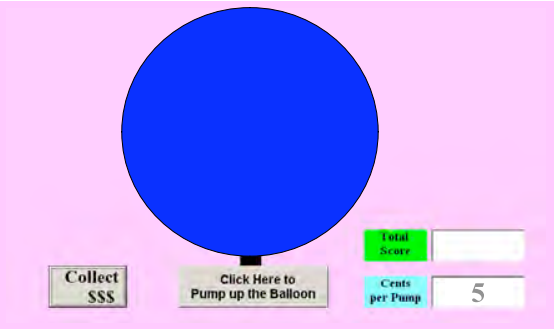
Balloon Analog Risk Task

Inflate Balloon by Pressing Key



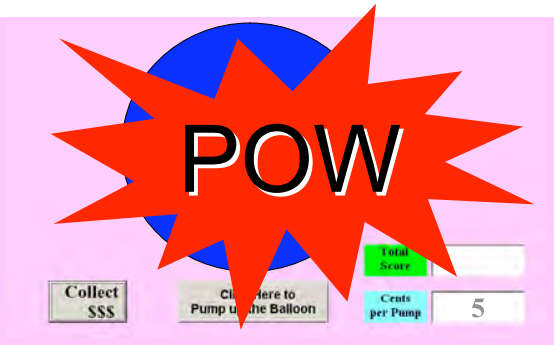
- The BART presents participants with 30 virtual balloons.
- Each balloon can be inflated one increment for each key press.

Balloon Grows in Size and $$$ Value



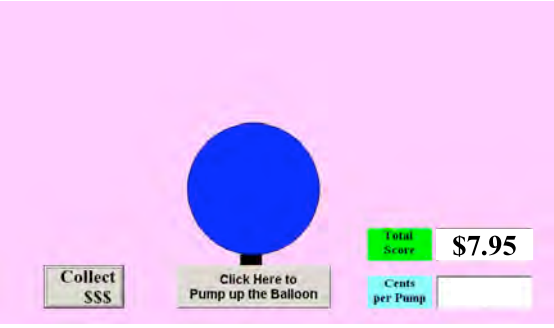
- With each key press the size of the balloon increases.
- Each increment also increases the potential value of the balloon by 5 cents.
- The balloon can be "cashed in" at any time and the total accumulated value retained.

If Balloon Explodes, All $$$ is Lost



- Each balloon can explode at any time.
- If a balloon explodes, all of the potential money accumulated *for that balloon* will be lost.

Goal: Earn as Much Money as Possible



- The goal is to maximize winnings.
- Only 30 balloons are presented

STAI Form S

Subject #_____ Date:_____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, THAT IS, at this moment.

There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm.	1	2	3	4
2. I feel secure.	1	2	3	4
3. I am tense	1	2	3	4
4. I feel regretful	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes.	1	2	3	4
8. I feel rested.	1	2	3	4
9. I feel anxious	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident.	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel "high strung"	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel over-excited and "rattled".	1	2	3	4
19. I feel joyful.	1	2	3	4
20. I feel pleasant.	1	2	3	4

STAI Form T

Subject #_____ DATE_____

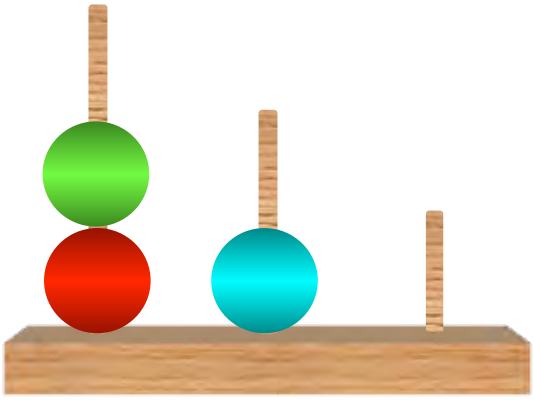
DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you generally feel.

There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

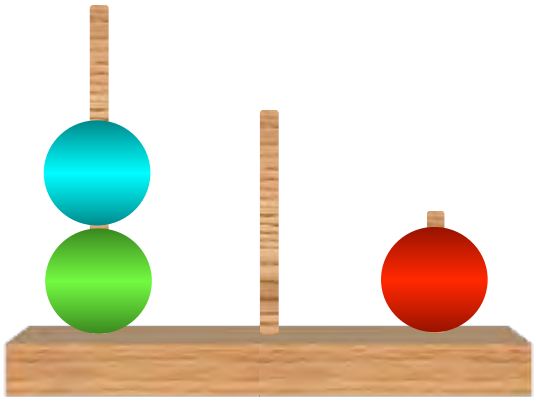
	Almost never	Sometimes	Often	Almost always
21. I feel pleasant	1	2	3	4
22. I tire quickly	1	2	3	4
23. I feel like crying	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I am losing out on things because I can't make up my mind soon enough	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I am inclined to take things hard	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I try to avoid facing a crises or difficulty	1	2	3	4
35. I feel blue	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Tower of London Task

Your Tower



Goal



Satisfaction with Life Scale

Below are five statements with which you may agree or disagree.
Indicate your agreement with each item by placing the appropriate number on the line preceding that item.

Please be open and honest in your responding.

The 7-point scale is as follows:

1 = strongly disagree
2 = disagree
3 = slightly disagree
4 = neither agree nor disagree
5 = slightly agree
6 = agree
7 = strongly agree

__ 1. In most ways my life is close to my ideal.
__ 2. The conditions of my life are excellent.
__ 3. I am satisfied with my life.
__ 4. So far I have gotten the important things I want in life.
__ 5. If I could live my life over, I would change almost nothing.

Subject ID: _____ Date: _____

Please rate each of the following items in terms of how characteristic they are of you. Use the following scale for answering these items.

1 2 3 4 5
extremely uncharacteristic of me — extremely characteristic of me

Once in a while I can't control the urge to strike another person.	1 2 3 4 5
Given enough provocation, I may hit another person.	1 2 3 4 5
If somebody hits me, I hit back.	1 2 3 4 5
I get into fights a little more than the average person.	1 2 3 4 5
If I have to resort to violence to protect my rights, I will.	1 2 3 4 5
There are people who pushed me so far that we came to blows.	1 2 3 4 5
I can think of no good reason for ever hitting a person.	1 2 3 4 5
I have threatened people I know.	1 2 3 4 5
I have become so mad that I have broken things.	1 2 3 4 5
I tell my friends openly when I disagree with them.	1 2 3 4 5
I often find myself disagreeing with people.	1 2 3 4 5
When people annoy me, I may tell them what I think of them.	1 2 3 4 5
I can't help getting into arguments when people disagree with me.	1 2 3 4 5
My friends say that I'm somewhat argumentative.	1 2 3 4 5
I flare up quickly but get over it quickly.	1 2 3 4 5
When frustrated, I let my irritation show.	1 2 3 4 5
I sometimes feel like a powder keg ready to explode.	1 2 3 4 5
I am an even-tempered person.	1 2 3 4 5
Some of my friends think I'm a hothead.	1 2 3 4 5
Sometimes I fly off the handle for no good reason.	1 2 3 4 5
I have trouble controlling my temper.	1 2 3 4 5
I am sometimes eaten up with jealousy.	1 2 3 4 5
At times I feel I have gotten a raw deal out of life.	1 2 3 4 5
Other people always seem to get the breaks.	1 2 3 4 5
I wonder why sometimes I feel so bitter about things.	1 2 3 4 5
I know that "friends" talk about me behind my back.	1 2 3 4 5
I am suspicious of overly friendly strangers.	1 2 3 4 5
I sometimes feel that people are laughing at me behind my back.	1 2 3 4 5
When people are especially nice, I wonder what they want.	1 2 3 4 5

Review

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Concussion

Potential for the development of light therapies in mild traumatic brain injury

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Light affects almost all aspects of human physiological functioning, including circadian rhythms, sleep–wake regulation, alertness, cognition and mood. We review the existing relevant literature on the effects of various wavelengths of light on these major domains, particularly as they pertain to recovery from mild traumatic brain injuries. Evidence suggests that light, particularly in the blue wavelengths, has powerful alerting, cognitive and circadian phase shifting properties that could be useful for treatment. Other wavelengths, such as red and green may also have important effects that, if targeted appropriately, might also be useful for facilitating recovery. Despite the known effects of light, more research is needed. We recommend a personalized medicine approach to the use of light therapy as an adjunctive treatment for patients recovering from mild traumatic brain injury.

First draft submitted: 29 June 2018; Accepted for publication: 1 August 2018; Published online: 15 October 2018

Keywords: blue light • brain injury • circadian rhythm • concussion • fatigue • mild TBI • phototherapy • sleep–wake disruption

Mild traumatic brain injuries (mTBIs) are currently among the most socially, medically and academically talked-about issues today. The annual mTBI incidence is at least 1.5 million reported injuries in the USA [1–3]. However, this number fails to capture the untold number of such injuries that likely go unreported [4,5]. The long-term consequences – plausibly including neurodegenerative conditions [6–10], impaired cognitive abilities [11–13] and altered psychosocial functioning [14–20] – necessitate the need for efficacious treatments following injury and proactive preventative methods for reducing injury risk and consequence.

Despite significant job-, school- and economic-related burdens associated with the medical management of mTBIs [1], there is no currently accepted gold standard treatment for mTBIs [21,22]. Historically, the treatment of choice was total rest to allow the brain to heal. However, recent research advances are giving way to more active treatments, with an emphasis on early intervention [23–25]. While early reports are promising for short-term management, the long-term impact of these active interventions is not well established. Additionally, there is little information on methods of optimizing these active approaches or complementary treatments that may enhance recovery in both the short and long term.

One complementary treatment method involves the use of light exposure. Light, both visible and invisible, can have powerful effects on numerous neurological and physiological systems [26–29]. Additionally, light is potentially a modifiable aspect of the environment in which one exists to allow for optimal healing, recovery and a return to homeostatic states following mTBI. The purpose of this narrative review is to provide a focused overview of the role and effect of light on neurological processes and to connect these effects with potential areas of intervention with respect to mTBI.

The fate of ambient light: image-forming & nonimage-forming pathways

The primary sensory function of the eyes is to translate information contained in light into images [30]. This is accomplished primarily through two classes of retinal photoreceptors. Cones are color-sensitive photoreceptors

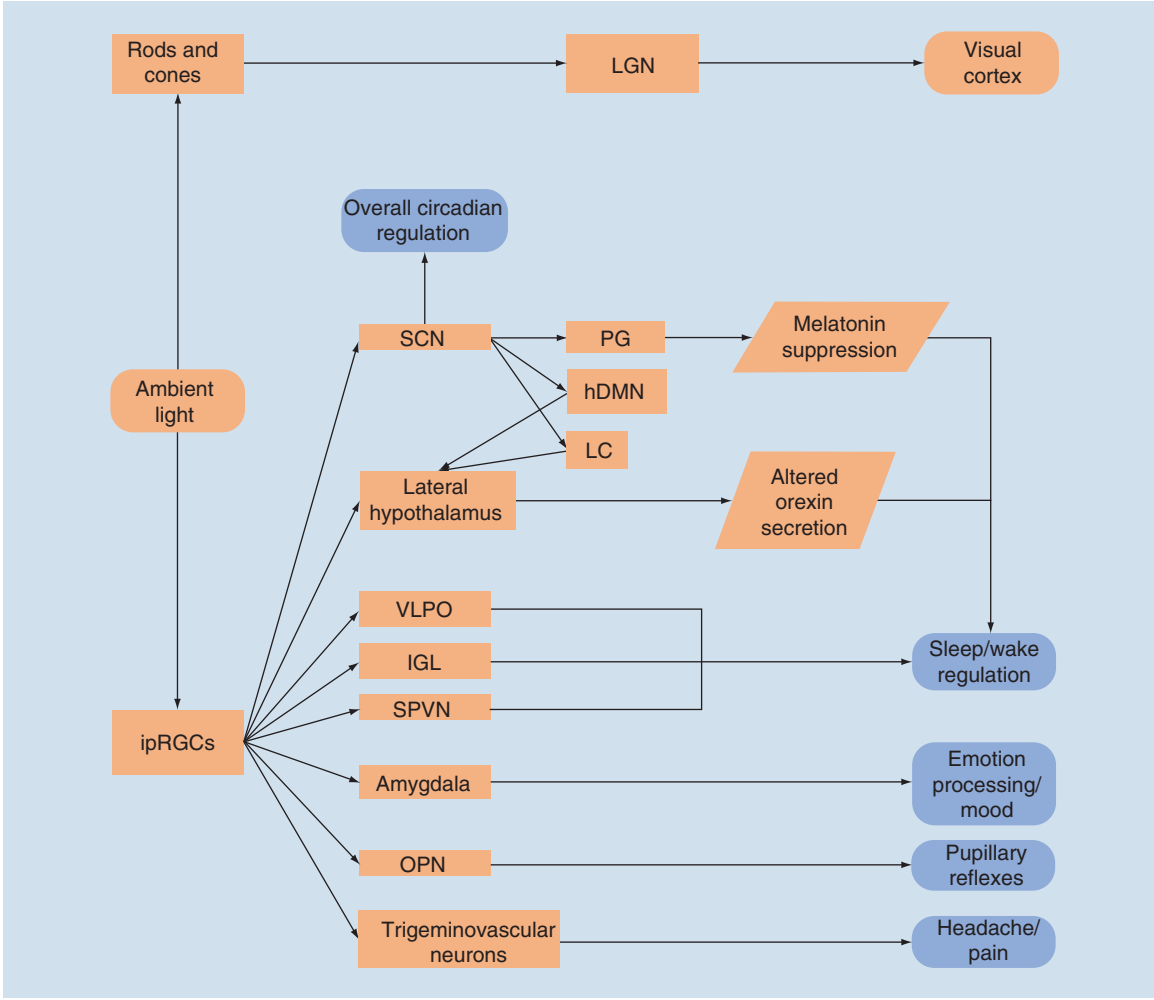


Figure 1. Schematic representation of the destinations for ambient light entering the eye.
hDMN: Hypothalamic dorsomedial nucleus; IGL: Intergeniculate leaflet; ipRGC: Intrinsically photosensitive retinal ganglion cell; LC: Locus coeruleus; LGN: Lateral geniculate nucleus; OPN: Olivary pretectal nucleus; PG: Pineal gland; SCN: Suprachiasmatic nucleus; SPVN: Supraparaventricular nucleus; VLPO: Ventrolateral preoptic nucleus.

while rods respond to changes in brightness and are particularly sensitive to dim light. Light information is converted by these photoreceptors, resulting in the stimulation of retinal ganglion cells (RGCs) that project to subcortical nuclei, including the lateral geniculate nucleus of the thalamus, ultimately terminating in the primary visual cortex and visual attention networks (Figure 1). These pathways provide the sensory information for vision and terminate in areas that process and interpret those sensory signals. For a complete review of the transformation from light information to visual interpretation, please see reference [30].

An additional class of photoreceptor was discovered in the early 2000s and is the starting point for the nonimage-forming (NIF) pathway [31–34]. This third type of photoreceptor is expressed directly by a small proportion of RGCs (termed intrinsically photosensitive RGCs; ipRGCs). These ipRGCs are maximally sensitive to blue light (λ = 460–480 nm) and less so to longer wavelengths including green, amber and red [31]. ipRGCs, combined with information regarding illuminance and color from the rods and cones, then directly project to regions involved in the regulation of or influence the actions of (Figure 1):

- Circadian rhythms. Projections from the ipRGCs to the suprachiasmatic nucleus (SCN), the primary biological clock for all circadian processes, can directly induce entrainment of either expected or aberrant circadian rhythms [31,35].

- Melatonin suppression. Stimulation of ipRGCs results in melatonin suppression via the SCN's projections to the pineal gland as well as the paraventricular nucleus of hypothalamus and superior cervical ganglion [34,36–38].
- Sleep–wake cycle regulation. In conjunction with the above-mentioned melatonin suppression pathways, direct projections from the ipRGCs go to the ventrolateral preoptic nucleus, subparaventricular nucleus and lateral hypothalamus [34]. The SCN may additionally influence the action of the hypothalamus's dorsomedial nucleus, and locus coeruleus, affecting the lateral hypothalamus secretion of orexin [33,34].
- Cognition. The aforementioned pathways regulating circadian rhythms, melatonin suppression and sleep–wake cycles additionally exert both direct and indirect influences on cognition and alertness [26].
- Emotional processing and mood. The amygdala, a primary site of emotional processing and integration, receives direct ipRGC projection [34,39].
- Intracranial nociception. ipRGCs project to the trigeminovascular neurons of the thalamus that transmit nociceptive information from the dura to the cortex [40].
- Pupillary constriction. ipRGCs directly project to the olivary pretectal nucleus [32–34], which in turn project to the Edinger–Westphal nucleus. The cumulative action of this pathway is pupillary constriction. For a complete review of the effects of mTBI on the pupillary light reflex, including NIF pathway contributions, please see [41].

As can be seen, light has the powerful potential to alter numerous biological and cognitive processes through this NIF pathway. Given the complex interactions between circadian timekeepers, hormone and neurotransmitter secretion pathways, cognition, and emotions, light has the potential to positively or negatively influence how individuals function at a very basic level. Consequently, using light as a therapeutic intervention has the potential to directly influence recovery and function following mTBI. In the following sections, we review potential areas of intervention and, where possible, expected outcomes from using light as a therapy.

mTBIs & their consequences

mTBIs are a change or disruption in the normal functioning of the brain subsequent to an external force applied to the head or body [42,43]. Typical guidelines for distinguishing mTBIs from more severe TBIs include a mechanism indicative of mTBI; loss of consciousness <30 min (if at all); post-traumatic amnesia <24 h; Glasgow Coma Scale scores 13–15; and lack of gross abnormalities on traditional neuroimaging [42,44,45]. The effects of a single mTBI are often viewed as transient and may include somatic symptoms, sleep–wake disturbances, and cognitive and behavioral disruptions. However, while these effects are common, the individual manifestations of these are highly individualized and may depend on premorbid functioning and the location and mechanism of injury [46]. Additionally, many individuals experience persistent symptoms associated with an mTBI, and recent findings indicate that the incidence of long-lasting mTBI-related functional decrements may be underestimated [42]. Here we provide an overview of mTBI-related consequences that may be positively affected by light therapy, with an emphasis on sleep and sleep-related consequences given the previously identified NIF-pathway effects.

Sleepiness & fatigue

High-quality sleep is an essential component of all aspects of human performance. Current recommendations for adequate sleep recommend 7–9 h of sleep per night for adults. Despite these recommendations, chronic sleep loss (<5.5 h/night of sleep) in the USA is reaching epidemic levels [47]. For individuals with chronic sleep loss, the consequences are numerous including increased somatization [48,49], poor emotional processing and responsiveness (e.g., increased incidence of depression and anxiety) [50–52], impaired cognition (vigilant attention, executive function, working and long-term memory) [53–56] and poor motor performance [57–59], as well as increased risk for general health issues including diabetes [60–62], cardiovascular disease [60,63], neurodegeneration [64,65] and overall poorer quality of life [66]. While the exact nature of this trend toward chronically undersleeping is not fully understood, work–life stress (e.g., increased expectations for high job-related hours, social stress) as well as the highly prevalent use of fluorescent lighting and blue-shifted light-emitting diode screens at night [67–69] are all implicated.

Compounding the endemic social issue of chronic sleep loss, detrimentally altered sleep is among the most common short- and long-term consequences of mTBI [70–74]. Indeed subjectively perceived traumatic brain injury (TBI)-related sleep–wake disruption is reported by plausibly as many as 70% of all individuals who sustain a TBI (regardless of severity) [70,74,75]. Individuals with mTBI commonly self report insomnia [74–79] and hypersomnolence (excessive sleepiness) [71,75,80–86], though hypersomnia [80,85,87,88] and circadian rhythm sleep disorders [82,89] are

also reported. Objectively, these reports are often corroborated by poor sleep efficiency, higher than usual wake after sleep onset and sleep latency, as well as more fragmented sleep and changes in sleep architecture [87,90–95]. Clinically, it is important to recognize that post-mTBI insomnia may be misdiagnosed as a circadian phase issue, specifically delayed sleep phase syndrome [89]. Consequently, individuals sustaining an mTBI may be at an increased risk for all of the aforementioned sleep-related health and performance outcomes without treatment for mTBI-related alterations.

The mechanisms by which mTBI induces altered sleep are not fully understood. However, there are implications from both human studies and animal models that suggest any combination of possible mechanisms including altered circadian hormone regulation (e.g., melatonin release) [96–98] and reductions in neurotransmitter function (e.g., loss of or damage to wake-promoting, orexin-secreting neurons in the hypothalamus) [99–101] among others may be responsible.

In addition to these possible mechanisms of post-mTBI sleep changes, sleep loss or low-quality sleep may impede and impair healing following mTBI. There is considerable evidence indicating that decreases in sleep quantity and quality, both in humans and animals as well as apart from and in relation to mTBI, may impair hippocampal neurogenesis, disrupt ATP production thereby extending the mTBI-initiated neurometabolic cascade [102,103], prolong neuroinflammation [104], impede metabolic waste removal in the brain [105], alter cerebrovascular responsiveness and compromise glymphatic removal of phosphorylated tau [105–107]. Collectively, these effects of sleep disruption may contribute to the short- and long-term clinical presentation of mTBI as well as precipitate the neurodegenerative conditions, particularly tau-related pathologies (e.g., chronic traumatic encephalopathy), commonly thought to be associated with repetitive head trauma.

Alertness

As noted, an mTBI may induce a sequela whereby disrupted circadian rhythms lead to sleep dysfunction, culminating in daytime sleepiness or fatigue. Broadly, daytime fatigue is associated with decreased alertness and vigilant attention capabilities. Indeed, a recent study demonstrates that evidence of increased fatigue and decreased alertness in an mTBI sample are closely related concepts that are difficult to disentangle [86]. Furthermore, mTBI is associated with degraded alertness and vigilance in both the short and long term [86,108,109]. With regards to daytime alertness, phototherapy may provide a nonpharmacological route for improving daytime functioning in post-mTBI individuals.

Cognition

mTBIs additionally exert a substantial, negative impact on various cognitive functions, including working memory, attention, executive function and visuospatial processing [20,110–117]. While deficits in these cognitive domains are generally resolved soon after injury (e.g., most within a month, many within 3 months postinjury), there is evidence to suggest subtle, persistent deficits that linger well beyond this clinically accepted time course. Additionally, there are individuals in whom the full impact of these deficits does not resolve quickly.

Apart from mTBI, increasing sleep need as well as sleep deprivation conditions induce marked deterioration in the cognitive capabilities of individuals [53,118–120]. Given the impact of mTBI on sleep, daytime sleepiness and fatigue, it is reasonable to posit that many of the observed cognitive deficits, particularly those that linger beyond the general clinical time course, may be mediated by sleep-related changes.

Depression

Depression and increased reporting of depressive symptoms are common following mTBI. The incidence of post-mTBI depression may be as high as 42% in adults and 22% in children and adolescents [121–124]. Premorbid depression is a risk factor for prolonged recovery from mTBI and may be associated with postconcussion symptoms, as well as sleep disruption, impaired cognition and other post-mTBI psychiatric symptoms (e.g., anxiety) [17,20,125–129]. Therefore, ameliorating post-mTBI depression may improve overall symptom presentation and be associated with improvements in sleep and cognitive function.

Post-traumatic headache & pain

Post-traumatic headaches (PTH) and chronic pain are among the most common symptoms experienced by individuals recovering from mTBI. The incidence of PTH likely may be as high 90% [130–135], and the incidence of chronic pain may be as high as 75% [136]. Additionally, both PTH and chronic pain may mediate, or be mediated

by, post-mTBI poor sleep, daytime sleepiness, cognitive deficits and depression [122,137–142]. Consequently, the aforementioned benefits of bright or blue light therapy for sleep, cognitive performance and depression may have positive effects on PTH and pain.

The effects of different types of light & applications to mTBI

Given the range of deficits and changes observed following mTBIs, as well as the known NIF pathways for light, light therapy has the potential to positively influence a wide range of cognitive, emotional and physiological functions. Below, we discuss the known effects of various aspects (colors, intensities) of light across the range of human performance. These findings are additionally summarized in Table 1.

Polychromatic white light

Polychromatic white light is essentially a broad-spectrum light. Because white light includes nearly all wavelengths, it also encompasses the blue light portion of the spectrum (~460–448 nm) that selectively activates ipRGCs and therefore has important circadian and hormone-secreting properties [31]. Consequently, it could be expected that white or bright light therapy would induce changes in post-mTBI circadian rhythms, sleep and alertness.

A recent meta-analysis indicates that light therapy in general is effective in the treatment of sleep disorders that include circadian rhythm sleep disorders, insomnia, and sleep problems associated with Alzheimer's disease and dementia [27]. This meta-analysis included randomized controlled trials and within-subject design studies utilizing polychromatic white light, and blue-enriched white light, as well as several studies utilizing monochromic blue light. Overall, positive effects for light therapy were observed for circadian shifts, bed and wake times, sleep onset latency, total sleep time, wake after sleep onset, sleep efficiency, sleepiness and alertness, sleep quality, insomnia symptoms and fatigue [27]. The authors additionally report that light intensity (ranging from 2000 to 10,000 lux in the majority of included studies) had positive effects on individuals with insomnia, with greater intensity increasing the beneficial effects of light therapy [27]. In estimating effect sizes, the authors did not distinguish the effects of bright light from those of blue light; however, only 9% of the included studies specifically examined blue light.

An additional systematic review by Souman *et al.* examined the effects of light therapy on alertness. Across the reviewed literature, there is the indication that increasing the intensity of polychromatic white light significantly increases subjective alertness [28]. However, this does not appear to translate into improved vigilance or reaction. Additionally, there is limited evidence for significant improvements in subjective or performance-based measures of alertness with blue-shifted polychromatic white light [28]. Cumulatively, these findings suggest that the intensity of polychromatic white light may have positive effects on subjective alertness.

Furthermore, polychromatic white light therapy has been shown to be effective in reducing depressive symptoms in individuals with diagnosed depression, including major depressive disorder. Recent meta-analyses indicate that light therapy, especially polychromatic white light, reduces depressive symptoms at post treatment compared with control participants and this effect is more pronounced for standalone light therapy than for studies using light as an adjunctive therapy [29,143]. The effect is additionally stronger when light therapy is used in the morning than any other time [29]. These effects were observed over studies including polychromatic white, green and pale blue light [29,143].

Monochromatic blue & blue-shifted white light

As previously noted with polychromatic white light, blue light therapy – including monochromatic blue and blue-enriched white light – alters circadian rhythms, particularly the timing of melatonin release, in individuals with a variety of sleep-disrupted conditions [27,144]. These studies demonstrate that short amounts (30 min or more) of focused and intentional daily light therapy in the morning effectively advances individuals' circadian rhythms, evidenced by the timing of melatonin secretion. In general, the effects of phototherapy are condition dependent, but may include changes in circadian rhythm and improvements in sleep duration, self-reported sleep quality, insomnia symptoms and fatigue [27].

In addition to the direct effects of monochromatic blue light therapy on sleep quantity and quality, the appropriate timing of melatonin secretion is essential for maintaining normal daytime arousal and minimizing fatigue. There is robust evidence that blue-wavelength light is effective in acutely decreasing sleepiness and fatigue [145–152] as well as increasing concentrations of arousal-promoting hormones (e.g., cortisol) [153]. Furthermore, blue light therapy has positive effects on increasing alertness [145,147,149,152,154–169]. This phenomenon is present both during the day (e.g., morning blue light exposure) and night.

Prior work has additionally demonstrated that blue light therapy increases activation in cognition-related, task-specific brain regions [157,159,170–176]. However, while light affects brain activation, the actual behavioral effects of blue light exposure are not quite as clear. Individual studies have demonstrated improvements in cognitive performance on working memory, digit recall, sustained attention and arithmetic tasks while others have shown no improvements or even reduced performance in response to light exposure [145,158,169,176–184]. It is thus unclear the extent to which blue light therapy may directly affect cognitive performance beyond those conferred by improvements or alterations in sleep, fatigue or overall alertness.

With respect to mood and affect, blue or blue-shifted light can variously cause [143,185] or improve [29,186] depressive symptoms depending on the timing of therapy (e.g., when timing coincides with or in opposition to naturally expected patterns). Mood disorders, including depression, are associated with the homeostatic maintenance of circulating stress hormones. Among these, glucocorticoids like cortisol exhibit circadian rhythmicity, with a night-time accumulation period and clearance during the day [187,188]. Thus, blue light that influences circadian rhythms, as previously described for sleep and melatonin, may impart a beneficial effect on glucocorticoid expression when utilized in circadian-optimal timings or may induce or worsen mood disorders when mistimed (e.g., night-time use of light-emitting diode screens).

However, one potential pitfall in the application of blue light therapy as described to this point is the exacerbation of PTH. The blue light-sensitive ipRGCs directly project to the trigeminovascular neurons in the thalamus [40]. Prior research related to migraine indicates that these neurons transmit nociceptive signals originating in the dura to cortex, thereby contributing to the perception of intracranial pain during a migraine [40]. Furthermore ipRGC inputs onto the trigeminovascular neurons may modulate the response to light by migraineurs. This neural mechanism may explain why individuals feel worse when exposed to light and preferentially seek dark rooms for relief (photophobia) when experiencing a migraine. While the overarching neural mechanisms of mTBI-related PTH resemble, but may not be exactly the same as those for migraine [140], light-based exacerbation of PTH and/or photophobic responses by individuals post-mTBI may likely have the same neural underpinning. Thus it is plausible that, despite the numerous potential benefits of blue light on circadian rhythms, fatigue, alertness and cognition following mTBI, blue-light or blue-shifted white light treatments may be poorly tolerated and may indeed worsen PTH in some individuals. At present, this specific possibility has not been directly explored in treatment studies using blue light for treating symptoms of mTBI, but research on this topic would be a welcome addition to the literature.

Monochromatic red light

For individuals seeking to enhance alertness without modifying their circadian rhythm (e.g., increasing daytime alertness in the presence of a normal circadian rhythm), utilizing blue light therapy may have unintended and unwanted effects, primarily on melatonin secretion. Interestingly, prior work has shown that longer wavelength light (e.g., red light) may have equally powerful alerting effects [157,160–164]. Red light is detected by L-cones in the retina, and the ipRGCs that are sensitive to blue light are not sensitive to the longer wavelengths (~630 nm) of red light [31,33]. In some preliminary work, the alerting effects of red light were present both in the late afternoon and at night, and were comparable to the effects of blue light. While the mechanisms by which red light has an alerting effect are not fully understood, a plausible explanation is that it may influence the actions of subcortical regions apart from SCN resulting in alerting effects unrelated to melatonin secretion or suppression [159,170].

Monochromatic green light

While the use of blue light may exert its most profound effects on circadian phase advancement or resetting circadian rhythms that mediate sleep, blue light specifically suppresses melatonin secretion thereby inhibiting or delaying the actual onset of sleep. Though possibly beneficial for altering post-mTBI sleep timing or reducing daytime sleepiness and fatigue, this effect on melatonin does nothing for actually promoting night-time sleep. On the other hand, preliminary evidence from animal models suggests that green light (~530 nm) indeed has a sleep-promoting function [189]. This has not yet been confirmed in human studies and the specific mechanisms are not described as yet, though multisynaptic M-cone projections to the ventrolateral preoptic area (involved in sleep promotion) and lateral hypothalamus (where wake-promoting orexin is secreted) may plausibly create this relationship [189,190].

As previously noted, blue light may also have the unintended consequence of aggravating PTHs. However, further research with migraineurs demonstrates that the use of green light has a positive effect on migraine symptoms, including at a minimum no exacerbation of the headache and at best a decrease in the intensity of symptoms [191].

This effect is observed relative to the use of white, blue, amber and red light. Additionally, animal models have demonstrated that green light confers antinociceptive benefits, both at the sensory threshold and with neuropathic pain [192]. Therefore, individuals with mTBI-related PTH or pain may benefit either from environments bathed in green light or from glasses, which preferentially filter the spectra of incoming light to preferentially include green light.

Light therapy following mTBI

To date, two published studies have specifically examined the effects of light therapy following mTBI. Sinclair *et al.* exposed participants to 45 min of morning blue or yellow light for 4 weeks [193]. They demonstrated that individuals receiving blue light, as opposed to yellow light or no treatment, reported less daytime fatigue and sleepiness, faster response times on a sustained psychomotor vigilance task, less self-reported sleep disruption and lower self reports of depression symptoms at 2 and 4 weeks than at baseline. These findings suggest that, for post-mTBI individuals who do self-report fatigue, daytime sleepiness or sleep disruption, daily blue light therapy may be an effective nonpharmacological method for improving function in these areas. It is unclear, however, whether these effects persist after treatment cessation.

Additionally, a study by Bajaj *et al.* had mTBI participants use blue-wavelength light therapy or an amber-wavelength placebo light for 30 min every morning for 6 weeks and found that it was associated with significant changes in white matter integrity (as measured by water diffusion along axonal tracts) within the corpus collosum, corona radiata and thalamus [194]. Moreover, for those receiving blue-light treatment, the magnitude of white matter changes was associated with greater sleep latency on the multiple sleep latency test, which is an objective measure of biological sleepiness. Additionally, they found that the increases in white matter integrity were associated with an improvement in delayed memory performance, but only among those receiving the blue light treatment. These associations were not significant among those receiving the amber light placebo condition. In other words, 6 weeks of blue light therapy appeared to increase the integrity of axonal white matter, and this change was associated with decreased tendency to fall asleep during the day as well as improved delayed memory performance.

Furthermore there is some evidence suggesting that there may be positive effects of blue light exposure on anxiety following mTBI [195,196]. In fact, even a single 30-min exposure to blue-wavelength light appears to increase activation of the anterior cingulate cortex when anticipating positive stimuli compared with an amber placebo light, which might help explain the mood and anxiety improvements that follow blue light exposure [196]. Thus, limited evidence suggests that blue-wavelength light may be effective for some aspects of recovery from mTBI, but more research is needed before the benefits of this approach are fully understood.

Extrapolating the findings from both healthy individuals and those with other neurological conditions as well as animal studies, there may be additional unidentified benefits of light therapy for mTBI beyond those that have been specifically identified. Both polychromatic white and blue lights may be useful for resetting aberrant circadian rhythms, improving sleep, decreasing daytime sleepiness and fatigue, increasing alertness, and decreasing depressive symptoms. Red light may be beneficial for improving alertness without inducing circadian shifts, but more work is needed. Green light may help to promote night-time sleep, minimize PTH and reduce pain. However, given the paucity of studies on post-mTBI light therapy, these applications are speculative at best. Though there is the indication of positive effects on both neural and behavioral outcomes, these findings require further corroboration with larger studies and diverse mTBI populations. Future research objectives are presented in Box 1.

Additional uses of light

In addition to the potential benefits of using visible light as a treatment method, low-level laser therapy (LLLT) has noted wound healing and anti-inflammatory properties, particularly in the near-infrared spectral range. While LLLT is beyond the scope of the present discussion, we encourage readers to see [197] for a recent review on the use of LLLT for TBI.

Current limitations to using phototherapy for mTBI

As has been indicated in the preceding sections, there are numerous potential benefits to using light as an adjunctive therapy in the management of mTBIs. However, there are some limitations that currently limit the scale and scope of the inference that can be made regarding the effects of phototherapy in the recovery from mTBI. Notably, there is significant heterogeneity in light characteristics, timing, duration and illuminance of light therapy between studies that may all influence the outcomes of these studies [26,27,29,198]. Thus considerably more work is required,

Box 1. Future research objectives in the development of light therapy for mild traumatic brain injury recovery.

In light of the potential benefits of light therapy in mild traumatic brain injury recovery as well as the physiological nonimage-forming light pathways, the following research objectives are reasonable targets for exploration:

Sleep-related research

- Expanding current efforts to identify the effects of monochromatic blue light to correct aberrant circadian rhythms, improve sleep, reduce daytime fatigue and improve white matter integrity
- Identifying the optimal dosage and timing of blue light
- Identifying positive effects and differences between polychromatic white light and monochromatic blue light as pertains to circadian rhythms and sleep metrics
- Identifying the optimal dosage and timing for the use of green light to improve night-time sleep onset
- Identifying the optimal dosage and timing for the use of red light to improve alertness without circadian shifting

Cognition

- Identifying the optimal color, timing and dosage of light to improve short-term activation related to cognitive function

Somatic

- Identifying whether green light reduces the presentation of post-traumatic headache
- Identifying whether green light reduces comorbid pain

Precision medicine

- Identifying the personal characteristics that will lead to responsiveness to light treatment (e.g., *PER3* polymorphisms, degree of circadian dysrhythmia, level of daytime sleepiness/fatigue)
- Development and refinement of treatment parameters throughout the day (i.e., timing of blue vs red vs green light therapy based on current symptoms and needs)

particularly for mTBI-related applications, to identify the optimal parameters that maximize the benefit to the individual.

Additionally, there is evidence that polymorphisms in the *PER3* clock gene may additionally explain interindividual differences in the relationship between light exposure and cognition [175]. Consequently, future studies and clinical applications of bright or blue light therapy, particularly for improving cognitive performance, should take genetic variations into account.

Furthermore, many studies employ some form of light box to deliver the phototherapy. These boxes are portable and allow individuals to be treated at home, which is a tremendous benefit. However, an unavoidable drawback to at-home treatments of this nature is compliance and adherence. Additionally, these boxes have limited spatial effectiveness and require the user to be within a certain distance from the light source in order to be effective. Consequently, treatment may be challenging or even impossible in individuals who are unable to remain in front of the light box for the treatment duration. Alternative light presentation methods, such as goggle-mounted light systems are currently being tested, and may afford greater ambulation and flexibility of use. At present, these devices have only been tested with a limited range of wavelengths and will require further research to determine their effectiveness.

Finally, safety concerns are always critical in deciding whether to use a particular treatment, and light therapy is no different. Some safety concerns have been raised for blue light, in particular. There is some evidence to suggest that retinal damage is possible with prolonged exposure to short-wavelength light. Though the optimal wavelength to stimulate ipRGCs (~480 nm) is considerably greater than violet and ultraviolet wavelengths where damage is more certain, it is a plausible concern [199]. However, there is no evidence in the published literature of such damage from the types of therapy described here [200]. Some companies who manufacture blue-wavelength light-box devices have had their products independently evaluated for blue-light retinal hazard and have reported the exposure hazard to be minimal at the distance, intensity and duration of light emitted for those devices. Another consideration is that the amount of blue-wavelength light emitted by most light-box devices is considerably less than that obtained by an equal duration of exposure to midday outdoor sunlight. Additionally, as noted with photophobia and PTH, many individuals do report headaches and other somatic symptoms with the use of light boxes [200]. Although there is no compelling evidence at this time that standard light therapy devices pose a significant optical hazard when used according to manufacturer's instructions, further research into the long-term safety and side effects of light exposure treatment is warranted. As with any treatment, decisions to engage in light therapy should involve judicious evaluation of the benefits and potential risks involved.

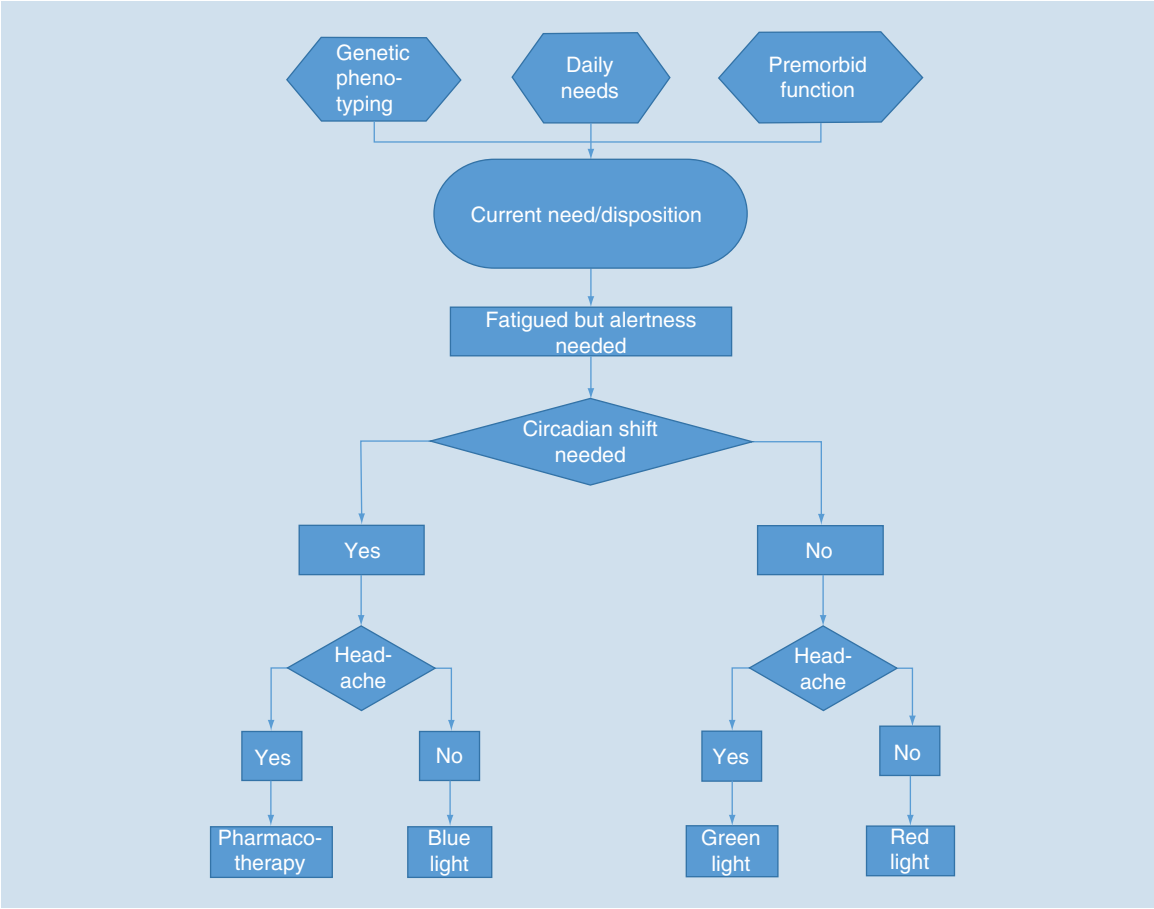


Figure 2. Example decision tree for a precision medicine, needs-based approach to light therapy.

Conclusions

Light is all around us and is an ingrained natural part of our biological rhythms and daily functioning. It is essential for image-forming vision and our ability to interact with the environment. The NIF impacts of light on physiology make it a powerful tool as well as a potent inhibitor of function. While considerable in-roads are being made to understand how early and active intervention may improve the outcomes from mTBIs, the individual's environment is an oft-ignored but important consideration. Light is a critical feature of our environment that has a powerful influence on our biology. There are numerous, interconnected systems that are impaired or altered by mTBIs and whose function can be influenced by exposure to light. Outcomes from two small-scale trials indicate that daily blue-wavelength light therapy may be effective for reducing daytime fatigue and improving sleep and efforts are underway to corroborate these findings. Further evidence from other populations indicates that other wavelengths may confer additional therapeutic benefits (e.g., green light for improving post-traumatic headache) and such findings require future research specific to mTBI.

Future perspective

We believe that significant advances in the use of light therapy can and will be made in the decade ahead to leverage these advantages and minimize the drawbacks. It is our position, though, that in order for light therapies to be effective for mTBI, or any condition, they must be specifically tailored to the individual (i.e., personalized medicine) and account for the uncontrollable aspects of the environment (e.g., sunlight during commuting, work environments with limited capacity to be modified). Accordingly, this requires a complete and ongoing needs assessment of the individual as well as an understanding of those aspects of the environment that can be adapted or modified to meet these needs.

For example, technological control of circadian lighting will require smart lights that shift dominant or active wavelengths throughout the day to mimic lighting patterns that more closely reflect sunlight while indoors (e.g., more blue light in the morning that gives way to more amber wavelengths in the late afternoon). These types of lights do not require a light box, but instead would completely replace existing ambient lighting methods. This technology could be leveraged at the home, or potentially the workplace, to ensure that ambient light maximizes the circadian benefit for the individual, and indeed entrains appropriate rhythms given individual needs. Furthermore, many of these circadian lighting systems could be internet connected. Therefore, tuning of ambient colors in response to an individual's daily needs could be accomplished through needs and symptom reporting via an internet-ready device (e.g., tablet, cellular phone).

Such a scenario would enable fine tuning the environment to meet daily, and even moment by moment, presentation of individualized mTBI-related symptoms. This may mean more blue in the morning for a person on a normal sleep–wake schedule, but for someone regularly engaged in shiftwork, this may mean more blue is presented in the evening as they prepare for work. Likewise, lighting could be manipulated to address symptom expression and behavioral needs, such as shifting to a more green-lit room if the individual reports pain or a headache on a given day or when falling asleep is a goal (Figure 2). Additionally, individuals could conceivably maximize cognitive performance and alertness by shifting to red light during the afternoon, evening or night for improved alertness without inducing an unwanted or unnecessary circadian shift that is associated with blue light.

In these scenarios, lighting patterns could be altered on a daily basis to reflect not only the individual's unchangeable physiology (e.g., *PER3* phenotype, which may limit the effect of blue light on sleep and cognition) and overarching needs (e.g., necessary wake times), but also day-to-day changes in mTBI-related symptoms, fatigue and cognitive demands. In so doing, and in conjunction with other medical management, we can leverage the environment to maximize recovery following mTBI and return biological systems to homeostatic states rapidly to facilitate full returns to work, school, sport and life.

Executive summary

Mild traumatic brain injury, sleepiness & fatigue

- Blue light is selectively absorbed by intrinsically photosensitive retinal ganglion cells. These cells project directly the suprachiasmatic nucleus and influence circadian rhythms and melatonin secretion.
- There is some evidence suggesting that mild traumatic brain injuries (mTBIs) induced circadian dysrhythmias.
- Targeted use of blue light can be used to shift circadian rhythms and improve nighttime sleeping and daytime fatigue.
- Emerging evidence suggests that green light may be an effective sleep promoter.

mTBI & alertness

- Blue light improves daytime fatigue and sleepiness, leading to greater alertness.
- Red light also improves alertness and may be useful when affecting circadian rhythms is undesired.

mTBI & cognition

- Blue light potentiates activation in areas associated with multidomain cognition. Further work is needed to more completely understand these mechanisms.

mTBI & depression

- Depression is a common post-mTBI complaint. Prior work demonstrates that blue light is effective in improving both seasonal and nonseasonal depression.

mTBI, post-traumatic headache & pain

- Despite the positive effects of blue light, the intrinsically photosensitive retinal ganglion cells also project to thalamic neurons that receive input from dural nociceptors that are active during migraine headaches. Blue light therapy may exacerbate post-traumatic headaches.
- Green light does not exacerbate migraine headaches and in some cases improves symptom presentation.

Future perspective

- Phototherapy has the potential to modify the brain's functioning across a wide range of affected systems following mTBI.
- Technology exists that enables ambient lighting to be modified on demand to change the visible spectrum to meet needs.
- A personalized medicine approach – combining genetic phenotyping, injury characteristics, current symptoms and current needs to create an optimal ambient light profile – could make phototherapy a potent, ever-present aspect of mTBI management and recovery.

Financial & competing interests disclosure

This work was supported by multiple grants from the US Army Medical Research and Materiel Command (USAMRMC) to W D S Killgore, including W81XWH-14-1-0570 and W81XWH-14-1-0571. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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References

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006 [Internet]. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Atlanta, USA Available from: http://origin.glb.cdc.gov/traumaticbraininjury/pdf/blue_book.docx
2. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. *Clin. Sports Med.* 30(1), 1–17 (2011).
3. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J. Head Trauma Rehabil.* 21(5), 375–378 (2006).
4. Kerr ZY, Register-Mihalik JK, Kroshus E, Baugh CM, Marshall SW. Motivations associated with nondisclosure of self-reported concussions in former collegiate athletes. *Am. J. Sports Med.* 44(1), 220–225 (2016).
5. Register-Mihalik JK, Guskiewicz KM, McLeod TCV, Linnan LA, Mueller FO, Marshall SW. Knowledge, attitude, and concussion-reporting behaviors among high school athletes: a preliminary study. *J. Athletic Training* 48(5), 645–653 (2013).
6. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nature Rev. Neurol.* 9(4), 211–221 (2013).
7. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. *Alzheimers Dement.* 10(3, Suppl.), S242–S253 (2014).
8. McKee AC, Alosco ML, Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurg. Clin. N. Am.* 27(4), 529–535 (2016).
9. Harris MA, Shen H, Marion SA, Tsui JK, Teschke K. Head injuries and Parkinson's disease in a case–control study. *Occup. environ. Med.* 70(12), 839–844 (2013).
10. Chiò A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 128(3), 472–476 (2005).
11. Martini DN, Broglio SP. Long-term effects of sport concussion on cognitive and motor performance: a review. *Int. J. Psychophysiol.* (2017). www.sciencedirect.com/science/article/pii/S0167876017305779
12. Dalecki M, Albines D, Macpherson A, Sergio LE. Prolonged cognitive-motor impairments in children and adolescents with a history of concussion. *Concussion* 1, CNC14 (2016).
13. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological profile of lifetime traumatic brain injury in older veterans. *J. Int. Neuropsychol. Soc.* 23(1), 56–64 (2017).
14. Goswami R, Dufort P, Tartaglia MC *et al.* Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct. Funct.* 221(4), 1911–1925 (2016).
15. Esopenko C, Chow TW, Tartaglia MC *et al.* Cognitive and psychosocial function in retired professional hockey players. *J. Neurol. Neurosurg. Psychiatry* 88(6), 512–519 (2017).
16. Rao V, Syeda A, Roy D, Peters ME, Vaishnavi S. Neuropsychiatric aspects of concussion: acute and chronic sequelae. *Concussion* 2(1), CNC29 (2017).
17. Guskiewicz KM, Marshall SW, Bailes J *et al.* Recurrent concussion and risk of depression in retired professional football players. *Med. Sci. Sports Exerc.* 39(6), 903–909 (2007).
18. Stein E, Howard W, Rowhani-Rahbar A, Rivara FP, Zatzick D, McCarty CA. Longitudinal trajectories of post-concussive and depressive symptoms in adolescents with prolonged recovery from concussion. *Brain Inj.* 31(13–14), 1736–1744 (2017).
19. Kontos AP, Deitrick JM, Reynolds E. Mental health implications and consequences following sport-related concussion. *Br. J. Sports Med.*50(3), 139–140 (2015).
20. Kontos AP, Covassin T, Elbin RJ, Parker T. Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. *Arch. Phys. Med. Rehabil.* 93(10), 1751–1756 (2012).

21. Maas AIR, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics* 7(1), 115–126 (2010).
22. Dobney DM, Miller MB, Tufts E. Non-pharmacological rehabilitation interventions for concussion in children: a scoping review. *Disabil. Rehabil.* 1–13 (2017).
23. Kontos AP, Collins MW, Holland CL *et al.* Preliminary evidence for improvement in symptoms, cognitive, vestibular, and oculomotor outcomes following targeted intervention with chronic mTBI patients. *Mil Med.* 183(Suppl. 1), 333–338 (2018).
24. Collins MW, Kontos AP, Reynolds E, Murawski CD, Fu FH. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surg. Sports Traumatol. Arthrosc.* 22(2), 235–246 (2014).
25. Dobney DM, Grilli L, Kocilowicz H *et al.* Evaluation of an active rehabilitation program for concussion management in children and adolescents. *Brain Inj.* 31(13/14), 1753–1759 (2017).
26. Gaggioni G, Maquet P, Schmidt C, Dijk D-J, Vandewalle G. Neuroimaging, cognition, light and circadian rhythms. *Front. Syst. Neurosci.* 8 (2014). www.frontiersin.org/articles/10.3389/fnsys.2014.00126/full
27. van Maanen A, Meijer AM, van der Heijden KB, Oort FJ. The effects of light therapy on sleep problems: a systematic review and meta-analysis. *Sleep Med. Rev.* 29, 52–62 (2016).
28. Souman JL, Tinga AM, te Pas SF, van Ee R, Vlaskamp BNS. Acute alerting effects of light: a systematic literature review. *Behav. Brain Res.* 337, 228–239 (2018).
29. Perera S, Eisen R, Bhatt M *et al.* Light therapy for non-seasonal depression: systematic review and meta-analysis. *BJPsych. Open* 2(2), 116–126 (2016).
30. Nassi JJ, Callaway EM. Parallel processing strategies of the primate visual system. *Nat. Rev. Neurosci.* 10(5), 360–372 (2009).
31. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295(5557), 1070–1073 (2002).
32. Dacey DM, Liao H-W, Peterson BB *et al.* Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature* 433(7027), 749–754 (2005).
33. Hattar S, Liao H-W, Takao M, Berson DM, Yau K-W. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295(5557), 1065–1070 (2002).
34. Hattar S, Kumar M, Park A *et al.* Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J. Comp. Neurol.* 497(3), 326–349 (2006).
35. Dewan K, Benloucif S, Reid K, Wolfe LF, Zee PC. Light-induced changes of the circadian clock of humans: increasing duration is more effective than increasing light intensity. *Sleep* 34(5), 593–599 (2011).
36. Klein DC, Smoot R, Weller JL *et al.* Lesions of the paraventricular nucleus area of the hypothalamus disrupt the suprachiasmatic→ spinal cord circuit in the melatonin rhythm generating system. *Brain Res. Bull.* 10(5), 647–652 (1983).
37. Moore RY, Lenn NJ. A retinohypothalamic projection in the rat. *J. Comp. Neurol.* 146(1), 1–14 (1972).
38. Pickard GE, Silverman A-J. Direct retinal projections to the hypothalamus, piriform cortex, and accessory optic nuclei in the golden hamster as demonstrated by a sensitive anterograde horseradish peroxidase technique. *J. Comp. Neurol.* 196(1), 155–172 (1981).
39. Vandewalle G, Schwartz S, Grandjean D *et al.* Spectral quality of light modulates emotional brain responses in humans. *PNAS* 107(45), 19549–19554 (2010).
40. Noseda R, Kainz V, Jakubowski M *et al.* A neural mechanism for exacerbation of headache by light. *Nat. Neurosci.* 13(2), 239–245 (2010).
41. Ciuffreda KJ, Joshi NR, Truong JQ. Understanding the effects of mild traumatic brain injury on the pupillary light reflex. *Concussion* 2(3), CNC36 (2017).
42. McCrory P, Meeuwisse W, Dvorak J *et al.* Consensus statement on concussion in sport – The 5th international conference on concussion in sport held in Berlin, October 2016. *Br. J. Sports Med.* 51, 838–847 (2017).
43. Basic information about traumatic brain injury and concussion | Concussion | Traumatic brain injury | CDC Injury Center [Internet]. www.cdc.gov/traumaticbraininjury/basics.html
44. O'Neil ME, Carlson K, Storzbach D *et al.* Definition of MTBI from the VA/DOD clinical practice guideline for management of concussion/mild traumatic brain injury (2009) [Internet]. Department of Veterans Affairs (US) www.ncbi.nlm.nih.gov/books/NBK189784/
45. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* 8(3), 86 (1993).
46. Makdissi M, Schneider KJ, Feddermann-Demont N *et al.* Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review. *Br. J. Sports Med.* 51(12), 958–968 (2017).
47. Institute of Medicine (US) Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation: an unmet public health problem [Internet]. National Academies Press, WA (DC), USA www.ncbi.nlm.nih.gov/books/NBK19960/
48. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J. Pain* 14(12), 1539–1552 (2013).

49. Schlarb AA, Claßen M, Hellmann SM, Vögele C, Gulewitsch MD. Sleep and somatic complaints in university students. *J. Pain Res.* 10, 1189–1199 (2017).
50. Minkel JD, Banks S, Htaik O *et al.* Sleep deprivation and stressors: evidence for elevated negative affect in response to mild stressors when sleep deprived. *Emotion* 12(5), 1015–1020 (2012).
51. Prather AA, Vogelzangs N, Penninx BWJH. Sleep duration, insomnia, and markers of systemic inflammation: results from the Netherlands Study of Depression and Anxiety (NESDA). *J. Psychiatr. Res.* 60, 95–102 (2015).
52. Samaranayake CB, Arroll B, Fernando AT. Sleep disorders, depression, anxiety and satisfaction with life among young adults: a survey of university students in Auckland, New Zealand. *N. Z. Med. J.* 127(1399), 13–22 (2014).
53. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136(3), 375–389 (2010).
54. Renn RP, Cote KA. Performance monitoring following total sleep deprivation: effects of task type and error rate. *Int. J. Psychophysiol.* 88(1), 64–73 (2013).
55. Nankar M, Szturm T, Marotta J, Shay B, Beauchet O, Allali G. The interacting effects of treadmill walking and different types of visuospatial cognitive task: discriminating dual task and age effects. *Arch. Gerontol. Geriatr.* 73, 50–59 (2017).
56. Heaton KJ, Maule AL, Maruta J, Kryskow EM, Ghajar J. Attention and visual tracking degradation during acute sleep deprivation in a military sample. *Aviat. Space Environ. Med.* 85(5), 497–503 (2014).
57. Furtado F, Gonçalves B da SB, Abranches ILL, Abrantes AF, Forner-Cordero A. Chronic low quality sleep impairs postural control in healthy adults. *PLoS ONE* 11(10), e0163310 (2016).
58. Martin T, Gauthier A, Ying Z *et al.* Effect of sleep deprivation on diurnal variation of vertical perception and postural control. *J. Appl. Physiol.* (2018). www.physiology.org/doi/abs/10.1152/japplphysiol.00595.2017
59. Watson AM. Sleep and athletic performance. *Curr. Sports Med. Rep.* 16(6), 413 (2017).
60. Altman NG, Izci-Balserak B, Schopfer E *et al.* Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. *Sleep Med.* 13(10), 1261–1270 (2012).
61. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. *Best Pract. Res. Clin. Endocrinol. Metab.* 24(5), 731–743 (2010).
62. Zizi F, Jean-Louis G, Brown CD, Ogedegbe G, Boutin-Foster C, McFarlane SI. Sleep duration and the risk of diabetes mellitus: epidemiologic evidence and pathophysiologic insights. *Curr. Diab. Rep.* 10(1), 43–47 (2010).
63. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens. Res.* 36(11), 985–995 (2013).
64. Tranah GJ, Blackwell T, Stone KL *et al.* Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann. Neurol.* 70(5), 722–732 (2011).
65. Stern AL, Naidoo N. Wake-active neurons across aging and neurodegeneration: a potential role for sleep disturbances in promoting disease. *SpringerPlus* 4, 25 (2015).
66. Tan SL, Storm V, Reinwand DA, Wienert J, de Vries H, Lippke S. Understanding the positive associations of sleep, physical activity, fruit and vegetable intake as predictors of quality of life and subjective health across age groups: a theory based, cross-sectional web-based study. *Front. Psychol.* 9 (2018). Available from: www.frontiersin.org/articles/10.3389/fpsyg.2018.00977/full
67. Figueiro M, Overington D. Self-luminous devices and melatonin suppression in adolescents. *Lighting Res. Technol.* 48(8), 966–975 (2016).
68. Gooley JJ. Light resetting and entrainment of human circadian rhythms [Internet]. In: *Biological Timekeeping: Clocks, Rhythms and Behaviour*. Springer, New Delhi, India, 297–313 (2017). https://link.springer.com/chapter/10.1007/978-81-322-3688-7_14
69. Zietzer JM, Dijk D-J, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J. Physiol.* 526(3), 695–702 (2004).
70. Wickwire EM, Williams SG, Roth T *et al.* Sleep, sleep disorders, and mild traumatic brain injury. what we know and what we need to know: findings from a National Working Group. *Neurotherapeutics* 13(2), 403–417 (2016).
71. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J. Head Trauma Rehabil.* 21(3), 199–212 (2006).
72. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Sleep–wake disturbances after traumatic brain injury. *Lancet Neurol.* 14(7), 746–757 (2015).
73. Wiseman-Hakes C, Colantonio A, Gargaro J. Sleep and wake disorders following traumatic brain injury: a systematic review of the literature. *Crit. Rev. Phys. Rehabil. Med.* 21(3–4), 317–374 (2009).
74. Gosselin N, Lassonde M, Petit D *et al.* Sleep following sport-related concussions. *Sleep Med.* 10(1), 35–46 (2009).
75. Theadom A, Cropley M, Parmar P *et al.* Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med.* 16(8), 926–932 (2015).

76. Sullivan KA, Edmed SL, Allan AC, Karlsson LJE, Smith SS. Characterizing self-reported sleep disturbance after mild traumatic brain injury. *J. Neurotrauma* 32(7), 474–486 (2014).

77. Hinds A, Jungquist CR, Leddy JJ, Seemant F, Baker JG, Willer B. Sleep disturbance in patients with chronic concussive effects. *Concussion* 1(3), CNC15 (2016).

78. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. *Brain Inj.* 16(3), 197–206 (2002).

79. Fichtenberg NL, Putnam SH, Mann NR, Zafonte RD, Millard AE. Insomnia screening in postacute traumatic brain injury: utility and validity of the Pittsburgh Sleep Quality Index. *Am. J. Phys. Med. Rehabil.* 80(5), 339–345 (2001).

80. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep–wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* 130(7), 1873–1883 (2007).

81. Theadom A, Rowland V, Levack W *et al.* Exploring the experience of sleep and fatigue in male and female adults over the 2 years following traumatic brain injury: a qualitative descriptive study. *BMJ Open.* 6(4), e010453 (2016).

82. Kempf J, Werth E, Kaiser PR, Bassetti CL, Baumann CR. Sleep-wake disturbances 3 years after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 81(12), 1402–1405 (2010).

83. Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. Prevalence and consequences of sleep disorders in traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 349–356 (2007).

84. Imbach LL, Büchele F, Valko PO *et al.* Sleep–wake disorders persist 18 months after traumatic brain injury but remain underrecognized. *Neurology* 86(21), 1945–1949 (2016).

85. Imbach LL, Valko PO, Li T *et al.* Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. *Brain* 138(3), 726–735 (2015).

86. Mollayeva T, Shapiro CM, Cassidy JD, Mollayeva S, Colantonio A. Assessment of concussion/mild traumatic brain injury-related fatigue, alertness, and daytime sleepiness: a diagnostic modelling study. *Neuropsychiatry* 7(2), 86–104 (2017).

87. Sommerauer M, Valko PO, Werth E, Baumann CR. Excessive sleep need following traumatic brain injury: a case–control study of 36 patients. *J. Sleep Res.* 22(6), 634–639 (2013).

88. Watson NF, Dikmen S, Machamer J, Doherty M, Temkin N. Hypersomnia following traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 363–368 (2007).

89. Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders following mild traumatic brain injury. *Neurology* 68(14), 1136–1140 (2007).

90. Verma A, Anand V, Verma NP. Sleep disorders in chronic traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 357–362 (2007).

91. Schreiber S, Barkai G, Gur-Hartman T *et al.* Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Med.* 9(5), 481–487 (2008).

92. Williams BR, Lazic SE, Ogilvie RD. Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clin. Neurophysiol.* 119(2), 429–438 (2008).

93. Khoury S, Chouchou F, Amzica F *et al.* Rapid EEG activity during sleep dominates in mild traumatic brain injury patients with acute pain. *J. Neurotrauma* 30(8), 633–641 (2013).

94. Lu W, Cantor JB, Aurora RN *et al.* The relationship between self-reported sleep disturbance and polysomnography in individuals with traumatic brain injury. *Brain Inj.* 29(11), 1342–1350 (2015).

95. Mollayeva T, Colantonio A, Cassidy JD, Vernich L, Moineddin R, Shapiro CM. Sleep stage distribution in persons with mild traumatic brain injury: a polysomnographic study according to American Academy of Sleep Medicine standards. *Sleep Med.* 34, 179–192 (2017).

96. Shekleton JA, Parcell DL, Redman JR, Phipps-Nelson J, Ponsford JL, Rajaratnam SMW. Sleep disturbance and melatonin levels following traumatic brain injury. *Neurology* 74(21), 1732 (2010).

97. Paparrigopoulos T, Melissaki A, Tsekou H *et al.* Melatonin secretion after head injury: a pilot study. *Brain Inj.* 20(8), 873–878 (2006).

98. Seifman MA, Gomes K, Nguyen PN *et al.* Measurement of serum melatonin in intensive care unit patients: changes in traumatic brain injury, trauma, and medical conditions. *Front. Neurol.* 5 (2014). http://journal.frontiersin.org/article/10.3389/fneur.2014.00237/abstract

99. Valko PO, Gavrilov YV, Yamamoto M *et al.* Damage to histaminergic tuberomammillary neurons and other hypothalamic neurons with traumatic brain injury. *Ann. Neurol.* 77(1), 177–182 (2015).

100. Baumann CR, Stocker R, Imhof H *et al.* Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology* 65(1), 147–149 (2005).

101. Baumann CR, Bassetti CL, Valko PO *et al.* Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann. Neurol.* 66(4), 555–559 (2009).

102. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J. Athl. Train.* 36(3), 228–235 (2001).

103. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery* 75(4), S24–S33 (2014).

104. Zielinski MR, Dunbrasky DL, Taishi P, Souza G, Krueger JM. Vagotomy attenuates brain cytokines and sleep induced by peripherally administered tumor necrosis factor-α and lipopolysaccharide in mice. *Sleep* 36(8), 1227–1238 (2013).

105. Xie L, Kang H, Xu Q *et al.* Sleep drives metabolite clearance from the adult brain. *Science* 342(6156), 373–377 (2013).

106. Lucke-Wold BP, Smith KE, Nguyen L *et al.* Sleep disruption and the sequelae associated with traumatic brain injury. *Neurosci. Biobehav. Rev.* 55, 68–77 (2015).

107. Iliff JJ, Chen MJ, Plog BA *et al.* Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J. Neurosci.* 34(49), 16180–16193 (2014).

108. Beaulieu C, Turcotte-Giroux A, Carrier-Toutant F, Brisson B, Jolicoeur P, De Beaumont L. Long-term effects of concussions on psychomotor speed and cognitive control processes during motor sequence learning. *J. Psychophysiol.* 1–13 (2018).doi:10.1027/0269-8803/a000213 .

109. Beaulieu-Bonneau S, Fortier-Brochu É, Ivers H, Morin CM. Attention following traumatic brain injury: neuropsychological and driving simulator data, and association with sleep, sleepiness, and fatigue. *Neuropsychol. Rehabil.* 27(2), 216–238 (2017).

110. Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J. Neurol. Neurosurg. Psychiatry* 77(2), 241–245 (2006).

111. McCrea M. Mild traumatic brain injury and postconcussion syndrome: the new evidence base for diagnosis and treatment [Internet]. Oxford University Press, NY, USA https: //books.google.com/books?hl=en&lr=&id=Y0M9LOL40EMC&oi=fnd&pg=PR5&dq=(%E2%80%9Cconcuss*%E2%80%9D+OR+%E2%80%9CmTBI%E2%80%9D+OR+%E2%80%9Cmild+traumatic+brain+injury%E2%80%9D+OR+%E2%80%9Cclosed+head+injury%E2%80%9D)+*cognitive+OR+%22*cognitive+test%22&ots=O-7Hb_xFz3&sig=5bYbyWPNwzegDkNwGnYlSloUQ5M

112. McCrea M, Guskiewicz K, Doncevic S *et al.* Day of injury cognitive performance on the Military Acute Concussion Evaluation (MACE) by US military service members in OEF/OIF. *Mil. Med.* 179(9), 990–997 (2014).

113. McCrea M, Guskiewicz KM, Marshall SW *et al.* Acute effects and recovery time following concussion in collegiate football players: The NCAA Concussion Study. *JAMA* 290(19), 2556–2563 (2003).

114. Gaines KD, Soper HV, Berenji GR. Executive functioning of combat mild traumatic brain injury. *Appl. Neuropsychol. Adult* 23(2), 115–124 (2016).

115. Sim A, Terryberry-Spohr L, Wilson KR. Prolonged recovery of memory functioning after mild traumatic brain injury in adolescent athletes. *J. Neurosurg.* 108(3), 511–516 (2008).

116. Covassin T, Elbin RJ, Nakayama Y. Tracking neurocognitive performance following concussion in high school athletes. *Phys. Sportsmed.* 38(4), 87–93 (2010).

117. Covassin T, Elbin RJ, Harris W, Parker T, Kontos A. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. *Am. J. Sports Med.* 40(6), 1303–1312 (2012).

118. Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Ann. N. Y. Acad. Sci.* 1129(1), 305–322 (2008).

119. Killgore WDS. Effects of sleep deprivation on cognition [Internet]. In: *Progress in Brain Research*. Kerkhof GA, van Dongen HPA (Eds). Elsevier, CambridgeMA. 105–129 (2010) www.sciencedirect.com/science/article/pii/B9780444537027000075

120. Killgore WD, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ. Sustaining executive functions during sleep deprivation: a comparison of caffeine, dextroamphetamine, and modafinil. *Sleep* 32(2), 205–216 (2009).

121. Yrondi A, Brauge D, LeMen J, Arbus C, Pariente J. Depression and sports-related concussion: a systematic review. *La Presse Médicale* 46(10), 890–902 (2017).

122. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N. Engl. J. Med.* 358(5), 453–463 (2008).

123. Decq P, Gault N, Blandeau M *et al.* Long-term consequences of recurrent sports concussion. *Acta Neurochir.* 158(2), 289–300 (2016).

124. Stazyk K, DeMatteo C, Moll S, Missiuna C. Depression in youth recovering from concussion: correlates and predictors. *Brain Inj.* 31(5), 631–638 (2017).

125. Vargas G, Rabinowitz A, Meyer J, Arnett PA. Predictors and prevalence of postconcussion depression symptoms in collegiate athletes. *J. Athl. Train.* 50(3), 250–255 (2015).

126. Yang J, Peek-Asa C, Covassin T, Torner JC. Post-concussion symptoms of depression and anxiety in division I collegiate athletes. *Dev. Neuropsychol.* 40(1), 18–23 (2015).

127. Theadom A, Parag V, Dowell T *et al.* Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand. *Br. J. Gen. Pract.* 66(642), e16–e23 (2016).

128. Chaput G, Giguère J-F, Chauny J-M, Denis R, Lavigne G. Relationship among subjective sleep complaints, headaches, and mood alterations following a mild traumatic brain injury. *Sleep Med.* 10(7), 713–716 (2009).

129. Kerr ZY, Marshall SW, Harding HP, Guskiewicz KM. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. *Am. J. Sports Med.* 40(10), 2206–2212 (2012).

130. Packard RC. Chronic post-traumatic headache: associations with mild traumatic brain injury, concussion, and post-concussive disorder. *Curr. Pain Headache Rep.* 12(1), 67–73 (2008).

131. Packard RC. Epidemiology and pathogenesis of posttraumatic headache. *J. Head Trauma Rehabil.* 14(1), 9 (1999).

132. Faux S, Sheedy J. A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Med.* 9(8), 1001–1011 (2008).

133. Stovner LJ, Schrader H, Mickevičiene D, Surkiene D, Sand T. Headache after concussion. *Eur. J. Neurol.* 16(1), 112–120 (2009).

134. Terrio H, Brenner LA, Ivins BJ *et al.* Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J. Head Trauma Rehabil.* 24(1), 14–23 (2009).

135. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache* 50(8), 1262–1272 (2010).

136. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* 300(6), 711–719 (2008).

137. Mollayeva T, Cassidy JD, Shapiro CM, Mollayeva S, Colantonio A. Concussion/mild traumatic brain injury-related chronic pain in males and females: a diagnostic modelling study. *Medicine* 96(7), e5917 (2017).

138. Kjeldgaard D, Forchhammer H, Teasdale T, Jensen RH. Chronic post-traumatic headache after mild head injury: a descriptive study. *Cephalalgia* 34(3), 191–200 (2014).

139. Grandhi R, Tavakoli S, Ortega C, Simmonds MJ. A review of chronic pain and cognitive, mood, and motor dysfunction following mild traumatic brain injury: complex, comorbid, and/or overlapping conditions? *Brain Sci.* 7(12), 1–8 (2017).

140. Ruff RL, Blake K. Pathophysiological links between traumatic brain injury and post-traumatic headaches. *F1000Res.* 5 (2016). www.ncbi.nlm.nih.gov/pmc/articles/PMC5007746/

141. Ruff RL, Ruff SS, Wang X-F. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. *J. Rehabil. Res. Dev.* 46(9), 1071–1084 (2009).

142. Ruff RL, Riechers RG II, Wang X-F, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *J. Rehabil. Res. Dev.* 49(9), 1305 (2012).

143. Mårtensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: a critical review of the evidence. *J. Affect. Disord.* 182, 1–7 (2015).

144. Najjar RP, Wolf L, Taillard J *et al.* Chronic artificial blue-enriched white light is an effective countermeasure to delayed circadian phase and neurobehavioral decrements. *PLoS One* 9(7), e102827 (2014).

145. Phipps-Nelson J, Redman JR, Dijk D-J, Rajaratnam SMW. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep* 26(6), 695–700 (2003).

146. Phipps-Nelson J, Redman JR, Schlangen LJM, Rajaratnam SMW. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiol. Int.* 26(5), 891–912 (2009).

147. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand. J. Work Environ. Health.* 34(4), 297–306 (2008).

148. Mills PR, Tomkins SC, Schlangen LJ. The effect of high correlated colour temperature office lighting on employee wellbeing and work performance. *J. Circadian Rhythms* 5, 2 (2007).

149. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS ONE* 6(1), e16429 (2011).

150. Münch M, Linhart F, Borisuit A, Jaeggi SM, Scartezzini J-L. Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. *Behav. Neurosci.* 126(1), 196–203 (2012).

151. Gordijn MC, Beerma DGM, Rüger M, Daan S. The effects of blue light on sleepiness. *Annu. Proc. Dutch Sleep-Wake Soc.* 16, 67–70 (2005).

152. Lockley SW, Evans EE, Scheer FAJL, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep* 29(2), 161–168 (2006).

153. Figueiro MG, Rea MS. Short-wavelength light enhances cortisol awakening response in sleep-restricted adolescents. *Int. J. Endocrinol.* 2012, 7 (2012).

154. Beaven CM, Ekström J. A comparison of blue light and caffeine effects on cognitive function and alertness in humans. *PLoS One* 8(10), e76707 (2013).

155. Rodríguez-Morilla B, Madrid JA, Molina E, Correa A. Blue-enriched white light enhances physiological arousal but not behavioral performance during simulated driving at early night. *Front. Psychol.* 8 (2017). www.frontiersin.org/articles/10.3389/fpsyg.2017.00997/full

156. Rodríguez-Morilla B, Madrid JA, Molina E, Pérez-Navarro J, Correa Á. Blue-enriched light enhances alertness but impairs accurate performance in evening chronotypes driving in the morning. *Front. Psychol.* 9 (2018). www.frontiersin.org/articles/10.3389/fpsyg.2018.00688/full

157. Łaszewska K, Goroncy A, Weber P *et al.* Daytime acute non-visual alerting response in brain activity occurs as a result of short- and long-wavelengths of light. *J. Psychophysiol.* 1–25 (2017).doi: 10.1027/0269-8803/a000199 .

158. Smolders KCHJ, de Kort YAW, Cluitmans PJM. A higher illuminance induces alertness even during office hours: findings on subjective measures, task performance and heart rate measures. *Physiol. Behav.* 107(1), 7–16 (2012).

159. Vandewalle G, Balteau E, Phillips C *et al.* Daytime light exposure dynamically enhances brain responses. *Curr. Biol.* 16(16), 1616–1621 (2006).

160. Figueiro MG, Bierman A, Plitnick B, Rea MS. Preliminary evidence that both blue and red light can induce alertness at night. *BMC Neurosci.* 10, 105 (2009).

161. Figueiro MG, Sahin L, Wood B, Plitnick B. Light at night and measures of alertness and performance: implications for shift workers. *Biol. Res. Nurs.* 18(1), 90–100 (2016).

162. Plitnick B, Figueiro M, Wood B, Rea M. The effects of red and blue light on alertness and mood at night. *Lighting Res. Technol.* 42(4), 449–458 (2010).

163. Sahin L, Figueiro MG. Alerting effects of short-wavelength (blue) and long-wavelength (red) lights in the afternoon. *Physiol. Behav.* 116–117, 1–7 (2013).

164. Sahin L, Wood BM, Plitnick B, Figueiro MG. Daytime light exposure: effects on biomarkers, measures of alertness, and performance. *Behav. Brain Res.* 274, 176–185 (2014).

165. Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 290(5), R1413–R1420 (2006).

166. Myers BL, Badia P. Immediate effects of different light intensities on body temperature and alertness. *Physiol. Behav.* 54(1), 199–202 (1993).

167. Chang A-M, Santhi N, St Hilaire M *et al.* Human responses to bright light of different durations. *J. Physiol.* 590(13), 3103–3112 (2012).

168. Cajochen C, Zeitzer JM, Czeisler CA, Dijk D-J. Dose–response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. *Behav. Brain Res.* 115(1), 75–83 (2000).

169. Badia P, Myers B, Boecker M, Culpepper J, Harsh JR. Bright light effects on body temperature, alertness, EEG and behavior. *Physiol. Behav.* 50(3), 583–588 (1991).

170. Vandewalle G, Schmidt C, Albouy G *et al.* Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. *PLoS ONE* 2(11), e1247 (2007).

171. Alkozei A, Smith R, Pisner DA *et al.* Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* 39(9), 1671–1680 (2016).

172. Perrin F, Peigneux P, Fuchs S *et al.* Nonvisual responses to light exposure in the human brain during the circadian night. *Current Biol.* 14(20), 1842–1846 (2004).

173. Vandewalle G, Gais S, Schabus M *et al.* Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cereb. Cortex.* 17(12), 2788–2795 (2007).

174. Okamoto Y, Nakagawa S. Effects of daytime light exposure on cognitive brain activity as measured by the ERP P300. *Physiol. Behav.* 138, 313–318 (2015).

175. Vandewalle G, Archer SN, Wuillaume C *et al.* Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *J. Biol. Rhythms* 26(3), 249–259 (2011).

176. Killgore WDS, Kent HC, Knight SA, Alkozei A. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. *Neuroreport* 29(6), 488–494 (2018).

177. Kretschmer V, Schmidt K-H, Griefahn B. Bright light effects on working memory, sustained attention and concentration of elderly night shift workers. *Lighting Res. Technol.* 44(3), 316–333 (2012).

178. Boyce PR, Beckstead JW, Eklund NH, Strobel RW, Rea MS. Lighting the graveyard shift: the influence of a daylight-simulating skylight on the task performance and mood of night-shift workerst. *Int. J. Lighting Res. Technol.* 29(3), 105–134 (1997).

179. Gabel V, Maire M, Reichert CF *et al.* Effects of artificial dawn and morning blue light on daytime cognitive performance, well-being, cortisol and melatonin levels. *Chronobiol. Int.* 30(8), 988–997 (2013).

180. Gabel V, Maire M, Reichert CF *et al.* Dawn simulation light impacts on different cognitive domains under sleep restriction. *Behav. Brain Res.* 281, 258–266 (2015).

181. Santhi N, Groeger JA, Archer SN, Gimenez M, Schlangen LJM, Dijk D-J. Morning sleep inertia in alertness and performance: effect of cognitive domain and white light conditions. *PLoS ONE* 8(11), e79688 (2013).

182. Smolders KCHJ, de Kort YAW. Investigating daytime effects of correlated colour temperature on experiences, performance, and arousal. *J. Environ. Psychol.* 50, 80–93 (2017).

183. Smolders KCHJ, de Kort YAW. Bright light and mental fatigue: effects on alertness, vitality, performance and physiological arousal. *J. Environ. Psychol.* 39, 77–91 (2014).

184. Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS ONE* 12(9), e0184884 (2017).

185. Bedrosian TA, Nelson RJ. Timing of light exposure affects mood and brain circuits. *Transl. Psychiatry* 7(1), e1017 (2017).

186. Golden RN, Gaynes BN, Ekstrom RD *et al.* The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *AJP* 162(4), 656–662 (2005).

187. Wolkowitz Owen M, Burke Heather, Epel Elissa S, Reus Victor I. Glucocorticoids. Mood, memory, and mechanisms. *Ann. N. Y. Acad. Sci.* 1179(1), 19–40 (2009).

188. Son GH, Chung S, Kim K. The adrenal peripheral clock: glucocorticoid and the circadian timing system. *Front. Neuroendocrinol.* 32(4), 451–465 (2011).

189. Pilorz V, Tam SKE, Hughes S *et al.* Melanopsin regulates both sleep-promoting and arousal-promoting responses to light. *PLoS Biol.* 14(6), e1002482 (2016).

190. Cajochen C, Chellappa SL. Commentary: melanopsin regulates both sleep-promoting and arousal-promoting responses to light. *Front. Neural Circuits* 10 (2016). www.frontiersin.org/articles/10.3389/fncir.2016.00094/full

191. Noseda R, Bernstein CA, Nir R-R *et al.* Migraine photophobia originating in cone-driven retinal pathways. *Brain* 139(7), 1971–1986 (2016).

192. Ibrahim MM, Patwardhan A, Gilbraith KB *et al.* Long-lasting antinociceptive effects of green light in acute and chronic pain in rats. *Pain* 158(2), 347 (2017).

193. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SMW. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil. Neural Repair* 28(4), 303–313 (2014).

194. Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore WDS. Blue-light therapy following mild traumatic brain injury: effects on white matter water diffusion in the brain. *Front. Neurol.* 8 (2017). www.frontiersin.org/articles/10.3389/fneur.2017.00616/full

195. Vanuk J, Shane B, Bajaj S, Millan M, Killgore WDS. 538. Blue light therapy following a mild traumatic brain injury improves MPFC-amygdala functional connectivity and mood. *Biol. Psychiatry* 81(10), S218 (2017).

196. Alkozei A, Smith R, Killgore WDS. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neurosci. Lett.* 616, 5–10 (2016).

197. Hamblin MR. Photobiomodulation for traumatic brain injury and stroke. *J. Neurosci. Res.* 96(4), 731–743 (2017).

198. Xu Q, Lang CP. Revisiting the alerting effect of light: a systematic review. *Sleep Med. Rev.* (2017). www.sciencedirect.com/science/article/pii/S1087079217300989

199. International Commission on Non-Ionizing Radiation Protection. ICNIRP guidelines on limits of exposure to incoherent visible and infrared radiation. *Health Physics.* 105(1), 74 (2013).

200. Brouwer A, Nguyen H-T, Snoek FJ *et al.* Light therapy: is it safe for the eyes? *Acta Psychiatrica Scandinavica* 136(6), 534–548 (2017).

Accepted Manuscript



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PII: S1389-9457(18)30496-9

DOI: 10.1016/j.sleep.2018.09.018

Reference: SLEEP 3836

To appear in: *Sleep Medicine*

Received Date: 31 July 2018

Revised Date: 6 September 2018

Accepted Date: 26 September 2018

Please cite this article as: Raikes AC, Satterfield BC, Killgore WDS, Evidence of Actigraphic and Subjective Sleep Disruption Following Mild Traumatic Brain Injury, *Sleep Medicine* (2018), doi: https://doi.org/10.1016/j.sleep.2018.09.018.

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Evidence of Actigraphic and Subjective Sleep Disruption Following Mild Traumatic Brain Injury

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Word Count: 3846

Tables: 2 (including 1 supplemental table)

Figures: 3

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Abstract

Objective/Background: Mild traumatic brain injuries (mTBI) are frequently associated with long-term, self-reported sleep disruption. Objective corroboration of these self-reports is sparse and limited by small sample sizes. The purpose of this study was to report on actigraphically-measured sleep outcomes in individuals with and without a history of recent mTBI in two U.S. cities (Boston, MA and Tucson, AZ).

Patients/Methods: 58 individuals with a recent (within 18 months) mTBI and 35 individuals with no prior mTBI history were recruited for one of four studies across two sites. Participants completed a minimum of one week of actigraphy. Additionally, mTBI participants self-reported daytime sleepiness, sleep disruption, and functional sleep-related outcomes.

Results: In Boston, mTBI participants obtained less average sleep with shorter sleep onset latencies (SOL) than healthy individuals. In Tucson, mTBI participants had greater SOL and less night-to-night SOL variability compared to healthy individuals. Across mTBI participants, SOL was shorter and night-to-night SOL variability was greater in Boston than Tucson. Sleep efficiency (SE) variability was greater in Tucson than Boston across both groups. Only SOL variability was significantly associated with daytime sleepiness ($r = 0.274$) in the mTBI group after controlling for location.

Conclusion: Sleep quality, SOL and SE variability, are likely affected by mTBIs. Between-group differences in each site existed but went in opposite directions. These findings suggest the possibility of multiple, rather than a singular, profiles of sleep disruption following mTBI. Precision medicine models are warranted to determine whether multiple sleep disruption profiles

22 do indeed exist following mTBI and the predisposing conditions that contribute to an
23 individual's experience of sleep disruption.

24

25 **Keywords:** actigraphy; daytime sleepiness; coefficient of variation; sleep disruption; mild
26 traumatic brain injury; mTBI; sleep onset latency; sleep efficiency; sleep quality

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1. Introduction

Each year, at least 1.5 million documented and undocumented mild traumatic brain injuries (mTBIs) occur in the United States each year.[1,2] mTBIs are the result of external forces to the head or body resulting in the disruption of normal brain function, with or without short-term loss of consciousness, and the absence of gross abnormalities on conventional diagnostic neuroimaging.[3,4] These injuries result in a wide range of somatic symptoms, as well as changes and impairments in cognitive, motor, and behavioral functioning.[3,5,6] Some of these changes appear to be transient, naturally recovering to preinjury levels within 1-3 months.[5,7–9] However many others – including depression, pain, and increased daytime fatigue and poor sleep – may have long-term sequelae that do not resolve without intervention.[10–15]

Post-mTBI sleep changes are a common complaint, with 30-70% of individuals reporting some form of sleep disruption.[10,16] The most frequent of these complaints are self-reported sleep disruption, insomnia, and daytime sleepiness or fatigue.[15,17–22] However, these self-reports are generally not corroborated by objective findings.[11,23–25] Objective findings of sleep disruption specific to mTBI are limited. Several studies employing polysomnography have demonstrated that individuals with a history of mTBI get poorer sleep (lower sleep efficiency, more frequent and longer nocturnal wakefulness) and have higher overall physiological arousal compared to either population norms or control participants.[26–29] However, these findings are inconsistent[11,24,30,31] and a recent meta-analysis suggests that such findings may not persist into the chronic phase (> 6 months post-injury).[32]

Additional studies employing actigraphy have corroborated findings of lower sleep efficiency and increased nighttime awakenings.[33–35] Actigraphy-based studies have further identified circadian rhythm sleep disorders following mTBI,[36] as well as findings indicating that total 24-

hour sleep time may be greater in individuals immediately after a mTBI, and that this recovers over time.[33,34] However, these findings are also not consistently observed,[37,38] and higher intra-individual variability following mTBI than in controls may partially explain inconsistent findings across both PSG and actigraphy studies.[34,37]

Two major challenges in post-mTBI sleep-related research are overall small sample sizes and the reliance on mixed severity TBI samples.[39] Consequently, the findings across the literature require further corroboration and exploration in order to more completely describe the generalizability. The purpose of this study was to compare individuals with a recent mTBI (< 18 months prior) to healthy controls with no prior history of mTBI on seven days of at-home actigraphy. We hypothesized that both sleep quantity and sleep quality (e.g., greater nighttime awakening, lower sleep efficiency) would be worse in those with a recent mTBI. We additionally hypothesized that post-mTBI individuals would exhibit greater night-to-night variability in these actigraphy-based sleep metrics than controls.

2. Material and Methods

Study procedures were evaluated and approved by the Institutional Review Boards of Partners Healthcare, the University of Arizona College of Medicine, and the U.S. Army's Human Research Protections Office. All participants provided written informed consent prior to participation.

2.1. Participants

Data for the present study were acquired from four samples of individuals enrolled in four separate studies that employed similar methodology for recruitment and collection of actigraphy.

Two of these studies were completed in Boston, MA and two are on-going in Tucson, AZ. Participant demographics are summarized in Table 1.

2.1.1. Mild traumatic brain injury participants

A total of 58 individuals with a recent mTBI (time since injury: 8 ± 4.74 months; male/female: 23/35) were recruited from the greater Boston (n = 28) and Tucson (n = 29) areas. In both locations, individuals were recruited via community fliering and were required to provide documentation indicating either direct observation of the injury and immediate sequalae (e.g., by a coach) or the diagnosis of a concussion by a qualified professional (e.g., physician, athletic trainer). For both locations, mild traumatic brain injury was defined according to criteria consistent with the American Congress of Rehabilitation Medicine[40] and VA/DoD Guidelines.[41] Specifically, a mTBI was defined as a physiological disruption of brain function caused by a traumatic injury to the head, resulting in a Glasgow Coma Scale (if obtained) between 13-15 within 24 hours of injury, loss of consciousness lasting no more than 30 minutes, posttraumatic amnesia lasting less than 24 hours, altered mental state lasting less than 24 hours, and/or focal neurological damage that may be transient.[40,41] Unrelated neuroimaging findings from these samples have been reported elsewhere[42,43] but the use of actigraphy in the present paper is novel and has not been previously published.

2.1.2. Healthy controls

Sleep-related data were additionally available from two separate groups of healthy control participants. 24 individuals were recruited in Boston. These healthy controls met the following criteria: no history of psychological, neurological, sleep, or other medical disorders; self-reported sleep duration within the top or bottom quartile of the population; no history of head injury with loss of consciousness or post-traumatic amnesia; daily caffeine intake less than 300 mg per day;

no drug or alcohol abuse in the past 6 months; no history of smoking; no use of medications with drowsiness as a side effect; and not pregnant. Unrelated results from the primary study for these participants have previously been published[44] or are currently under review. However, their use in this study provides novel insights.

An additional 11 healthy individuals were recruited in Tucson. These healthy controls met the following criteria: no history of psychological, neurological, sleep, or other medical disorders; no history of concussion or TBI; no history of cardiac conditions; no presence of excessive daytime sleepiness; no presence of irregular circadian schedule (e.g., shift work); daily caffeine intake less than 300 mg per day; no current use of medications (except birth control), recreational drugs, or tobacco; and not pregnant.

2.2. Actigraphy

All participants completed a minimum 7 days of actigraphy using either a Philips Respironics Actiwatch Spectrum (mTBI groups) or the Philips Respironics Actiwatch-2 (healthy control groups). Data for the Tucson mTBI and healthy controls groups were collected using 1 min epochs. Data for the Boston mTBI group was collected using 2 min epochs.

Actigraphy data were processed in the Philips Actiware 6 software. All data were scored automatically in the software using the default scoring algorithm, with sleep time scored based on minutes of immobility. The algorithm analysis criteria were set as follows for all subjects: wake threshold value of 40 activity counts, 10 immobile minutes for sleep onset and sleep end; white light threshold of 1,000 lux. Automatic scoring was visually inspected by a trained technician and scores were modified as needed based on sleep diary data to reconcile unclear recordings. Sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (total sleep time / total time-in-bed; SE), and total nighttime sleep duration were extracted. The

coefficient of variation (standard deviation/mean; CV) as a measure of intra-individual variation for each individual was calculated for each measure.

2.3 Self-reported outcomes

Participants in each of the parent studies completed comprehensive battery of neuropsychological exams and self-reported questionnaires. Here we report the outcomes from three of these self-report questionnaires only.

2.3.1. The Epworth Sleepiness Scale (ESS)

All participants completed the ESS, a self-report measure of daytime sleepiness.[45] Scores range from 0-24 and a cutoff score of 10 has been identified to indicate excessive daytime sleepiness.[46]

2.3.2. The Pittsburgh Sleep Quality Index (PSQI)

Participants in the mTBI groups completed the PSQI, a self-report measure regarding overall sleep quality.[47] Lower scores indicate better sleep quality. Total scores greater than 5 indicate poor sleep in the general public,[47] though scores greater than 8 have been identified as more sensitive in TBI samples.[48] The PSQI has both good test-retest reliability ($r > 0.80$)[47] and post-mTBI sleep disruption sensitivity.[15,49]

2.3.3 The Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a self-report questionnaire designed to identify the impact of sleep, particularly excessive daytime sleepiness on activities of daily living.[50] Scores on the FOSQ range from 5-20, and higher scores are better (greater overall function).[51]

2.3. Statistical Analyses

All statistical analyses were conducted in R (including the tidyverse,[52–54] lmerTest,[55] and rsq[56] packages) with *a priori* significance set at $p < 0.05$. Group differences in demographic and

personal characteristics were computed using two-sample *t*-tests a χ^2 tests as appropriate. To identify differences in sleep measures over the seven days of actigraphy, we fit individual linear mixed effects models using the lmerTest package. Main effects included mTBI group (healthy vs. mTBI) and location (Boston vs. Tucson) as well as the interaction term. These models utilized all available days of actigraphy for each individual, as between-group differences in weekly means may be obscured by high intra-individual variability.[28,34,37] Planned post-hoc comparisons were made within site (e.g., healthy vs. mTBI in Boston) and within group (e.g., Boston vs. Tucson mTBI) but not fully crossed (e.g., not Boston healthy vs. Tucson mTBI). We also computed group x location ANOVAs on the CV data to identify intra-individual variability differences. We further report Cohen's d as a measure of effect size for reported post-hoc comparisons. For the linear mixed models, these effect sizes were computed on the estimated marginal means after adjusting for the random effects in the models,

We additionally performed exploratory analyses within the mTBI participant group to evaluate the relationship between sleep and self-reported outcomes. First, to assess whether sleep parameters improve over time since injury, we fit a linear model to the weekly mean and CV data with months since injury as the independent variable and controlled for location. We also fit individual linear models to the ESS, PSQI, and FOSQ scores with mean and CV data from the preceding week while controlling for location. These models allowed us to determine the extent to which prior sleep predicts self-reported sleep quality and sleep-related outcomes.

3. Results

3.1. Demographic data

Demographic and self-report outcomes are presented in Table 1. Healthy controls in Tucson were significantly younger than both the Boston healthy controls and Tucson mTBI participants.

ESS total scores were higher in the mTBI groups than the matched controls in each respective location.

3.2. Linear mixed effects models of actigraphy

3.2.1. Total nighttime sleep

Post-hoc analyses revealed that healthy control participants in Boston slept approximately 30 minutes more on average per night than both mTBI participants in Boston ($t = 2.716$, $p = 0.007$, $d = 0.76$; Figure 1A) and healthy controls in Tucson ($t = 1.915$, $p = 0.056$, $d = 0.70$).

3.2.2 Sleep quality measures

SOL data required transformation ([$y = \ln(x + 1)$]) prior to model fitting in order to reduce positive skewness in the residuals. SOL was shorter for the Boston mTBI subgroup than for the Boston healthy controls ($t = 5.060$, $p < 0.0001$, $d = 1.41$; Figure 1B) and Tucson mTBI participants ($t = 8.275$, $p < 0.0001$, $d = 2.28$). Additionally, SOL was longer in the Tucson mTBI subgroup than the Tucson healthy controls ($t = 4.238$, $p < 0.0001$, $d = 1.5$).

Nightly WASO data required fourth root transformation to reduce positive skewness in the residuals. No statistically significant differences were observed for any post-hoc comparisons (Figure 1C).

Sleep efficiency data required fourth power transformation to reduce negative skewness in the residuals. Post-hoc analyses demonstrated greater SE for mTBI participants in Boston compared to those in Arizona ($t = 3.428$, $p = 0.001$, $d = 0.91$) as well as healthy controls in Boston ($t = 2.568$, $p = 0.01$, $d = 0.71$).

3.3. Intra-individual variability

All CV data required log transformation prior to model fitting to address non-normality in the residuals. mTBI participants in Tucson had less variable SOL (t = 3.137, $p = 0.002$, $d = 0.83$; Figure 2B) and more variable SE (t = 2.866, $p = 0.005$, $d = 0.76$; Figure 2D) than mTBI participants in Boston. Additionally, Tucson mTBI participants had less variable SE than the Tucson healthy controls (t = 2.616, $p = 0.011$, $d = 0.93$; Figure 2D). Finally, overall SE variability was greater in Tucson than Boston (t = 2.628, $p = 0.010$, $d = 0.55$; Figure 2D) No other statistically significant pairwise comparisons were observed (Figure 2A-D).

3.4. Relationship between Actigraphy and Self-reported outcomes

After controlling for location, SOL coefficient of variation significantly predicted ESS (Figure 3). No other sleep measures were related to time since injury or self-reported outcomes.

4. Discussion

The purpose of this study was to identify differences in actigraphically-measured sleep characteristics between individuals with and without a history of mild traumatic brain injury. We hypothesized that individuals with a recent mTBI would have greater nighttime sleep duration and worse sleep quality, as well as greater night-to-night variability, than healthy controls, regardless of data collection location. These hypotheses were partially confirmed.

4.1 Objective sleep findings

Our initial hypotheses concerned the differences between healthy individuals and mTBI participants. Given the multi-site nature of our data, we included location in the models to address potentially systematic between-site differences. While not hypothesized, we found differing patterns of actigraphic sleep outcomes between the two sites. Individuals in the Boston

mTBI group obtained, on average, 32 fewer minutes of sleep per night than their location-matched healthy controls. By contrast, the Tucson mTBI participants slept approximately 18 minutes longer per night than their location-matched healthy controls, though this finding was not statistically significant. Importantly, the healthy controls in Tucson slept approximately 32 minutes less than the Boston healthy control group, putting them at a similar level as the Boston mTBI group. Thus, no consistent pattern of findings was observed for total sleep time between those with a prior mTBI and healthy controls, although this may have been obscured by the between-location variability.

We observed similarly conflicting within and cross-location findings for average SOL (longer for mTBI in Tucson; shorter for mTBI in Boston), as well as intra-individual variability in SOL (more for mTBI in Boston; less for mTBI in Tucson). Collectively, average SE was lower in Tucson than in Boston while intra-individual variability was higher. However, there were no between group (mTBI vs. control) differences.

4.1.1 Potentially multiple profiles of post-mTBI sleep disturbance

Taken individually, the findings from the Boston subgroups showing reduced sleep in the mTBI sample would stand in opposition to other actigraphy-based studies indicating no differences or greater sleep duration in those with mTBI compared to population norms or controls.[23,33,34,37] However, the Tucson sub-samples would seem to confirm the no difference findings.[37,38] Additionally, no between-group differences were observed in night-to-night sleep duration variability, in contrast to prior findings.[37] Similarly, prior work generally reports no differences in actigraphically-measured SOL following mTBI,[25,38,57] though one report suggests SOL may be decreased.[33] Our present findings suggest that SOL may be affected after mTBI, though the direction is unclear.

Taken together with the inconsistently reported effects of mTBI on sleep across the literature, these seemingly conflicting findings yield a critical observation on post-mTBI sleep. To date, studies in this area have employed small sample sizes from a single location and may or may not include a control group. As evident in the patterns of differences between healthy individuals and mTBI participants across the two sites, as well as the differences between the two groups of mTBI participants reported here, it is likely that, similar to the heterogeneity of mTBI mechanisms and individual responses to injury,[6,58,59] self-reported and actigraphic sleep findings are highly individualized. Recent reports highlight the fact that there are multiple divergent clinical profiles of mTBI (i.e., cognitive fatigue; oculomotor).[6,60–63] Sleep disruption of all kinds, however, is considered a sub-component modifier of these clinical profiles, but not in itself a primary profile.

The findings in the present study suggest that there may likewise be multiple profiles of sleep disruption (e.g., long latency vs. short latency; increased night-to-night variability vs. no change in variability; shorter sleep duration vs. unaffected sleep duration but longer onset latency). In light of the individually small sample sizes in each of our groups, this explanation is speculative at present. However multiple sleep disruption profiles, rather than a one-size-fits-all approach, are consistent with emerging clinical views of mTBI and would explain the inconsistent findings resulting from single, small cohorts of individuals following injury. The possibility of multiple sleep outcome profiles following mTBI merits further investigation with larger samples of not only individuals following mTBI but also reference cohorts.

4.1.2 Additional explanations for the observed patterns of responses.

There are several other possible explanations for the pattern of findings in the present study. As stated, there are multiple mTBI clinical profiles.[6,60–63] Given the various mechanisms of injury

leading to the most recent mTBI in the present participants, the clinical profiles in the present study may have varied significantly. We were unable to retrospectively create these profiles for our mTBI participants. As the relationship between current views of clinical profiles and sleep is unknown, there may be sleep effects driven by differences in injury mechanism and potentially varied clinical presentations leading to inconsistent between- and within-group findings, particularly the between-site differences in SE and SOL for the mTBI participants.

Second, a recent meta-analysis of sleep architecture in chronic (> 6 months) TBI identified no overall differences in sleep architecture (measured via PSG) for those with mTBI compared to control participants. The authors, however, suggest caution when interpreting these findings in light of several limitations including inconsistent definitions of mTBI and the possibility that injury-related changes may resolve within six months.[32] Thus our inconsistent pattern of findings may be driven by the varied time since injury for our participants. However, we find this explanation unlikely because of A.) the lack of relationship between time since injury (in months) and any of the reported measures, even after accounting for location differences; and B.) post-hoc assessments of our models including time since injury as a covariate did not significantly improve the fits of any of our models.

Finally, in light of the between-site differences, particularly in both average SE and intra-individual variability, it is possible that location matters when interpreting actigraphy results. Prior work has shown that perceptions of sleep quality differ by geographic region.[64,65] Furthermore, sleep-related circadian rhythms are influenced by the amount of exposure to blue wavelength light, of which sunlight is a major contributor.[66,67] Given the seasonal differences between Boston and Tucson (e.g., year-round availability of sunlight in Tucson) as well as a difference of just over 10 degrees in latitude, the amount of daily light exposure may have

differed significantly across sites and between individuals. Consequently, geographic and seasonal variation in sunlight exposure may exert influences on sleep timing, quantity, and quality that affect the findings of individual studies.[68,69] However, the implications of strictly geographic and seasonal influences on the outcomes reported here are not identified or well-supported by any extant literature and therefore require further exploration.

Regardless, this is the first multi-site mTBI-specific analysis of actigraphically-measured sleep with location-matched controls of which we are aware. Further work using tightly controlled geographic and season-matched samples is needed to identify the extent to which geographic location and seasonal variation may impact sleep-related outcomes.

4.2 Relationship between subjective and objective findings

An additional important finding from the present study is the further corroboration of prior studies identifying a discrepancy between perceived and objective sleep quality following mTBI. Across both mTBI groups, 50.9% (n = 29/57) of participants reported excessive daytime sleepiness (ESS score ≥ 10), 84.2% (n = 48/57) reported clinically significant PSQI total scores ≥ 5,[47] and 47.4% (n = 27/57) reported PSQI scores ≥ 8.[48] Collectively, these self-reports indicate a high prevalence of *perceived* sleep disruption and daytime sleepiness in the mTBI group. However, only intra-individual variability in SOL significantly predicted ESS total scores. Higher variability in SOL was associated with greater daytime sleepiness, though the model including CV and location explained very little overall variance in ESS scores (R^2 = 0.1). Thus, individuals *perceive* poorer sleep and greater daytime fatigue, despite no relationship between objective and subjective measures. As previous authors have suggested, it may be that these objective and subjective measures are capturing differing aspects of the sequelae of post-mTBI recovery, and therefore provide complementary rather than conflicting outcomes.[23]

4.3 Limitations

The findings from this study should be interpreted in light of several limitations. First, the participants in all of our groups were recruited for different studies, each with individually small sample sizes. This is particularly true of the Tucson healthy control group (n = 11). Consequently, these findings should be conservatively viewed as preliminary results that require further corroboration.

Second, as noted previously, geographic and seasonal, as well as genetic, sociodemographic, and cross-cultural effects on actigraphically-quantified sleep remain largely unclear and, with the exception of geographic location, were not accounted for in these analyses. While the month (as a proxy for season) of participation is available, there were too few individuals at any given time point to adequately model the across-season variability. Future work should address these considerations in larger multi-site samples with seasonally-matched controls.

Third, the four samples reported here were recruited for four different studies with varied methods and goals. Consequently, there were between-sample differences in the actigraph models used as well as the epoch length for the Boston mTBI sample was longer than any of the other groups. To minimize the effects of these differences, all of the data were analyzed using the same software, visually inspected by similarly trained technicians, and verified against sleep diary data. It is possible that between-model differences account for some variability in the data. Additionally, the differing epoch length for the Boston mTBI sample may have reduced the sensitivity of the automatic scoring algorithm to sleep-wake transitions. We were unable to statistically control for these differences in the models (this variance is already captured by the group x location interaction term) and this remains a potential confound to these findings. Future

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multi-site studies employing consistent hardware and epoch lengths are needed in order address these concerns.

Finally, we were unable to capture any pre-injury data from the mTBI participants. Consequently, it is unclear what their level of premorbid sleep was. In spite of these important limitations, this study is the first reported multi-site actigraphy-based sleep study with an mTBI-only (rather than mixed severity) sample. These findings provide critical insight into the need for multi-site post-mTBI sleep related research that additionally addresses diverse clinical profiles of mTBI presentation, geographic and seasonal variation in sleep, and the relationship between objective measurement and subjective perceptions of sleep.

5. Conclusions

Sleep quality, particularly night-to-night sleep onset latency and sleep efficiency variability, are likely affected by mTBIs. While between-group differences in each site were apparent for these measures, the patterns of differences were not consistent across the two sites in this study. This highlights the fact that post-mTBI sleep outcomes reported from a single cohort may be insufficient to capture the spectrum of sleep disruption following injury. Furthermore, these findings suggest the possibility of multiple, rather than a singular, profile of sleep disruption following mTBI. Additionally, these results further confirm that self-reported and objectively quantified sleep quantity and quality following mTBI are largely unrelated. Precision medicine models derived from large cohorts across multiple sites are warranted to determine whether multiple sleep disruption profiles do indeed exist following mTBI and the conditions (e.g., injury mechanism, other symptom presentation, social pressures) that may predispose or contribute to an individual's experience of sleep disruption.

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Acknowledgements

We are grateful to Bradley R. Shane and Melissa Millan for their work on scoring the actigraphy.

Funding

This research was supported by multiple grants from the US Army Medical Research and Materiel Command (USAMRMC) to Dr. William D. S. Killgore, including W81XWH-11-1-0056, W81XWH-14-1-0571, W81XWH-17-C-008, and D12AP00241. The content, opinions, interpretations, conclusions, and recommendations are solely the responsibility of the authors and do not necessarily represent the views of Partners Healthcare, the University of Arizona College of Medicine, the Department of Defense, or the U.S. Army Medical Research and Materiel Command.

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354 **References**
355

356 1. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States:*
357 *Emergency Department Visits, Hospitalizations and Deaths 2002-2006*. Atlanta (GA): Centers
358 for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
359 http://origin.glb.cdc.gov/traumaticbraininjury/pdf/blue_book.docx. Accessed April 25, 2015.

360 2. Kerr Z, Roos K, Dompier T, et al. Estimating concussion incidence in college sports:
361 Rates, risks, average per team and proportion of teams with concussions. In: *BRAIN INJURY*.
362 Vol 30. TAYLOR & FRANCIS INC 530 WALNUT STREET, STE 850, PHILADELPHIA, PA
363 19106 USA; 2016:504–504.

364 3. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport -
365 The 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports*
366 *Med*. 2017;51:838-847. doi:10.1136/bjsports-2017-097699

367 4. Basic Information about Traumatic Brain Injury and Concussion | Concussion |
368 Traumatic Brain Injury | CDC Injury Center.
369 https://www.cdc.gov/traumaticbraininjury/basics.html. Accessed July 17, 2018.

370 5. McCrea M, Guskiewicz KM, Randolph C, et al. Incidence, clinical course, and predictors
371 of prolonged recovery time following sport-related concussion in high school and college
372 athletes. *J Int Neuropsychol Soc*. 2013;19(1):22–33. doi:10.1017/S1355617712000872

373 6. Collins MW, Kontos AP, Okonkwo DO, et al. Statements of Agreement From the
374 Targeted Evaluation and Active Management (TEAM) Approaches to Treating Concussion
375 Meeting Held in Pittsburgh, October 15-16, 2015. *Neurosurgery*. 2016;79(6):912-929.
376 doi:10.1227/NEU.0000000000001447

377 7. Kontos AP, Braithwaite R, Dakan S, Elbin RJ. Computerized Neurocognitive Testing
378 within 1 Week of Sport-Related Concussion: Meta-analytic Review and Analysis of Moderating
379 Factors. *Journal of the International Neuropsychological Society*. 2014;20(3):324-332.
380 doi:10.1017/S1355617713001471

381 8. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time
382 following concussion in collegiate football players: The NCAA Concussion Study. *JAMA*.
383 2003;290(19):2556-2563.

384 9. Nelson LD, Guskiewicz KM, Barr WB, et al. Age differences in recovery after sport-
385 related concussion: a comparison of high school and collegiate athletes. *Journal of athletic*
386 *training*. 2016;51(2):142–152.

387 10. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Sleep-wake disturbances after traumatic
388 brain injury. *The Lancet Neurology*. 2015;14(7):746-757. doi:10.1016/S1474-4422(15)00068-X

389 11. Gosselin N, Lassonde M, Petit D, et al. Sleep following sport-related concussions. *Sleep*
390 *Medicine*. 2009;10(1):35-46. doi:10.1016/j.sleep.2007.11.023

12. Stein E, Howard W, Rowhani-Rahbar A, Rivara FP, Zatzick D, McCarty CA. Longitudinal trajectories of post-concussive and depressive symptoms in adolescents with prolonged recovery from concussion. *Brain Injury*. 2017;31(13-14):1736-1744. doi:10.1080/02699052.2017.1380843

13. Martini DN, Broglio SP. Long-term effects of sport concussion on cognitive and motor performance: A review. *International Journal of Psychophysiology*. October 2017. doi:10.1016/j.ijpsycho.2017.09.019

14. McMahon P, Hricik A, Yue JK, et al. Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. *J Neurotrauma*. 2014;31(1):26-33. doi:10.1089/neu.2013.2984

15. Theadom A, Cropley M, Parmar P, et al. Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Medicine*. 2015;16(8):926-932. doi:10.1016/j.sleep.2015.04.013

16. Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: A meta-analysis. *Sleep Medicine*. 2012;13(7):898-905. doi:10.1016/j.sleep.2012.04.006

17. Towns SJ, Silva MA, Belanger HG. Subjective sleep quality and postconcussion symptoms following mild traumatic brain injury. *Brain Injury*. 2015;29(11):1337-1341. doi:10.3109/02699052.2015.1045030

18. Sullivan KA, Berndt SL, Edmed SL, Smith SS, Allan AC. Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. *Applied Neuropsychology: Adult*. 2016;23(6):426-435. doi:10.1080/23279095.2016.1172229

19. Mollayeva T, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. Insomnia in workers with delayed recovery from mild traumatic brain injury. *Sleep Medicine*. 2016;19:153-161. doi:10.1016/j.sleep.2015.05.014

20. Mollayeva T, Pratt B, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. The relationship between insomnia and disability in workers with mild traumatic brain injury/concussion: Insomnia and disability in chronic mild traumatic brain injury. *Sleep Medicine*. 2016;20:157-166. doi:10.1016/j.sleep.2015.09.008

21. Sullivan KA, Edmed SL, Allan AC, Karlsson LJE, Smith SS. Characterizing Self-Reported Sleep Disturbance after Mild Traumatic Brain Injury. *Journal of Neurotrauma*. 2015;32(7):474-486. doi:10.1089/neu.2013.3284

22. Farrell-Carnahan L, Barnett S, Lamberty G, et al. Insomnia symptoms and behavioural health symptoms in veterans 1 year after traumatic brain injury. *Brain Injury*. 2015;29(12):1400-1408. doi:10.3109/02699052.2015.1063161

ACCEPTED MANUSCRIPT

23. Berger I, Obeid J, Timmons BW, DeMatteo C. Exploring Accelerometer Versus Self-Report Sleep Assessment in Youth With Concussion. *Global Pediatric Health*. 2017;4:2333794X17745973. doi:10.1177/2333794X17745973

24. Mantua J, Mahan KM, Henry OS, Spencer RMC. Altered sleep composition after traumatic brain injury does not affect declarative sleep-dependent memory consolidation. *Frontiers in Human Neuroscience*. 2015;9. doi:10.3389/fnhum.2015.00328

25. Sinclair KL, Ponsford JL, Rajaratnam SM. Actigraphic assessment of sleep disturbances following traumatic brain injury. *Behavioral Sleep Medicine*. 2014;12(1):13-27. doi:10.1080/15402002.2012.726203

26. Mollayeva T, Colantonio A, Cassidy JD, Vernich L, Moineddin R, Shapiro CM. Sleep stage distribution in persons with mild traumatic brain injury: a polysomnographic study according to American Academy of Sleep Medicine standards. *Sleep Medicine*. 2017;34:179-192. doi:10.1016/j.sleep.2017.02.021

27. Arbour C, Khoury S, Lavigne GJ, et al. Are NREM sleep characteristics associated to subjective sleep complaints after mild traumatic brain injury? *Sleep Medicine*. 2015;16(4):534-539. doi:10.1016/j.sleep.2014.12.002

28. Williams BR, Lazic SE, Ogilvie RD. Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clinical Neurophysiology*. 2008;119(2):429-438. doi:10.1016/j.clinph.2007.11.003

29. Mantua J, Henry OS, Garskovas NF, Spencer RMC. Mild Traumatic Brain Injury Chronically Impairs Sleep- and Wake-Dependent Emotional Processing. *Sleep*. 2017;40(6). doi:10.1093/sleep/zsx062

30. Modarres MH, Kuzma NN, Kretzmer T, Pack AI, Lim MM. EEG slow waves in traumatic brain injury: Convergent findings in mouse and man. *Neurobiology of Sleep and Circadian Rhythms*. 2017;2:59-70. doi:10.1016/j.nbscr.2016.06.001

31. Schreiber S, Barkai G, Gur-Hartman T, et al. Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Medicine*. 2008;9(5):481-487. doi:10.1016/j.sleep.2007.04.014

32. Mantua J, Grillakis A, Mahfouz SH, et al. A systematic review and meta-analysis of sleep architecture and chronic traumatic brain injury. *Sleep Medicine Reviews*. February 2018. doi:10.1016/j.smrv.2018.01.004

33. Chiu H-Y, Chen P-Y, Chen N-H, Chuang L-P, Tsai P-S. Trajectories of sleep changes during the acute phase of traumatic brain injury: A 7-day actigraphy study. *Journal of the Formosan Medical Association*. 2013;112(9):545-553. doi:10.1016/j.jfma.2013.06.007

34. Sufrinko AM, Howie EK, Elbin RJ, Collins MW, Kontos AP. A Preliminary Investigation of Accelerometer-Derived Sleep and Physical Activity Following Sport-Related

462 Concussion. *The Journal of Head Trauma Rehabilitation*. 2018;Publish Ahead of Print.
463 doi:10.1097/HTR.0000000000000387

464 35. Tham SW, Fales J, Palermo TM. Subjective and Objective Assessment of Sleep in
465 Adolescents with Mild Traumatic Brain Injury. *Journal of Neurotrauma*. 2015;32(11):847-852.
466 doi:10.1089/neu.2014.3559

467 36. Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders
468 following mild traumatic brain injury. *Neurology*. 2007;68(14):1136-1140.
469 doi:10.1212/01.wnl.0000258672.52836.30

470 37. Raikes AC, Schaefer SY. Sleep quantity and quality during acute concussion: A pilot
471 study. *Sleep*. 2016;39(12):2141-2147. doi:10.5665/sleep.6314

472 38. Allan AC, Edmed SL, Sullivan KA, Karlsson LJE, Lange RT, Smith SS. Actigraphically
473 Measured Sleep-Wake Behavior After Mild Traumatic Brain Injury: A Case-Control Study. *The*
474 *Journal of Head Trauma Rehabilitation*. 2017;32(2):E35. doi:10.1097/HTR.0000000000000222

475 39. Wickwire E, Schnyer DM, Germain A, et al. Sleep, sleep disorders, and circadian health
476 following mild traumatic brain injury: Review and research agenda. *Journal of Neurotrauma*.
477 June 2018. doi:10.1089/neu.2017.5243

478 40. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury.
479 *The Journal of Head Trauma Rehabilitation*. 1993;8(3):86.

480 41. STATEMENTS Q. VA/DoD Clinical Practice Guideline for the Management of
481 Concussion - mild Traumatic Brain Injury. 2016.
482 https://www.healthquality.va.gov/guidelines/Rehab/mtbi/mTBICPGFullCPG50821816.pdf.
483 Accessed July 27, 2018.

484 42. Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore WDS. Blue-Light Therapy following
485 Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. *Front*
486 *Neurol*. 2017;8. doi:10/gcnnrw

487 43. Bajaj S, Dailey NS, Rosso IM, Rauch SL, Killgore WDS. Time-dependent differences in
488 cortical measures and their associations with behavioral measures following mild traumatic brain
489 injury. *Human Brain Mapping*. 2018;39(5):1886-1897. doi:10.1002/hbm.23951

490 44. Cui J, Tkachenko O, Gogel H, et al. Microstructure of frontoparietal connections predicts
491 individual resistance to sleep deprivation. *NeuroImage*. 2015;106:123-133.
492 doi:10.1016/j.neuroimage.2014.11.035

493 45. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness
494 scale. *Sleep*. 1991;14(6):540–545.

495 46. Johns M, Hocking B. Daytime Sleepiness and Sleep Habits of Australian Workers. *Sleep*.
496 1997;20(10):844-847. doi:10.1093/sleep/20.10.844

47. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4

48. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. *Brain Inj*. 2002;16(3):197-206. doi:10.1080/02699050110103940

49. Mani A, Dastgheib SA, Chanor A, Khalili H, Ahmadzadeh L, Ahmadi J. Sleep quality among patients with mild traumatic brain injury: A cross-sectional study. *Bull Emerg Trauma*. 2015;3(3):93-96.

50. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835–843.

51. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis Care & Research*. 63(S11):S287-S296. doi:10.1002/acr.20544

52. Wickham H. *Tidyr: Easily Tidy Data with `spread()` and `gather()` Functions*.; 2016. https://CRAN.R-project.org/package=tidyr.

53. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag; 2009. //www.springer.com/us/book/9780387981413.

54. Wickham H, Francois R. *Dplyr: A Grammar of Data Manipulation*.; 2015. https://CRAN.R-project.org/package=dplyr.

55. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*. 2017;82(13):1–26. doi:10.18637/jss.v082.i13

56. Zhang D. *Rsq: R-Squared and Related Measures*.; 2018. https://CRAN.R-project.org/package=rsq.

57. Chiu H-Y, Lo W-C, Chiang Y-H, Tsai P-S. The effects of sleep on the relationship between brain injury severity and recovery of cognitive function: A prospective study. *International Journal of Nursing Studies*. 2014;51(6):892-899. doi:10.1016/j.ijnurstu.2013.10.020

58. Broglio SP, Collins MW, Williams RM, Mucha A, Kontos AP. Current and emerging rehabilitation for concussion: a review of the evidence. *Clinics in sports medicine*. 2015;34(2):213–231. doi:10.1016/j.csm.2014.12.005

59. Okonkwo D, Brooks J, Kontos A, et al. TEAM-TBI: A MONITORED MULTIPLE INTERVENTIONAL TBI RESEARCH TRIAL. *Journal of Neurotrauma*. 2016;33(13):A-38.

60. Kontos AP, Collins MW, Holland CL, et al. Preliminary Evidence for Improvement in Symptoms, Cognitive, Vestibular, and Oculomotor Outcomes Following Targeted Intervention with Chronic mTBI Patients. *Mil Med*. 2018;183(suppl_1):333-338. doi:10.1093/milmed/usx172

61. Henry LC, Elbin RJ, Collins MW, Marchetti G, Kontos AP. Examining Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach. *Neurosurgery*. 2016;78(2):232-241. doi:10/f77kw7

62. Sandel N, Reynolds E, Cohen PE, Gillie BL, Kontos AP. Anxiety and Mood Clinical Profile following Sport-related Concussion: From Risk Factors to Treatment. *Sport Exerc Perform Psychol*. 2017;6(3):304-323. doi:10.1037/spy0000098

63. Reynolds E, Collins MW, Mucha A, Troutman-Ensecki C. Establishing a Clinical Service for the Management of Sports-Related Concussions. *Neurosurgery*. 2014;75(suppl_4):S71-S81. doi:10.1227/NEU.0000000000000471

64. Dregan A, Armstrong D. Cross-country variation in sleep disturbance among working and older age groups: an analysis based on the European Social Survey. *International Psychogeriatrics*. 2011;23(9):1413-1420. doi:10.1017/S1041610211000664

65. Soldatos CR, Allaert FA, Ohta T, Dikeos DG. How do individuals sleep around the world? Results from a single-day survey in ten countries. *Sleep Medicine*. 2005;6(1):5-13. doi:10.1016/j.sleep.2004.10.006

66. Berson DM, Dunn FA, Takao M. Phototransduction by Retinal Ganglion Cells That Set the Circadian Clock. *Science*. 2002;295(5557):1070-1073. doi:10.1126/science.1067262

67. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews Neuroscience*. 2014;15(7):443-454. doi:10.1038/nrn3743

68. Hashizaki M, Nakajima H, Shiga T, Tsutsumi M, Kume K. A longitudinal large-scale objective sleep data analysis revealed a seasonal sleep variation in the Japanese population. *Chronobiology International*. 2018;0(0):1-13. doi:10.1080/07420528.2018.1443118

69. Kantermann T, Juda M, Merrow M, Roenneberg T. The Human Circadian Clock's Seasonal Adjustment Is Disrupted by Daylight Saving Time. *Current Biology*. 2007;17(22):1996-2000. doi:10.1016/j.cub.2007.10.025

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561 Figure captions:

562 Figure 1. Mean values for actigraphically-measured sleep variables by location (Boston, MA and
563 Tucson, AZ) and group (healthy control or mild traumatic brain injury (mTBI)). Bars are
564 presented as estimated marginal means ± standard error based on the linear mixed models. †: $p <$
565 0.1; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

566 Figure 2. Coefficient of variation (CV) for actigraphically-measured sleep variables by location
567 (Boston, MA and Tucson, AZ) and group (healthy control or mild traumatic brain injury
568 (mTBI)). Bars are presented as estimated marginal means ± standard error based on the linear
569 mixed models. †: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

570 Figure 3. Relationship between sleep onset latency coefficient of variation (CV) and daytime
571 sleepiness scores (Epworth Sleepiness Scale; ESS). A significant positive association between
572 increased sleep onset latency intra-individual variability and self-reported daytime sleepiness
573 was observed in both sites. No between site differences were observed.

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Table 1. Demographic characteristics, self-reported outcomes, and actigraphy measures by site and group				
	Boston		**Tucson**	
	HC	**mTBI**	**HC**	**mTBI**
N	24	28	11	29
Age (years)	25.8 ± 5.33	22.8 ± 7.16	19.9 ± 1.51[a***]	26 ± 8.22[b***]
Sex (M/F)	10/14	13/15	3/8	10/19
BMI (kg/m^2)	24.0 ± 3.72	25.4 ± 3.67	21.8 ± 3.66[a]	25.4 ± 6.26[b*]
Months post-injury		6.77 ± 3.97		9.21 ± 5.30
Mechanism of Injury (n)				
SRC[c]	-	17	-	7
MVA	-	5	-	13
Environmental[d]	-	4	-	4
Bicycle	-	1	-	2
Violence[e]	-	1	-	3
Participation month (n)				
January	2	1		1
February	4	4	3	1
March	4	6	6	2
April	1		2	3
May				1
June	1	6		4
July		3		3
August	1	1		1
September	1	2		7
October	4	2		2
November	5	2		2
December	1	1		2
Self-report Measures				
ESS Score	5.92 ± 3.82	10.2 ± 3.19 [f***]	5.55 ± 3.39	8.62 ± 3.24 [b*]
PSQI Total Score	-	7.14 ± 2.27	-	7.76 ± 3.24

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FOSQ Total Score	-	16.47 ± 1.95	-	15.90 ± 3.34
Actigraphy Measures				
Sleep duration				
Mean (min)	439.98 ± 38.99	407.51 ± 59.64	405.30 ± 68.59	425.55 ± 53.01
CV	0.16 ± 0.07	0.18 ± 0.08	0.17 ± 0.07	0.18 ± 0.08
SOL				
Mean (min)	8.98 ± 5.59	3.43 ± 2.53	10.13 ± 9.17	20.66 ± 14.27
CV	1.17 ± 0.39	1.40 ± 0.56	1.40 ± 0.44	1.04 ± 0.52
WASO				
Mean (min)	52.23 ± 17.64	56.39 ± 29.60	62.05 ± 37.18	52.36 ± 19.01
CV	0.39 ± 0.16	0.44 ± 0.24	0.43 ± 0.24	0.43 ± 0.37
SE				
Mean (%)	85.31 ± 3.78	85.94 ± 6.43	82.21 ± 7.93	82.24 ± 5.34
CV	0.06 ± 0.03	0.05 ± 0.04	0.09 ± 0.08	0.08 ± 0.04

Note. Values are provided as mean ± SD unless otherwise indicated. Two sample *t*-tests were used to identify significant differences between groups for continuous variables. PSQI and FOSQ outcomes were not recorded for the healthy control participants in Boston or Tucson. HC: Healthy Control; mTBI: Mild Traumatic Brain Injury; BMI: Body Mass Index; SRC: Sports-related concussion; MVA: Motor vehicle accident; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; FOSQ: Functional Outcomes of Sleep Questionnaire; CV: Coefficient of Variation; SOL: Sleep Onset Latency; WASO: Wake After Sleep Onset; SE: Sleep Efficiency

[a]Boston vs. Tucson HC

[b]Tucson mTBI vs HC

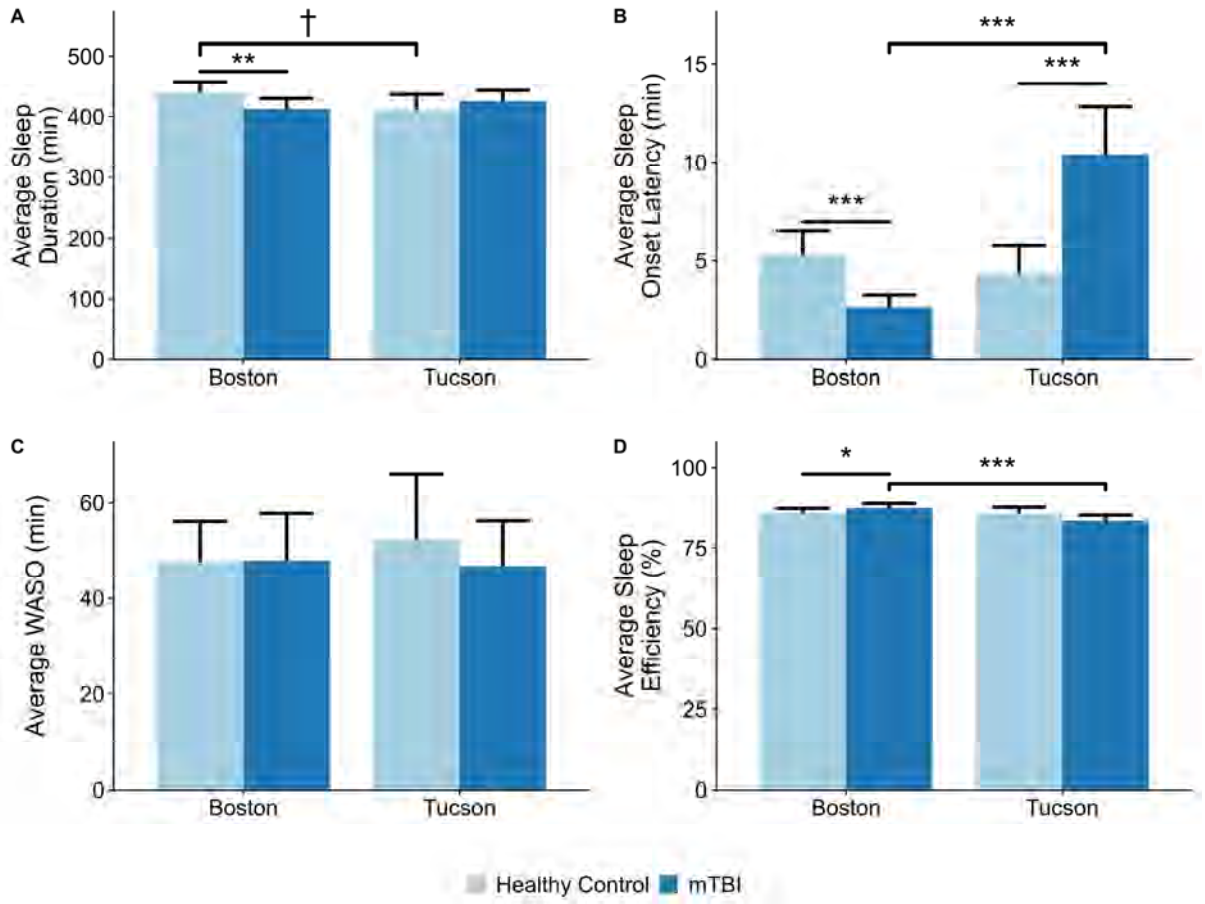
[c]Includes competitive and recreational (i.e. $n = 1$ boating accident) sports

[d]Includes contact with the environment due to slipping/tripping, alcohol-related mTBI, and falling objects

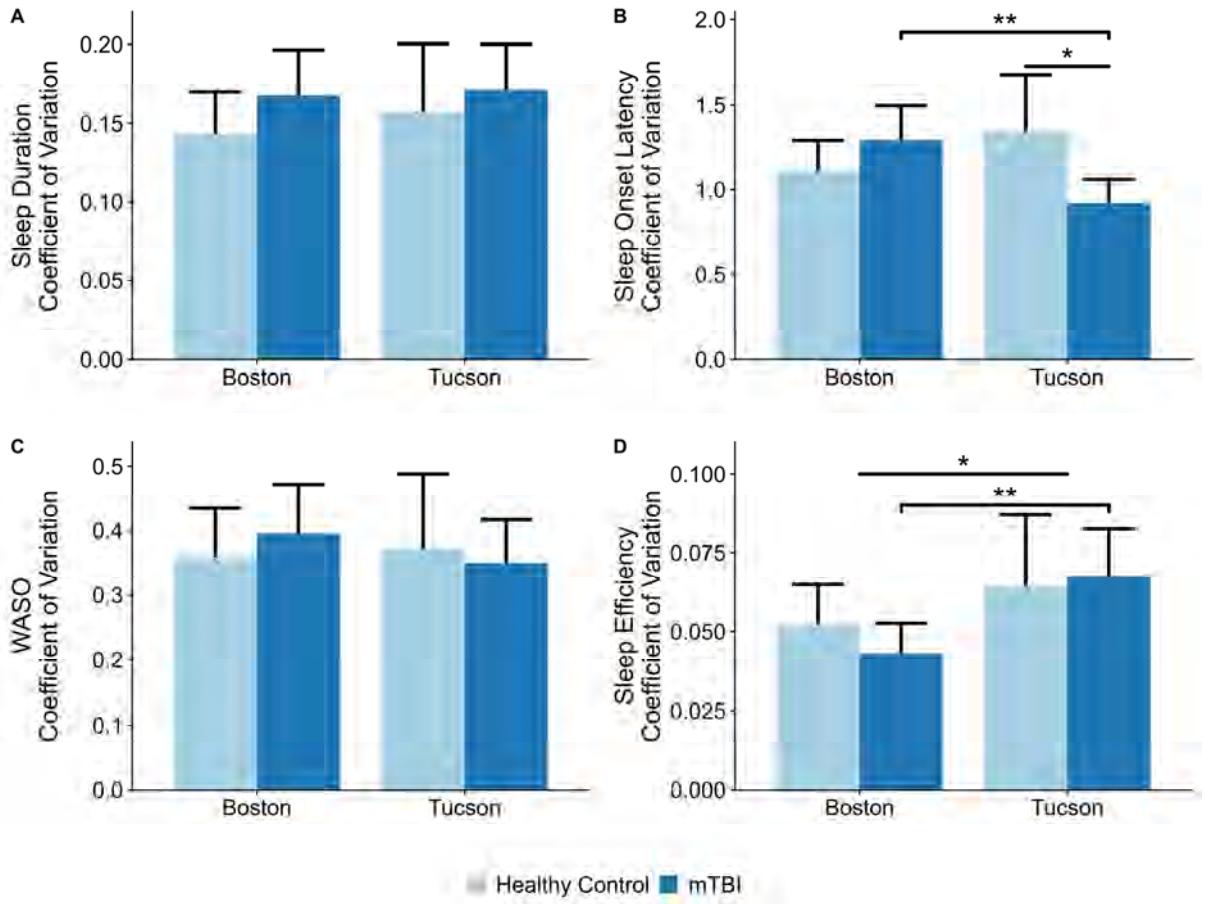
[e]Includes interpersonal violence and animal attacks

[f]Boston mTBI vs HC

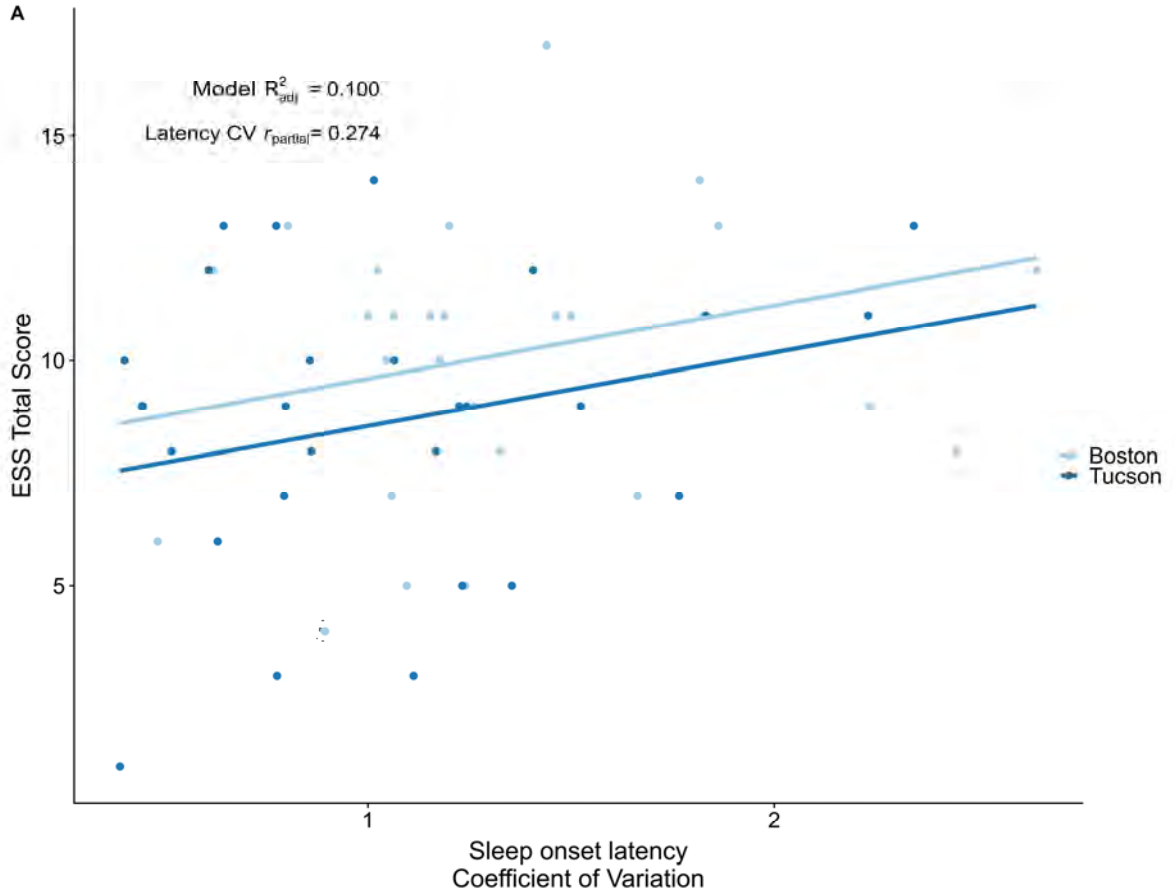
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$



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Highlights

- Daytime sleepiness and disrupted sleep are common after mild traumatic brain injury
- Sleep onset latency and sleep efficiency were susceptible to disruption after mTBI
- mTBIs were also associated with altered night-to-night sleep quality variability
- Consistent disruption patterns across independent samples were not evident
- Post-mTBI sleep disruption may not have a one-size-fits-all interpretation

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Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance

William D.S. Killgore, Haley C. Kent, Sara A. Knight and Anna Alkozei

Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle, with profound increases in circulating levels during the nighttime and nearly nonexistent levels during daylight hours. Although melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and executive function. We measured the change in salivary melatonin from mid-morning to late-morning in 26 healthy young adults who were also exposed to a 30-min period of blue or amber light followed by functional MRI during a working memory task (*N*-back). Brain activation was regressed on the change in melatonin scores from the mid-morning to late-morning saliva samples and the role of light exposure was also assessed. Although overall melatonin levels did not change significantly over the morning at the group level, individual declines in salivary melatonin were associated with significant increases in activation within the left dorsomedial and right inferior lateral prefrontal cortex during the 2-back condition ($P < 0.05$, cluster corrected). Medial prefrontal activation also correlated modestly with better vigilance performance during the 0-back ($P < 0.05$), but not the 1-back or 2-back conditions. The light condition did not affect the outcomes. These findings suggest declining melatonin levels in the morning are associated with increased prefrontal cortex functioning and may play a role in the increased frontal activation that occurs following awakening. *NeuroReport* **29:488–494** **Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

NeuroReport 2018, **29**:488–494

Keywords: functional magnetic resonance imaging, lateral prefrontal cortex, light exposure, medial prefrontal cortex, melatonin, neuroimaging, vigilance

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Received 12 February 2018 **accepted** 14 February 2018

Introduction

Nearly all living organisms demonstrate an innate biological rhythm that is closely entrained to the 24-h light/dark cycle produced by the Earth's rotation. Among mammals, this pattern is particularly notable in terms of the circadian rhythm of the circulating neurohormone melatonin [1]. For humans, melatonin secretion closely tracks the normal light/dark cycle, increasing in the evening near sunset and declining during the early morning hours before awakening, leading it to be dubbed the 'hormone of darkness' [2]. Although melatonin does not directly induce sleep, it appears to play a key role in preparing the brain for the sleep period [3]. Indeed, sleep onset is facilitated when melatonin levels are high, and there is evidence that increased melatonin is associated with more rapid sleep onset and longer sleep duration [4]. The circadian regulation of melatonin is directly tied to light exposure, and melatonin levels normally drop quickly in the early morning and remain at low to nonexistent levels throughout the light period of the day [1,3]. In fact, exposure to bright light, especially in the blue wavelengths, has been shown to actively suppress melatonin when administered soon after awakening in the morning, a finding that has been associated with improved alertness and vigilance [5].

The neurocognitive effects of melatonin are unclear and may depend on the time of day and body temperature. Early evidence suggested that circulating endogenous melatonin levels alone may not have a significant direct effect on cognition, but may have an indirect effect on logical reasoning, serial add/subtract, mental rotation, and choice reaction time by reductions in core body temperature [6]. Daytime administration of exogenous melatonin has been shown to increase self-rated sleepiness [7–9], and produce mild neurocognitive declines in psychomotor vigilance and attention [9,10], visual tracking speed, and spatial working memory [8]. The neural underpinnings of these effects, however, are still largely unknown. As melatonin is important for preparing the brain for sleep, we hypothesized that greater declines in salivary melatonin levels after awakening in the morning would be associated with increased functional activation responses and improved performance during a sustained working memory task using functional MRI (fMRI). Although any number of cognitive tasks could have been chosen for this study, we selected the classic *N*-back

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working memory task because it is one of the most widely used cognitive tasks in neuroimaging studies [11] and has previously been investigated for its association with cognitive processes associated with melatonin production, such as light exposure [12,13].

Participants and methods

Participants

Twenty-five (12 male; 13 female) right-handed, primary English speaking, healthy adults ranging in age from 18 to 32 years (mean = 22.2, SD = 3.7) provided multiple saliva samples and completed a neuroimaging scan (26 participants initially provided full data, but one male participant was dropped as an extreme outlier because of baseline melatonin levels exceeding 3 SDs from the sample mean). Participants were recruited from the metropolitan area of Tucson, Arizona, USA through posted flyers and internet advertisements and were screened to exclude any history of severe medical, neurological, or psychiatric conditions, head injury, alcohol or drug treatment, or current use of psychoactive drugs. Participants had obtained an average of 14.1 years (SD = 1.9) of formal education, and described themselves as normal sleepers, averaging 7.3 h (SD = 1.0) on weeknights, and 8.3 h (SD = 0.8) on weekends. The night before testing, participants self-reported sleeping an average of 7.0 h (SD = 0.4). Although we have published other data from this sample previously [12,14], the current paper presents novel data on a subset of participants who also provided salivary melatonin data. The analyses reported herein linking change in melatonin levels with brain activation are novel and have not been reported previously. This project was reviewed and approved by the University of Arizona College of Medicine Institutional Review Board and the US Army Human Research Protections Office.

Materials and procedure

A detailed description of the study methods is provided elsewhere [12]. Briefly, participants began the study at 0945 by sitting in a dimly lit room for 30-min (i.e. light washout), with ambient lighting provided by two amber light exposure devices, which were activated on the desk in front of participants and located 45° to the left and right of center, ~80 cm from the participant's nasion (Fig. 1). The light devices consisted of a plastic table-mounted chassis with a 10 × 6 array of light emitting diodes peaking at λ of 578 nm, at 188 Lx, and total irradiance (mW/cm^2) of 0.35, encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover (i.e. the housing was the same as the Philips goLITE BLU Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, Connecticut, USA). At the outset of this light washout session, participants also provided a saliva sample (MEL1).

At 1015, while seated in same location, participants completed an additional 30-min bright light exposure period (Fig. 1) in which they were exposed to an array of four devices fitted with either amber (n = 11), or four identical appearing fitted with blue wavelength light emitting diodes (peaking at λ = 469 nm, at 214 Lx, and panel irradiance (mW/cm^2) = 1.23 at 20 cm; n = 14). At 1045, the light period ended and participants provided a second saliva sample (MEL2), donned amber colored glasses (to block ambient blue light), and were escorted to the MRI scanner room next door, where they underwent fMRI while completing an *N*-back working memory task. At the completion of the fMRI scan, participants exited the scanner and provided a third saliva sample (MEL3) at 1245.

Melatonin assay and analysis

All materials for salivary melatonin collection were acquired from Salimetrics (State College, Pennsylvania, USA). Saliva was collected by passive drool method and stored in a 2 ml cryovial made of polypropylene. Within 3 min of collection, samples were placed in a Styrofoam cooler with ice packs and subsequently transferred to and stored in a freezer set and monitored to maintain sample storage at a temperature of −20°C. Samples were analyzed using Salimetrics Salivary Melatonin EIA kits according to standard procedures (*https://www.salimetrics.com/assets/documents/1-3402n.pdf*).

Neuroimaging

N-back task

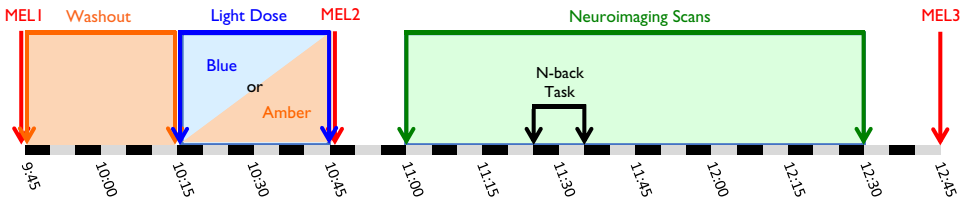
We used a variant of the visually presented *N*-back task [15] to assess working memory. Participants were presented with a black screen with centered white letters, appearing one at a time and were required to use the index or middle finger of their right hand to indicate whether the current letter presented was identical to the letter presented during the immediately preceding trial (1-back) or was identical to the letter presented two trials previously (2-back), or a control condition (i.e. 0-back), whereby they were asked to identify whether the letter on the screen matched a predetermined letter (e.g. 'P'). Each condition lasted 52 s and was repeated in a pseudorandom order. During each block, a crosshair fixation point was shown for 10 s, followed by the instructions for the next block (0-back, 1-back, or 2-back) for 6000 ms. During each trial, each letter was presented for 500 ms with a total of 1750 ms provided to respond to each item. The task concluded with a final crosshair screen for 10 s. The entire task lasted 7 min and 58 s.

Neuroimaging parameters

Neuroimaging data were collected on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were acquired using a T1-weighted three-dimensional MPRAGE sequence (TR/TE/flip angle = 2.1 s/2.33 ms/12°) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted fMRI scans were collected over 32 transverse slices and a

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Fig. 1



Overview of the study procedure. Between 9:45 a.m. and 10:15 a.m., participants completed 30 min of amber light 'washout' exposure period, followed by an additional 30 min of either amber placebo light or blue light exposure (i.e. between 10:15 a.m. and 10:45 a.m.). The neuroimaging scan began at 11:00 a.m. and the *N*-back task was initiated at 11:25 a.m., and ended at 11:33 a.m. Neuroimaging ended at 12:30 p.m. Participants provided a salivary melatonin sample (MEL) three times during the procedure, including just before the start of the washout period, immediately after the light exposure, and at 12:45 a.m. after exiting the functional MRI scanner.

slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/25.0 ms/90°) with 239 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

Image processing and statistical analysis

Processing and analysis was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; *http://www.fil.ion.ucl.ac.uk/spm*) following standard procedures [12], including realignment, unwarping, co-registration, normalization to Montreal Neurological Institute (MNI) coordinate space, spatial smoothing (6 mm full-width at half maximum), and reslicing to 2 × 2 × 2 mm voxels. Low-frequency confounds were removed with a high pass filter (128 s cutoff period). Motion artifacts were removed using the Artifact Detection Tool (*http://www.nitrc.org/projects/artifact_detect/*). Individual general linear models were specified to contrast activation relevant to working memory (i.e. 2-back > 0-back condition) and simple alertness and vigilance (i.e. 1-back > 0-back, 1-back > cross-hair fixation, and 0-back > cross-hair fixation point) for each participant.

Our interest was to examine the brain activation responses predicted by changes in salivary melatonin from prelight to postlight exposure. Therefore, melatonin data from the 0945 (MEL1) sample were subtracted from the mean of the 1045 (MEL2) and 1245 (MEL3) samples [i.e. (MEL2 + MEL3)/2 − MEL1] to derive a melatonin change score (MEL change). The individual contrast images for the *N*-back task, as described above, were entered as the dependent variable in an SPM12 linear regression analysis with MEL change as the independent variable. Significant clusters were identified by initially thresholding the statistical maps at P less than 0.001, and then applying a P less than 0.05 false discovery rate (FDR) cluster extent threshold. The data from significant clusters were extracted and transferred for further analysis in IBM SPSS 20 (IBM Corp., IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, New York, USA). Further regression analyses were conducted to determine the individual and combined effects of light exposure, MEL change, and their interaction on brain activation.

Results

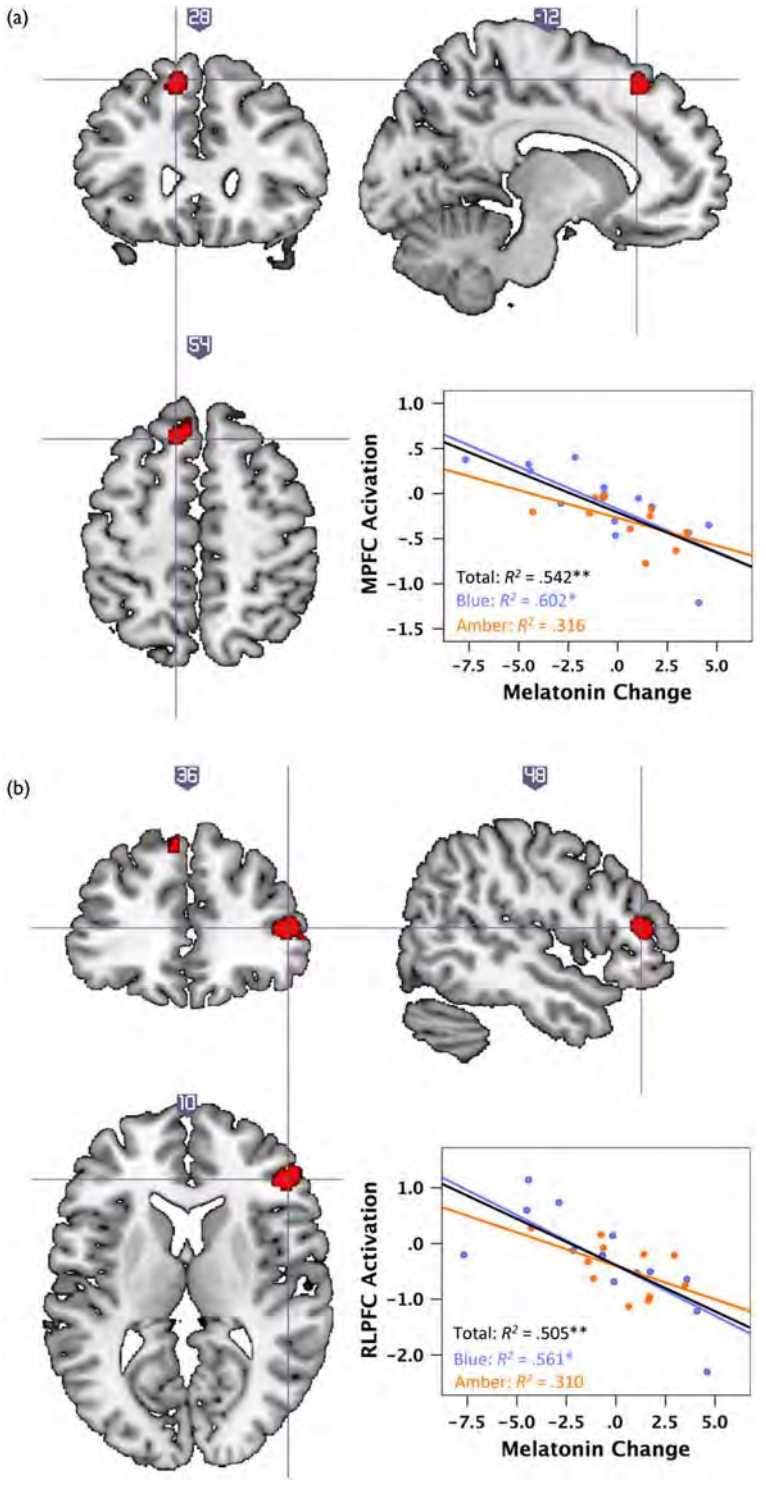
There was considerable individual variability in the magnitude and direction of change in melatonin across the morning, with 14 individuals showing a decline and 11 showing an increase from mid-morning to late-morning. Consequently, when the sample was considered as a whole, salivary melatonin levels did not decline significantly during the study period [MEL change, mean = −0.18, SD = 3.01, $t(24) = -0.31$, $P = 0.76$], and this change did not differ significantly between the blue (mean = −0.59, SD = 3.53) and amber (mean = 0.33, SD = 2.24) light groups, $t(23) = 0.75$, $P = 0.46$. Behaviorally, greater decline in melatonin levels was associated with marginally better throughput [i.e. the number of correct responses per second; (% correct/RT) × 1000] for the 0-back ($r = -0.32$. $P = 0.055$, one tailed), but not for the 1-back ($r = -0.22$, $P = -0.14$, one tailed) or 2-back ($r = -0.15$, $P = 0.23$, one tailed) conditions, suggesting that declines in melatonin were associated with improved vigilance.

Our primary hypothesis focused on the association between changes in melatonin and brain activation associated with working memory. However, it was first important to rule out any potential effects of melatonin change on simple vigilance performance. Thus, we first conducted three correlational analyses to examine the relation between melatonin change and brain activation for the pure vigilance (0-back > fixation), and low working memory load (1-back > fixation), and low working memory minus vigilance conditions (1-back > 0-back). At our a priori statistical threshold of P less than 0.001, with cluster correction of P less than 0.05, we found no activations that survived in any of these correlation analyses.

However, for our primary hypothesis regarding activation during high working memory load, the decline in melatonin levels during the morning was associated with increased task-related activation in two clusters within the prefrontal cortex for the 2-back > 0-back contrast

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Fig. 2



Three-dimensional views of the cortical regions showing significant ($P < 0.05$, false discovery rate cluster corrected) correlation with melatonin change for the contrast of interest (i.e. 2-back > 0-back), including (a) the left superior medial frontal gyrus (x, y, z: −12, 28, 54, respectively), and (b) the right inferior frontal gyrus (trigone region) (x, y, z: 48, 36, 10, respectively). The scatterplots show the association between melatonin change from baseline to the time of the scan and its association with prefrontal activation for the group as a whole (black line), and the blue and amber light conditions separately. *$P < 0.005$, **$P < 0.001$. MPFC, medial prefrontal cortex; RLPFC, rostrolateral prefrontal cortex.

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(Fig. 2). The first was a cluster ($k=75$) located within the left medial superior frontal gyrus (MNI coordinates: $x=-12$, $y=28$, $z=54$, $T=5.21$, $P=0.046$, FDR cluster corrected, Fig. 2a), and the second was a cluster ($k=76$) located within the right inferior frontal gyrus (MNI coordinates: $x=48$, $y=36$, $z=10$, $T=4.85$, $P=0.046$, FDR cluster corrected, Fig. 2b). As shown in the scatterplots of Fig. 2, MEL change accounted for more than 50% of the variance in brain responses in these two regions.

Activation within the medial prefrontal cortex cluster was significantly associated with better throughput (i.e. correct responses per second) performance on the 0-back ($r=0.34$, $P=0.047$, one tailed), and marginally so for the 1-back ($r=0.29$, $P=0.08$, one tailed), but not the 2-back ($r=0.22$, $P=0.14$, one tailed) conditions. The activation cluster in the lateral prefrontal cortex was not significantly associated with any level of *N*-back performance (all rs <0.25).

It was also of interest to determine whether the associations between MEL change and brain activation differed as a function of the light exposure. We, therefore, conducted a stepwise multiple linear regression analysis to evaluate the contribution of the light category to the models. For the first cluster, located in the left medial superior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (change in $R^2=0.016$, $P=0.38$) above and beyond the effects of MEL change, and the addition of the light condition × MEL change interaction term also did not contribute significant prediction to the model (change in $R^2=0.013$, $P=0.44$). Similarly, for the second cluster located in the right inferior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (change in $R^2<0.001$, $P=0.998$), and the addition of the light condition × MEL change interaction term also did not contribute significantly to the model (change in $R^2=0.012$, $P=0.45$).

Discussion

Changes in morning salivary melatonin over a 3-h period were associated with reliable differences in prefrontal brain activation during a sustained working memory task, even after removing activation associated with simple vigilance. For those individuals showing the greatest decline in melatonin over the course of the morning, there was correspondingly greater brain activation within the left medial superior frontal gyrus, a region involved in vigilance, self-monitoring, conflict monitoring, and response action selection [16–18], and the right inferior frontal gyrus, a region involved in working memory and cognitive control [19]. However, those individuals showing increases in melatonin levels during the same 3-h time period showed correspondingly lower task-related activation responses in these same regions. It is interesting that changes in melatonin levels were not directly associated with brain responses during the simple vigilance components of the task, but were associated with activation specific to the working memory components of the task. It is also interesting that the melatonin-related activation in medial prefrontal cortex, whereas only apparent for the working memory condition, was modestly associated with better performance on the simplest vigilance condition of the *N*-back task, but not for the performance of the more demanding working memory conditions. This suggests that the greater activation of this area may still indirectly play a role in vigilance processes and would be an important topic for further exploration. Finally, we also found that the slopes of these associations were not differentially affected by the administration of an intervening half-hour pulse of blue or amber light, suggesting that the general association between melatonin changes and brain function is robust and reliable regardless of recent light exposure.

Melatonin has long been known as the 'hormone of darkness' [2], and is believed to play a role in preparing the brain for sleep [20]. Acute melatonin administration has a soporific effect, generally reducing vigilance levels [10] and facilitating sleep onset [4,21]. For example, a single 5 mg dose of melatonin administered during the early morning leads to a significant worsening of vigilance performance relative to placebo [10]. Among individuals with a normal sleep/wake rhythm, circulating melatonin levels drop rapidly in the early morning hours, remain near zero during the typical daylight waking period, and rapidly increase in the early evening as natural sunlight recedes and blue wavelengths of light are minimized [1]. There is, however, considerable variation in individual timing of endogenous melatonin onset and offset [22,23], and very little is known about how melatonin levels relate to brain activation. Early work showed that exogenous administration of melatonin led to decreased activation within the visual cortex during a visual search task and decreased activation within the auditory cortex during a music perception task, both of which correlated with self-reported fatigue [20]. A later study by the same group confirmed the association of decreased occipital cortex activation on a visual search task in response to exogenous melatonin administration during the late afternoon [24]. These studies, however, only focused on late day associations between melatonin administration and brain function. A recent study examined the circadian modulation of brain activation across the entire day and night to a psychomotor vigilance task and an *N*-back task similar to the one used here [25]. The *N*-back data from their study showed that cortical responses within the insula were tightly coupled with melatonin levels and showed increased functional brain activation as morning melatonin levels declined, a finding consistent with our results. Here, we expand on those results by showing that the magnitude of the decline in melatonin observed over a 3-h period in the morning is significantly correlated

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with greater task-related activation in the medial prefrontal cortex and right lateral inferior frontal cortex.

We interpret these melatonin-neuroimaging data as reflecting differences in circadian phase among individuals. Specifically, we speculate that those individuals who showed the largest declines in melatonin were those who were the most phase delayed (i.e. late risers whose melatonin was still relatively high at the outset of the study and thus dropped more precipitously relative to the early risers whose melatonin was already at a relatively low point at the start of testing). This interpretation would be consistent with previous work showing that the process of awakening involves increased metabolic activity within the prefrontal cortex [26]. Additional research will be necessary to determine whether the changes in melatonin play a causal role in the pattern of brain activation or are simply correlated with increased prefrontal activation during the awakening process.

Findings from this study need to be considered in the context of potential methodological limitations. First, melatonin samples were collected at only a few time points, so it is not possible to determine the precise circadian phase of the participants. Although all participants self-reported normal bed-times and wake-times, and normal sleep the night before the study, it is possible that some may display extreme chronotypes or arrived more sleep deprived than reported. Second, we found that blue light had no appreciable effect on melatonin, despite considerable evidence that morning short wavelength light exposure suppresses morning melatonin [27]. However, our data collections occurred late in the morning, and melatonin levels are likely to have already dropped close to their nadir, minimizing any appreciable suppressive effect of blue light.

Conclusion

Changes in morning salivary melatonin were associated with functional brain responses during a working memory task. The magnitude of the decline in salivary melatonin during the late-morning hours was associated with increased brain activation within dorsomedial and lateral prefrontal cortex, brain regions involved in vigilance, action selection, and cognitive control. These changes were modestly associated with improved vigilance performance during the task, but not with complex executive function. These findings suggest that changes in morning melatonin levels are associated with differences in prefrontal cortex functioning. We interpret these associations as reflecting individual differences in circadian phase of melatonin and their potential impact on the morning establishment of prefrontal functioning in the hours following awakening.

Acknowledgements

This work was supported by a grant from the US Army Medical Research and Materiel Command to WDSK (W81XWH-14-0571) and an Arizona Area Health Education Centers (AzAHEC) Research Grant to AA.

Conflicts of interest

There are no conflicts of interest.

References

1 Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. *Ann Clin Biochem* 2006; **43** (**Pt 5**): 344–353.
2 Utiger RD. Melatonin – the hormone of darkness. *N Engl J Med* 1992; **327**:1377–1379.
3 Cajochen C, Krauchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 2003; **15**:432–437.
4 Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, *et al*. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev* 2005; **9**:41–50.
5 Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J Clin Endocrinol Metab* 2003; **88**:4502–4505.
6 Slotten HA, Krekling S. Does melatonin have an effect on cognitive performance? *Psychoneuroendocrinology* 1996; **21**:673–680.
7 Arendt J, Borbely AA, Franey C, Wright J. The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neurosci Lett* 1984; **45**:317–321.
8 Rogers NL, Kennaway DJ, Dawson D. Neurobehavioural performance effects of daytime melatonin and temazepam administration. *J Sleep Res* 2003; **12**:207–212.
9 Crowley SJ, Eastman CI. Melatonin in the afternoons of a gradually advancing sleep schedule enhances the circadian rhythm phase advance. *Psychopharmacology (Berl)* 2013; **225**:825–837.
10 Ghattassi K, Hammouda O, Graja A, Boudhina N, Chtourou H, Hadhri S, *et al*. Morning melatonin ingestion and diurnal variation of short-term maximal performances in soccer players. *Physiol Int* 2016; **103**:94–104.
11 Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 2005; **25**:46–59.
12 Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, *et al*. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* 2016; **39**:1671–1680.
13 Munch M, Linhart F, Borisuit A, Jaeggi SM, Scartezzini JL. Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. *Behav Neurosci* 2012; **126**:196–203.
14 Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS ONE* 2017; **12**:e0184884.
15 Gevins A, Cutillo B. Neuroelectric evidence for distributed processing in human working memory. *Electroencephalogr Clin Neurophysiol* 1993; **87**:128–143.
16 Hinds O, Thompson TW, Ghosh S, Yoo JJ, Whitfield-Gabrieli S, Triantafyllou C, *et al*. Roles of default-mode network and supplementary motor area in human vigilance performance: evidence from real-time fMRI. *J Neurophysiol* 2013; **109**:1250–1258.
17 Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, Carter CS. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn* 2004; **56**:129–140.
18 Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proc Natl Acad Sci USA* 1993; **90**:873–877.
19 Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 2004; **8**:170–177.
20 Gorfine T, Assaf Y, Goshen-Gottstein Y, Yeshurun Y, Zisapel N. Sleep-anticipating effects of melatonin in the human brain. *Neuroimage* 2006; **31**:410–418.
21 Pires ML, Benedito-Silva AA, Pinto L, Souza L, Vismari L, Calil HM. Acute effects of low doses of melatonin on the sleep of young healthy subjects. *J Pineal Res* 2001; **31**:326–332.
22 Burgess HJ, Fogg LF. Individual differences in the amount and timing of salivary melatonin secretion. *PLoS One* 2008; **3**:e3055.
23 Crowley SJ, Van Reen E, LeBourgeois MK, Acebo C, Tarokh L, Seifer R, *et al*. A longitudinal assessment of sleep timing, circadian phase, and

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phase angle of entrainment across human adolescence. *PLoS One* 2014; **9**:e112199.
24 Gorfine T, Zisapel N. Late evening brain activation patterns and their relation to the internal biological time, melatonin, and homeostatic sleep debt. *Hum Brain Mapp* 2009; **30**:541–552.
25 Muto V, Jaspar M, Meyer C, Kusse C, Chellappa SL, Degueldre C, *et al*. Local modulation of human brain responses by circadian rhythmicity and sleep debt. *Science* 2016; **353**:687–690.
26 Balkin TJ, Braun AR, Wesensten NJ, Jeffries K, Varga M, Baldwin P, *et al*. The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. *Brain* 2002; **125** (**Pt 10**):2308–2319.
27 West KE, Jablonski MR, Warfield B, Cecil KS, James M, Ayers MA, *et al*. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J Appl Physiol (1985)* 2011; **110**:619–626.

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PLOS ONE

RESEARCH ARTICLE

Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance

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Citation: Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS (2017) Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. PLoS ONE 12(9): e0184884. https://doi.org/10.1371/journal.pone.0184884

Editor: Etsuro Ito, Waseda University, JAPAN

Received: June 20, 2017

Accepted: September 3, 2017

Published: September 18, 2017

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by a U.S. Army US Army MOMRP Grant (W81XWH-11-1-0056) as well as by an Arizona Health Education Centers (AHEC) Research Grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Acute exposure to light within the blue wavelengths has been shown to enhance alertness and vigilance, and lead to improved speed on reaction time tasks, possibly due to activation of the noradrenergic system. It remains unclear, however, whether the effects of blue light extend beyond simple alertness processes to also enhance other aspects of cognition, such as memory performance. The aim of this study was to investigate the effects of a thirty minute pulse of blue light versus placebo (amber light) exposure in healthy normally rested individuals in the morning during verbal memory consolidation (i.e., 1.5 hours after memory acquisition) using an abbreviated version of the California Verbal Learning Test (CVLT-II). At delayed recall, individuals who received blue light (n = 12) during the consolidation period showed significantly better long-delay verbal recall than individuals who received amber light exposure (n = 18), while controlling for the effects of general intelligence, depressive symptoms and habitual wake time. These findings extend previous work demonstrating the effect of blue light on brain activation and alertness to further demonstrate its effectiveness at facilitating better memory consolidation and subsequent retention of verbal material. Although preliminary, these findings point to a potential application of blue wavelength light to optimize memory performance in healthy populations. It remains to be determined whether blue light exposure may also enhance performance in clinical populations with memory deficits.

Introduction

Short-wavelength light exposure (~480nm, blue light) plays multiple important roles in biopsychological functioning. Specifically, in addition to its role in conscious visual perception through the lateral geniculate nucleus and projection to primary and secondary visual cortex, light exposure can also influence the timing of circadian rhythms, the magnitude of alertness, and quality and duration of sleep through a secondary non-image forming light response system [1, 2]. When light strikes the retina, the blue wavelengths specifically stimulate intrinsically photosensitive retinal ganglion cells (ipRGCs), which respond by transmitting irradiance

signals to a number of sub-cortical nuclei, including the the suprachiasmatic nucleus (SCN) and other nuclei of the hypothalamus. The SCN serves as the body's master clock and regulates the production of melatonin (a hormone secreted by the pineal gland that prepares the brain for sleep) and circadian rhythms of sleep and wake [2]. In addition, the SCN has projections to the locus coeruleus (LC) in the brain stem [3]. Acute short bursts of exposure to blue wavelength light have been shown to increase activation in the brainstem, in an area consistent with the brain coordinates of the LC [4]. Importantly, stimulation of the LC has been shown to promote greater release of norepinephrine throughout the cerebral cortex [5], which in turn influences a variety of brain functions including alertness [6]. It has therefore been proposed that blue light may activate the LC through projections from the SCN, and that such stimulation of the LC may lead to increased norephineprhine release throughout the brain which in turn increases alertness [4].

Blue light exposure (or bright light more generally) at night leads to increases in subjectively and objectively measured alertness and vigilance, likely as a consequence of suppression of melatonin production [7±9]. However, studies have also shown that blue light (or blue-enriched white light) exposure during the day, a time when melatonin levels are naturally low, also leads to an increase in alertness and vigilance, as well as improvements in working memory performance [10±12]. For example, we have recently shown that 30 minutes of exposure to blue versus amber (placebo) wavelength light during the day led to *subsequently* faster performance on a working memory task (i.e., 45 minutes after light exposure) and increased functional brain responses in regions that are important for working memory processes, such as the dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC) [10]. This alerting effect has even been demonstrated in visually blind individuals, further suggesting that it is produced by activation of the non-image forming ipRGCs [13]. The mechanisms underlying this alerting effect remain to be fully elucidated but one potential explanation that has been proposed as a result of these findings involves the potential stimulating effect of blue light on the LC, leading to increased noradrenergic activation within other areas of the brain (i.e., the PFC), resulting in increased alertness and speed of responding [4, 10].

While studies have shown that blue light increases performance in both simple reaction time tasks and in working memory tasks, it is unclear whether other aspects of cognition may also be affected. Long-term memory (LTM), in particular, is a critical aspect of cognition that could potentially be affected above and beyond the simple effects of blue light on alertness. Although the effects of blue light exposure on memory have not been studied, evidence suggests that norepinephrine has a positive effect on memory consolidation (i.e., the period after memory acquisition) [for a review see 14]. In particular, a number of animal studies have shown that increases in norepinephrine (as a result of drug administration) after memory acquisition led to better LTM [14, 15]. Importantly, the timing of norepinephrine administration appears to play a crucial role, but the optimal timing of stimulation to enhance LTM is unclear and may depend specifically on the type of memory studied. However, it appears that noradrenergic influences are particularly prominent during later stage memory consolidation processes. For example, studies have shown that rats who were administered beta blockers 2 hours after memory acquisition showed amnesia 48 hours later, whereas no effect was seen when beta blockers were administered 5 minutes after learning [16, 17].

In summary, daytime exposure to blue light has been shown to activate functional brain responses in brainstem areas consistent with the LC, a region which, when stimulated, has been shown to release norepinephrine throughout the brain. Because increased norepinephrine during memory consolidation is known to improve memory due to neuromodulatory effects on multiple LTM-related brain areas, it follows that blue light exposure may therefore enhance memory performanceÐa prediction that remains untested to date. To fill this critical

gap in knowledge, we therefore tested the hypothesis that daytime exposure to blue wavelength light for 30 minutes during memory consolidation (~1.5 hours after encoding) would lead to better verbal LTM performance when compared to equal exposure to a placebo (amber) light.

Materials and methods

Participants

Thirty healthy 18±32 year olds (17 female; mean age = 21.87± 3.74) took part in the study. Participants were all right handed, native English speakers, free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 10pm and 1am and waking between 6am and 9am. Participants self-reported that they obtained, on average, 6 hours and 45 minutes (SD = 49 minutes) of sleep the night preceding the day of testing.

California Verbal Learning Test, Version II (CVLT-II)

The CVLT-II [18] is an individually administered test of verbal memory and associated cognitive processes. Participants completed the immediate recall, short-delay, and long-delay free recall parts of the CVLT-II. Participants were read a list of words and told they would be asked to repeat as many words as possible. This test-recall procedure was repeated 5 times (*immediate recall*, *trials 1–5*). The list consisted of 15 neutral words evenly divided into the following categories: animals, furniture, vegetables, and modes of transportation. After the 5^{th} trial, participants were read a second list (i.e., distractor list) and asked to repeat only words from the second list. Immediately following recall of the second list, participants were asked to recall only words presented in initial list (*short-delay free recall*). Approximately 1.5 hours after the short-delay free recall subtest, participants were asked to recall as many words from the initial list (*long-delay recall*). Raw scores (i.e., total number of words recalled) as well as standard scores (i.e., raw scores converted to norm-referenced scores) were calculated for each trial.

Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI-II) [19] is a 21-item self-report questionnaire used to assess depressive symptoms over the preceding 2 weeks. The BDI-II has been shown to have good psychometric properties [19]. Scores of 13 or higher have been shown to discriminate well between clinical and non-clinical populations, therefore only participants who scored lower than 13 on the BDI-II were eligible for this study [20]. BDI-II scores were nevertheless included as a covariate in the analysis, as depressive symptoms have consistently been shown to influence CVLT-II performance [18].

Two-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI-FSIQ)

The Full Scale-II Wechsler Abbreviated Scale of Intelligence (WASI-II FSIQ) [21] was used as a measure of intellectual ability or ªIQº. The WASI-II FSQI is one of the most widely used intelligence scales and correlates highly (r = .92) with the Wechsler Adult Intelligence Scale-III (WAIS; Pearson Assessment, Inc., San Antonio, TX) [21]. The instrument yields scores for Full Scale IQ, Verbal IQ, and Performance IQ. The WASI-II FSQI was individually administered by a trained research technician under the supervision of a licensed doctoral level neuropsychologist. WASI-II FSQI scores were used as a covariate in the analysis, as IQ has been shown to influence performance on the CVLT-II [18].

Light exposure protocol

The light exposure protocol is described in detail in Alkozei et al. (2016) [10]. In brief, all participants began with a half-hour blue light Washout Period (described in more detail under Procedure) that involved sitting in a dark room while only exposed to two amber light devices (described below) mounted on a desk at a distance of approximately 80 cm from the participant's nasion, with each light centered at a 45 degree angle from midline (see Fig 1A). During the Exposure Period, light was administered by a similar configuration of four light devices, also centered at 45 degrees to each side of the participant with a distance of approximately 80 cm from the participant's nasion (see Fig 1B). In the Exposure Period, participants were randomly assigned to undergo a half hour of exposure to an array of either blue or amber light devices. Blue light exposure utilized an array four of commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). Each device consisted of a plastic table-mounted chassis with a 10 x 6 array of light emitting diodes (LEDs),

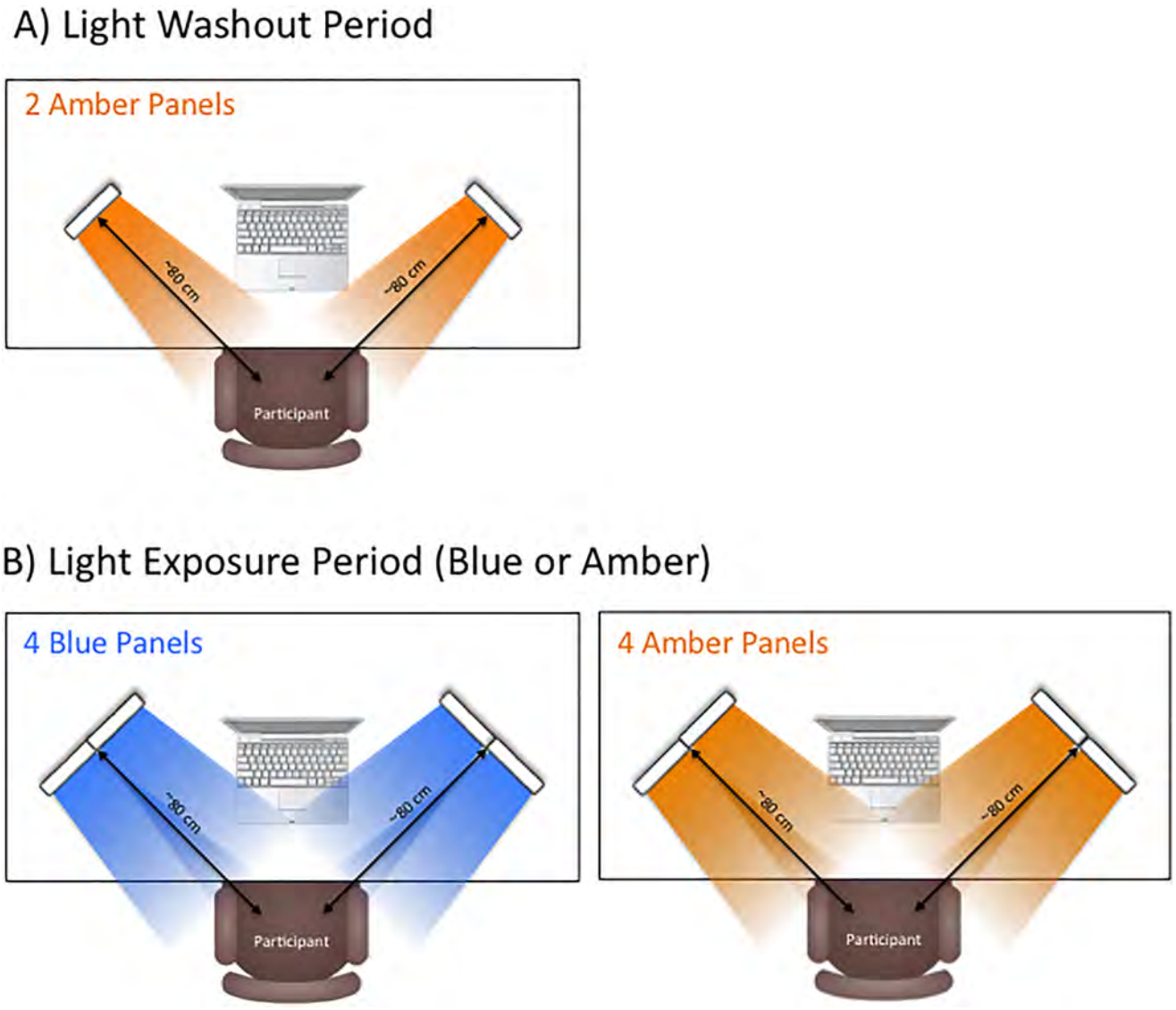


Fig 1. Illustration of the light exposure study design set-up.

https://doi.org/10.1371/journal.pone.0184884.g001

encased in 1 x 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU Energy Light is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm). The amber placebo devices were provided by the manufacturer for research purposes and were essentially identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm).

Procedure

While participants completed the study on an individual basis, all participants were tested at the same time of day to control for circadian time-of-day effects. To avoid potential caffeine withdrawal effects, participants were asked to consume their normal levels of morning caffeine before arrival for the study at 0745. For the first portion of the day, participants completed the informed consent process, basic information questionnaires, and cognitive tasks. At approximately 0905, participants were administered the first 5 encoding trials and the short-delay recall portion of the CVLT-II. Participants were then randomized to receive either 30 minutes of blue (n = 12) or amber (n = 18) light exposure. At approximately 0945, participants underwent the [a]blue light washout[o] period (see above) for 30 minutes to ensure that residual effects of outdoor and ambient lighting dissipated before the beginning of the light exposure period. At 1015, the two Washout Period light devices were replaced with the four Exposure Period devices (i.e., either blue or amber). During the two light exposure periods, participants completed a number of computerized tasks. The laptop monitors were fitted with an amber colored Plexiglas panel to block blue wavelength light. At approximately 1100, participants were asked to complete the long delay portion of the CVLT-II. Fig 2 illustrates the timeline of the study design.

Ethical considerations

The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office. All participants provided written informed consent.

Data analysis

Change in performance from CVLT-II short-delay free recall to long-delay free recall raw and standard scores between the blue and amber light exposure groups were analyzed using

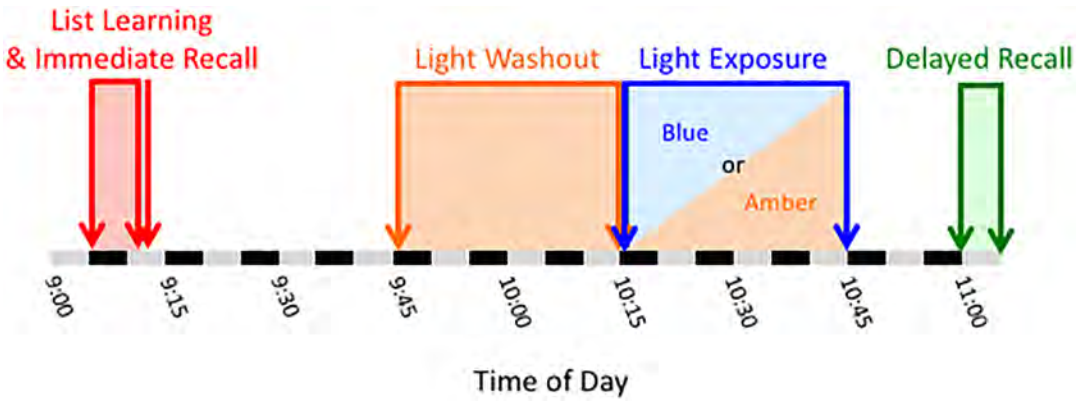


Fig 2. Illustration of the study timeline.

https://doi.org/10.1371/journal.pone.0184884.g002

repeated-measures analysis of covariance (ANCOVA), using WASI-FSQI and BDI-II scores as covariates. As the two groups differed in habitual wake time (see Results section below), we also included habitual wake times as an additional covariate.

Results

Preliminary analyses

In order to rule out any group differences prior to the light exposure, independent samples t-tests were conducted comparing performance on the CVLT-II between the blue and amber light group. There were no differences in standard scores on the CVLT between the two groups at trial 1 ($t(28) = .56$, $p = .57$), trial 5 ($t(28) = -1.29$, $p = .21$), or on total performance standard scores (sum of trials 1±5) ($t(28) = .17$, $p = .87$). These findings suggest that the two groups did not differ in their initial learning or retention of the word list prior to exposure to the light conditions.

In addition, the two groups did not differ in age, sex, sleep duration the night before the day of testing, number of caffeinated products consumed on the morning before testing, WASI-II FSQI total and Vocabulary subscale scores (see Table 1). Participants also did not differ on habitual bedtime, or habitual sleep duration. However, participants in the amber light group did report significantly earlier habitual wake times (7:20 am; SD = 60 min) than participants in the blue light group (8:07 am; SD = 54 min; $t(28) = -2.15$, $p = .04$), and it was therefore included as an additional covariate in the analyses below.

Hypothesis testing

The repeated-measures ANCOVA showed a significant main effect of time ($F(1, 25) = 5.06$, $p = .03$, $d = .09$) as well as a group x time interaction ($F(1, 25) = 4.39$, $p = .05$, $d = .84$). Post-hoc pairwise comparisons showed that while there was no significant difference from pre- to post-light exposure for the blue light group ($p = .13$), there was a significant decline in CVLT standard scores from pre- to post-light exposure for the amber light group ($p < .001$). However,

Table 1. Descriptive statistics.

	Blue light group n = 12	Amber light group n = 18	Statistic
Age	21.50 (3.34)	22.11 (4.07)	$t(28) = .42$
Sex	50% female	61% female	$\chi^2(1) = .36$
Sleep duration the night before (in hours)	6.87 (.71)	6.88 (.90)	$t(28) = .05$
Habitual bedtime	11:33pm (66 min)	11::16pm (55 min)	$t(28) = -.70$
Habitual waketime	8:07am (54 min)	7:20am (60 min)	$t(28) = -2.15$*
Habitual sleep duration (in hours)	7.54 (.78)	7.33 (1.02)	$t(28) = -.59$
Number of caffeinated products	1	3	$\chi^2(1) = .43$
WASI-FSQI	104.75 (12.82)	106.61 (11.50)	$t(28) = .68$
WASI-FSQI Vocabulary Subscale	54.28 (8.92)	54.75(9.62)	$t(28) = -.14$
BDI-II	1.75 (2.00)	2.94 (3.40)	$t(28) = 1.01$
CVLT-II Trial 1 standard score	0.42 (.86)	.28 (1.25)	$t(28) = .57$
CVLT-II Trial 5 standard score	.45 (.97)	.00 (.91)	$t(28) = -1.29$
CVLT Trial 1±5 standard score	55.83 (8.89)	56.39 (8.75)	$t(28) = .16$

WASI-FSQI: Wechsler Abbreviated Scale of Intelligence Full Scale-II; BDI-II: Beck Depression Inventory; CVLT-II: California Verbal Learning Test
*p <.05

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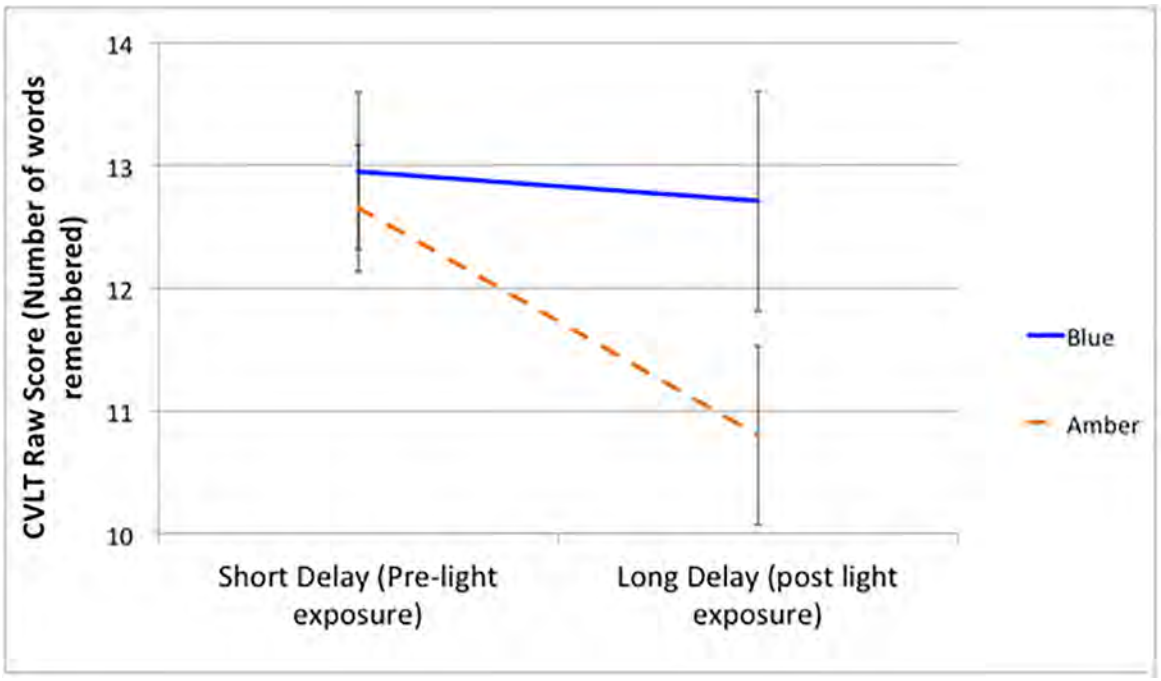


Fig 3. Estimated marginal means and error bars (1SE) for CVLT ±II short-delay and long-delay raw scores for individuals in the blue (n = 12) and amber (n = 18) light groups. CVLT-II: California Verbal Learning Test (Version 2).

https://doi.org/10.1371/journal.pone.0184884.g003

there was no significant difference between the two groups for CVLT long-delay recall scores ($p = .20$).

As standard scores can be difficult to interpret because they include corrections for age and gender, we re-ran the analysis using CVLT raw scores. While, there was no significant main effect of time ($F(1, 25) = 2.45$, $p = .13$, $d = .62$), there was a significant group x time interaction ($F(1, 25) = 4.50$, $p = .04$, $d = .85$). Fig 3 shows participants in the blue light group forgot an average of 0.19 words, whereas participants in the amber light group forgot an average of 1.88 words from short-delay to long-delay recall. This translates to an average decline of only 1.48% in delayed verbal recall for individuals receiving the active blue light treatment, but an average decline of 14.62% for individuals in the amber placebo light group.

Discussion

The aim of the present study was to investigate the effect of blue wavelength light exposure during memory consolidation on later memory performance in healthy participants. As expected, after learning a list of words, individuals who were exposed to 30 minutes of blue wavelength light during the consolidation period (approximately 1.5 hours after learning) showed greater memory retention than individuals who were exposed to an amber wavelength (placebo) light.

This effect of blue light exposure on memory consolidation was predicted based on its role in promoting activation of the LC [4] which, when stimulated, is known to increase norephinephine release throughout the brain [5]. Norephinephrine, in turn, has been shown to have beneficial effects on LTM systems, leading to enhanced recall [14, 22]. However, while our results provide some initial evidence that blue light exposure sustains better memory recall performance relative to placebo, and the previous literature provides a strong basis for our hypothesis regarding the potential underlying mechanisms, it is important to stress that we did

not directly assess neurotransmitter release or brain activation within the noradrenergic system in the present study. It therefore remains necessary for future work to determine whether the beneficial effect of blue light on memory is, in fact, explained by the proposed underlying neural mechanisms.

LTM is the outcome of successful learning and is crucial for normal cognitive functioning. The results from the present study raise the intriguing possibility that blue light exposure during the consolidation period might prove useful as a strategy to optimize the retention of verbal memory. In the present study, we found that those who were exposed to blue light during the consolidation period showed only a 1.48% decline in retention of previously learned words after two hours, compared to a 14.62% decline for those in the placebo group. If confirmed in future work, this strategy could be of potential benefit to nearly any population engaged in active learning, such as school-aged children, college students, vocational students, and those invested in learning even in later adulthood, just to name a few.

While not tested here, it is likely that blue light might also prove beneficial for individuals whose memory is compromised, due to disease or injury. In fact, our results complement a previous longitudinal study (average duration 15 months) that investigated the effects of continuous exposure to either bright light (1000 lux) or dim (300 lux) light in an elderly residential group facility [23]. Older adults who were continually exposed to bright light showed attenuated cognitive deterioration, as measured by the Mini Mental State Examination (MMSE), as well as diminished depressive symptoms when compared to individuals who were exposed to dim light. While the MMSE measures aspects of short-term and long-term memory, it also measures other aspects of cognitive functioning. It is therefore unclear whether bright light influenced learning and memory in particular, or whether other cognitive processes were also positively influenced. In addition, it is unclear how continuous exposure to bright light may influence memory and learning differently when compared to short, targeted exposure to blue wavelength light. Future studies will be necessary to investigate whether the beneficial effects of blue light exposure on memory would also be found using broad spectrum bright light (which contains a large proportion of light within the blue wavelengths), or whether longer durations of bright light exposure would be necessary to achieve the same effect as targeted blue light exposure specifically. However, these results provide promise that using blue (or broad spectrum bright) light may be useful in different settings where learning and memory are important. For example, blue light exposure could be implemented during memory training for elderly individuals, or it could be used selectively by students to improve memory for important test material. In addition, exposure to blue wavelength light from natural sun exposure may have similar beneficial effects on memory; however future research will be necessary to investigate whether the results from this study are also found in such naturalistic settings.

The results from this study focused specifically on the effects of blue wavelength light during memory consolidation (i.e., 1.5 hours after memory acquisition). The present study focused on brief, targeted, blue light exposure within the period where consolidation should be occurring, which resulted in no significant change in word retention and recall after a two hour delay, when compared to an amber placebo group which showed a significant decline in verbal memory performance. It may be that light exposure during memory consolidation is more adventatgeous than light exposure during the learning/encoding phase. However, this is an open question for further research, as it remains unclear whether blue light exposure before, during, or at different time points after learning would lead to similar or enhanced effects. Future studies will be necessary to conduct a systematic comparison of memory performance after blue light exposure at various time points. In addition, this study focused exclusively on verbal memory; thus, the effects of blue light exposure on other types of memory, such as visuo-spatial, temporal, or prospective memory, are unclear and require future investigation.

It has also been shown that gray matter volume changes across the menstrual cycle are associated with changes in verbal memory performance [24]. We did not control specifically for menstrual phase in our analyses, so it is conceivable that exposure to blue wavelength light could potentially have different effects for women at different stages of their menstrual cycle. In addition, while 30 minutes of blue wavelength light has been used as a standard duration of exposure across a number of studies [10, 25], it will be necessary to investigate the duration of exposure that is necessary or sufficient to improve memory performance.

One important consideration is the potential role of accumulated sleep debt on testing performance. The participants reported sleeping on average 6.8 hours the night before the assessment, which is slightly less than the recommended 7±8 hours per night for most healthy individuals. Other than self-reported sleep for the night before testing, there was no extensive assessment of pre-study sleep, so it is not possible to establish the extent of sleep debt or whether participants were in fact fully rested when they took part in the study. However, participants were randomly assigned to the treatment conditions, so this should not have influenced the effects of light. It is also worth considering that the study began at 7:40 in the morning, at a time proximal to most participants' habitual wake up time, suggesting that many individuals may have truncated their sleep time the day of the study. Further, the two groups differed slightly in terms of habitual wake times, with amber normally awakening about 47 minutes earlier on average relative to the blue group. Conceivably, this could have placed the blue group in a particularly suboptimal positioning for cognitive performance relative to the amber group. However, we controlled for this statistically in our analyses and this did not appear to affect the outcomes. As such, it is possible that blue light may in fact lead to enhanced effects particularly when sleep pressure is high. It is therefore unclear whether our findings are generalizable to situations where individuals had the opportunity to be fully rested.

It should also be mentioned that the two light conditions were not equated for light intensity. The light emitted from the blue light devices emitted nearly three times greater irradiance as the light from the amber devices, although they appeared similar in overall visual brightness and averge lux. It is therefore possible that the improvements in memory consolidation seen in the blue light group could be attributed to light intensity rather than light color. However, studies have shown that 50 second bursts of blue light specifically, in comparison to violet light of the same intensity, led to increases in functional brain activation in the LC, supporting our proposed mechanism [4]. Replications of our findings while comparing the effects of different wavelengths of light of the same intensity on memory consolidation are nevertheless needed. In addition, it has been shown that 15 minutes of exposure to orange versus blue wavelength light 1 hour before a second exposure to blue light increased functional brain responses within the prefrontal cortex during a working memory task [26]. It is therefore possible that exposure to amber light during the ªwashoutº period in the present study, led to an enhanced effect of blue light exposure during memory consolidation. This intriguing possibility should be investigated further. Finally, this study was conducted with a relatively small sample of healthy adults; future research will therefore be necessary to replicate these findings across larger sample sizes and perhaps even in clinical populations with memory impairments.

Conclusion

In summary, exposure to a half hour of blue wavelength light during memory consolidation led to better subsequent delayed verbal memory recall, when compared to an amber (placebo) light condition. These findings may have important implications for clinical populations with memory impairments, as well as for healthy individuals who want to improve their ability to

retain newly learned material. Considering this is the first study to investigate whether 30 minutes of blue light exposure can influence memory performance, future research will be necessary to confirm this effect, and to investigate the precise mechanisms, optimal dose/timing of administration, and possible application to clinical samples.

Supporting information

S1 Dataset. Dataset for analyses.
(SAV)

Author Contributions

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Data curation: Anna Alkozei.

Formal analysis: Anna Alkozei.

Funding acquisition: William D. S. Killgore.

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Project administration: William D. S. Killgore.

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Supervision: William D. S. Killgore.

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References

1. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 2002; 295(5557):1070±3. https://doi.org/10.1126/science.1067262 PMID: 11834835
2. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. PLoS Biol. 2009; 7(6): e1000145. https://doi.org/10.1371/journal.pbio.1000145 PMID: 19547745
3. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nature neuroscience. 2001; 4(7):732±8. https://doi.org/10.1038/89522 PMID: 11426230
4. Vandewalle G, Schmidt C, Albouy G, Sterpenich V, Darsaud A, Rauchs G, et al. Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. PloS one. 2007; 2(11):e1247. https://doi.org/10.1371/journal.pone.0001247 PMID: 18043754
5. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. Brain research. 1996; 742(1):89±97.
6. Foote S, Berridge C, Adams L, Pineda J. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Progress in brain research. 1991; 88:521±32. PMID: 1813932
7. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? PloS one. 2011; 6 (1):e16429. https://doi.org/10.1371/journal.pone.0016429 PMID: 21298068
8. Cajochen C, Munch M, Kobialka S, Krauchi K, Steiner R, Oelhafen P, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. The Journal of Clinical Endocrinology & Metabolism. 2005; 90(3):1311±6.
9. Lockley SW, Evans EE, Scheer F, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 2006; 29(2):161. PMID: 16494083

10. Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, et al. Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. Sleep. 2016; 39(9):1671±80. https://doi.org/10.5665/sleep.6090 PMID: 27253770

11. Rüger M, Gordijn MC, Beersma DG, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. American Journal of Physiology-regulatory, integrative and comparative physiology. 2006; 290(5):R1413±R20. https://doi.org/10.1152/ajpregu.00121.2005 PMID: 16373441

12. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scandinavian journal of work, environment & health. 2008:297±306.

13. Vandewalle G, Collignon O, Hull JT, Daneault V, Albouy G, Lepore F, et al. Blue light stimulates cognitive brain activity in visually blind individuals. Journal of cognitive neuroscience. 2013; 25(12):2072±85. https://doi.org/10.1162/jocn_a_00450 PMID: 23859643

14. McGaugh JL, Roozendaal B. Drug enhancement of memory consolidation: historical perspective and neurobiological implications. Psychopharmacology. 2009; 202(1±3):3±14. https://doi.org/10.1007/s00213-008-1285-6 PMID: 18704369

15. Tully K, Bolshakov VY. Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. Molecular brain. 2010; 3(1):15.

16. Tronel S, Feenstra MG, Sara SJ. Noradrenergic action in prefrontal cortex in the late stage of memory consolidation. Learning & Memory. 2004; 11(4):453±8.

17. Sara SJ, Roullet P, Przybyslawski J. Consolidation of memory for odor±reward association: β-adrenergic receptor involvement in the late phase. Learning & memory. 1999; 6(2):88±96.

18. Delis DC, Kramer J, Kaplan E, Ober BA. CVLT-II: California verbal learning test: adult version: Psychological Corporation; 2000.

19. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996; 78(2):490±8.

20. Lasa L, Ayuso-Mateos J, Vazquez-Barquero J, Dõez-Manriqıe F, Dowrick C. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. Journal of affective disorders. 2000; 57(1):261±5.

21. Wechsler D. WASI II: Wechsler Abbreviated Scale of Intelligence. 2nd. Psychological Corporation. 2011.

22. Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nature reviews neuroscience. 2009; 10(3):211±23. https://doi.org/10.1038/nrn2573 PMID: 19190638

23. Riemersma-Van Der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. Jama. 2008; 299(22):2642±55. https://doi.org/10.1001/jama.299.22.2642 PMID: 18544724

24. Protopopescu X, Butler T, Pan H, Root J, Altemus M, Polanecsky M, et al. Hippocampal structural changes across the menstrual cycle. Hippocampus. 2008; 18(10):985±8. https://doi.org/10.1002/hipo.20468 PMID: 18767068

25. Vandewalle G, Maquet P, Dijk D-J. Light as a modulator of cognitive brain function. Trends in cognitive sciences. 2009; 13(10):429±38. https://doi.org/10.1016/j.tics.2009.07.004 PMID: 19748817

26. Chellappa SL, Ly JQ, Meyer C, Balteau E, Degueldre C, Luxen A, et al. Photic memory for executive brain responses. Proceedings of the National Academy of Sciences. 2014; 111(16):6087±91.

pii: sp-00684-15 http://dx.doi.org/10.5665/sleep.6090

SLEEP COGNITION AND BEHAVIOR

Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task

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Study Objectives: Prolonged exposure to blue wavelength light has been shown to have an alerting effect, and enhances performance on cognitive tasks. A small number of studies have also shown that relatively short exposure to blue light leads to changes in functional brain responses *during* the period of exposure. The extent to which blue light continues to affect brain functioning during a cognitively challenging task *after* cessation of longer periods of exposure (i.e., roughly 30 minutes or longer), however, has not been fully investigated.

Methods: A total of 35 healthy participants (18 female) were exposed to either blue (469 nm) (n = 17) or amber (578 nm) (n = 18) wavelength light for 30 minutes in a darkened room, followed immediately by functional magnetic resonance imaging (fMRI) while undergoing a working memory task (*N*-back task).

Results: Participants in the blue light condition were faster in their responses on the *N*-back task and showed increased activation in the dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex compared to those in the amber control light condition. Furthermore, greater activation within the VLPFC was correlated with faster *N*-back response times.

Conclusions: This is the first study to suggest that a relatively brief, single exposure to blue light has a subsequent beneficial effect on working memory performance, even after cessation of exposure, and leads to temporarily persisting functional brain changes within prefrontal brain regions associated with executive functions. These findings may have broader implication for using blue-enriched light in a variety of work settings where alertness and quick decision-making are important.

Keywords: blue light, amber light, working memory, functional magnetic resonance imaging, fMRI, prefrontal cortex, PFC, N-back task

Citation: Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, Shane BR, Knight SA, Killgore WD. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *SLEEP* 2016;39(9):1671–1680.

Significance

This study shows that exposure to thirty minutes of blue wavelength light in the morning subsequently leads to faster response times on a cognitive working memory task and greater functional brain responses within the prefrontal cortex than comparable exposure to amber light. This is the first study to show that a short, single exposure to blue light during the daytime can lead to enduring measurable changes in brain activation and speed of performance during subsequent completion of a cognitively challenging task. While these findings may have important implications for using blue light in occupational settings, future research will be necessary to establish whether these findings generalize to naturalistic settings.

INTRODUCTION

Exposure to light has important effects on human physiology that are independent of visual perception. These non-image forming effects of light include the regulation of circadian rhythms, melatonin production, changes in core body temperature, sleep propensity, and alertness.[1,2] Many of these effects of light are due to activation of retinal ganglion cells, which are maximally sensitive to light within the short wavelength (~480 nm; blue light). These cells transmit irradiance signals to hypothalamic nuclei (e.g., the suprachiasmatic nucleus [SCN]), which are responsible for regulating circadian rhythms and melatonin production.[1,2] Exposure to blue light in the evening or at night has been shown to increase alertness and improve performance on reaction time tasks, most likely as a result of the suppression of the evening onset of melatonin, which leads to a phase delay of the circadian rhythm.[3–6] In a similar vein, morning blue light exposure suppresses melatonin in the early part of the day and leads to a phase advance of the circadian rhythm by inducing the onset of plasma melatonin earlier in the evening.[7] In addition, blue light, and bright white light exposure more generally, during the day, has also been shown to have beneficial effects on alertness in a number of studies. One study compared the effects of bright (5,000 lux) versus dim light (< 10 lux) exposure during the day (between 12:00 and 16:00) and at night (between 00:00 and 04:00), and found that participants reported lower levels of sleepiness and fatigue, and greater energy during bright versus dim light exposure, regardless of time of day.[8] In addition, the effects of daytime blue light exposure appear to have beneficial effects over longer periods of exposure. In a work place office setting, participants who were exposed to blue-enriched white light during the work day for 4 weeks reported increased subjective alertness, performance, positive mood, and concentration, in comparison to 4 weeks of white light exposure.[9] Further evidence suggests that blue light can also be superior to caffeine for sustaining performance on tasks requiring psychomotor functioning.[10]

While the alerting effects of nighttime exposure to blue light appear to be produced predominantly by the suppression of melatonin, the increases in daytime alertness after blue light exposure are thought to be largely due to effects other than melatonin regulation.[11] In particular, the daytime alerting effect of blue light may come from the indirect effects of melanopsin photosensitive retinal ganglion cells, which also project to brain regions other than the hypothalamus. For example, these cells can also indirectly influence activation of the locus coeruleus (LC),[12] which in turn releases norepinephrine broadly throughout the cerebral cortex,[13] leading to increases in alertness.[14] Such downstream influences may explain some of the effects of blue light on alertness during the daytime, independent of the effects of melatonin. In fact, a functional magnetic resonance imaging (fMRI) study of in-scanner acute light exposure demonstrated that short 50-second bursts of

blue light increased activation within the middle frontal gyrus and the brainstem, in comparison to violet light, while participants completed an auditory working memory task.[15] While precise identification of brainstem nuclei is difficult using fMRI techniques, the location of the activation was consistent with the general stereotaxic coordinates of the LC.[15] Thus, it appears plausible that blue light exposure may result in increased noradrenergic influence over cortical regions involved in controlled cognitive processing.

The aforementioned research suggests that blue light exposure activates brain networks that underlie many aspects of cognitive performance. One especially important cognitive function that may benefit from blue light exposure is working memory. Working memory comprises a set of cognitive processes that allow information to be actively held in mind in order to guide decision-making.[16] Studies of healthy populations as well as patients with brain lesions have shown that working memory performance is associated with increased activation within the prefrontal cortex (PFC), and especially the dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC).[16,17] Since blue light exposure appears to influence the LC, which can increase the release of norepinephrine and lead to subsequent neural activation within the PFC, this may plausibly influence neural processes associated with working memory.

Neurocomputational models suggest that decision-making processes, such as those supported by working memory, require a trade-off between speed and accuracy. In this case, either a lot of time is spent to accumulate evidence for "safe and slow" decision-making, or less time is spent for "fast but risky" decision-making.[18] These models also suggest that changes in baseline activation levels, as opposed to changes in the decision-threshold itself, may control this trade-off. For example, increases in baseline activation levels would decrease the distance from threshold, leading to faster but less reliable choices.[18] One might therefore predict that blue light exposure would lead to faster response times within this type of task by increasing baseline activation levels. However, the few studies that have actually examined the effects of blue wavelength light during working memory performance (e.g., an auditory *N*-back task and an oddball task) have not found significant effects in terms of response time or accuracy when compared to non-blue wavelengths, despite significant increases in the activation of arousal and working memory systems of the brain.[15,19,20] It should be noted that the duration of blue light exposure was considerably longer in those behavioral studies[9] mentioned above (where a significant effect on performance was observed) compared to those fMRI studies finding no effect[15,19,20] (one to several hours of blue light exposure in behavioral studies in comparison to 50 seconds up to 21 minutes in fMRI studies). Importantly, a recent review has suggested that the performance-enhancing effects of blue light at night as well as during the day usually occur with an exposure duration of roughly 30 minutes or longer.[21] It is therefore possible that the shorter durations (e.g., 18 minutes) of blue light exposure applied in prior fMRI studies may not have been long enough to induce measurable behavioral changes. Furthermore, it has not been investigated in detail whether blue light exposure has the ability to affect functional brain responses and working memory performance *after* cessation of a single dose of daytime blue light exposure. While it has been shown that self-reported sleepiness is reduced after blue light exposure at nighttime,[3] it is unclear whether a single dose of daytime blue light exposure can lead to enduring effects in terms of cognitive performance and functional brain responses. It is also possible that the lack of findings in previous fMRI studies may have been the result of participants completing the working memory task *during* light exposure, and not afterwards.

The goal of the present study was therefore to examine how 30 minutes of continuous blue wavelength light exposure would affect subsequent working memory performance and associated functional brain responses after cessation of the light exposure. We hypothesized that the enduring effects of blue wavelength light exposure would be associated with greater activation during a working memory task (*N*-back task) within areas usually recruited by such tasks, specifically the DLPFC and VLPFC, and that this increased activation would be associated with faster response times during the task, in comparison to a control exposure of amber light under the same conditions.

METHODS

Participants

Thirty-five healthy 18- to 32-year olds (18 female; 17 male) took part in the study. Participants completed an average of 12.5 years of education, were all right handed, primary English speaking, free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 22:00 and 01:00 and waking between 06:00 and 09:00.

Materials

Light Exposure

Participants underwent the controlled light exposure while sitting in an otherwise completely darkened room. All participants began with a blue light *Washout Period* (described in more detail under Procedure) that involved sitting in a dark room while only exposed to two amber light devices (described below) mounted on a desk at a distance of approximately 80 cm from the participant's nasion, with each light centered at a 45-degree angle from midline (see Figure 1A). Actual distance and angle of the light devices were adjusted manually until the pair of amber devices used during the initial washout period resulted in a 20-lux reading as measured by a light meter (Digital Lux Meter LX1330B) on each side of the participant's nose. During the *Exposure Period,* light was administered by a similar configuration of 4 light devices, also centered at 45 degrees to each side of the participant with a distance of approximately 80 cm from the participant's nasion (see Figure 1B). During the *Exposure Period*, the light devices were either blue or amber depending on random assignment. Blue light exposure utilized an array of commercially available Philips goLITE BLU Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). Each device consisted of a plastic table-mounted chassis with

a 10 × 6 array of light emitting diodes (LEDs), encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU Energy Light is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 lux, and panel irradiance [mW/cm^2] = 1.23 at 20 cm). The amber devices were provided by the manufacturer for research purposes and were essentially identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 lux, and total irradiance [mW/cm^2] = 0.35).

N-back Task

This task was used during functional neuroimaging. The *N*-back task is a widely used task for assessing working memory[22] and is typically applied in either auditory or visual modalities. In the present study, we employed a widely used visual variant of the task whereby participants viewed and responded to a series of letters appearing in serial order on the screen.[16] Participants were presented with white letters appearing one letter at a time centered on a black screen. The *N*-back task included 3 conditions of varying cognitive load. During the control condition (i.e., "zero-back"), participants were asked to identify by button press whether each letter on the screen matched a predetermined letter (e.g., "P") by pressing "yes" with their middle finger or "no" with the index finger of their right hand. In the "one-back" condition, participants responded with a button press using their right hand to indicate whether the letter presented in the current trial was identical to the letter presented in the immediately preceding trial. In the same way, during the "two-back" condition, participants indicated whether the letter shown in the current trial was identical to the letter presented 2 letter trials previously. Each cognitive load condition was presented as a block lasting 42 seconds. These blocks each consisted of a 6-s instruction screen followed by 16 trials (trial = stimulus displayed for 500 ms + 1,750 ms blank screen, ISI = 2,250 ms). Each cognitive load block was presented 3 times in pseudo-random order for a total of 9 blocks (3 "zero-back"; 3 "one-back"; 3 "two-back") throughout the task. The task began and ended with a 10-s crosshair image requiring only visual fixation, and each block was also separated by a 10-s crosshair fixation image, for a total task run of 478 seconds (7 min 58 sec). Prior to neuroimaging, participants underwent a practice version of the task outside of the scanner. This involved completing each cognitive load condition once (i.e., 16 trials each) with immediate visual feedback on each trial to ensure that they understood the task before completing it in the scanner. Verbal instructions were given to participants while in the scanner and they were encouraged to ask any questions before beginning the task.

Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale (SSS)[23] is a one-item measure to assess participants' current level of sleepiness on a 1–7 point scale, ranging from "feeling active, vital, alert, or wide awake" to "no longer fighting sleep, sleep onset soon, having dream-like thoughts." Higher scores on the SSS indicate higher levels of sleepiness.

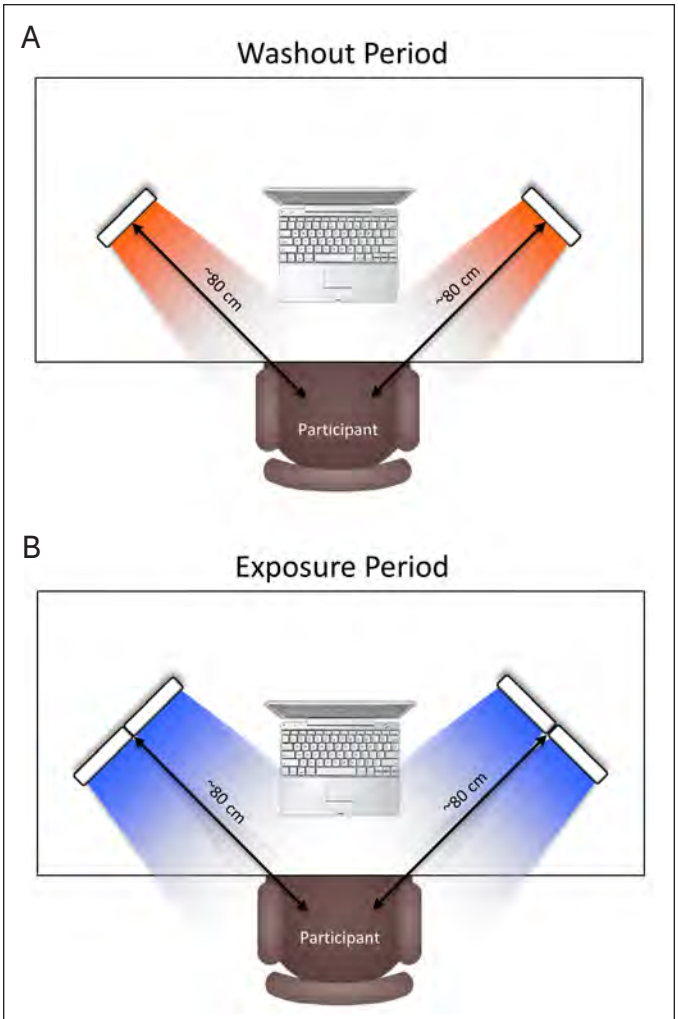


Figure 1—Diagram of light device placements. Participants were seated at a desk in a darkened room with light devices placed at a 45-degree angle to the right and left of center at a distance of approximately 80 cm. (A) During the 30-minute blue light Washout Period, 2 devices (one on the left and one on the right) fitted with amber light emitting diodes (LEDs; λ = 578 nm) were directed toward the participant, with each device centered at a 45-degree angle). (B) During the 30-minute *Exposure Period*, 4 devices (2 on the left and 2 on the right) were directed toward the participant, with each pair centered at a 45-degree angle. Devices were fitted with either blue (λ = 469 nm) or amber (λ = 578 nm) LEDs, according to random assignment.

Procedure

Participants completed the study on an individual basis, but all participants were run at the same time each day to control for circadian time of day effects. To ensure that participants were not in caffeine withdrawal during the procedure, they were asked to consume their normal levels of morning caffeine before arrival for the study. Participants arrived for the study at 07:45 and were escorted to the laboratory. For the first portion of the day, participants completed the informed consent process, and completed some basic information questionnaires and cognitive tasks. Participants were randomized to receive either 30 min of blue (n = 17) or amber (n = 18) light exposure. At approximately 09:15, participants were then fitted with wrap around polycarbonate blue light-blocking

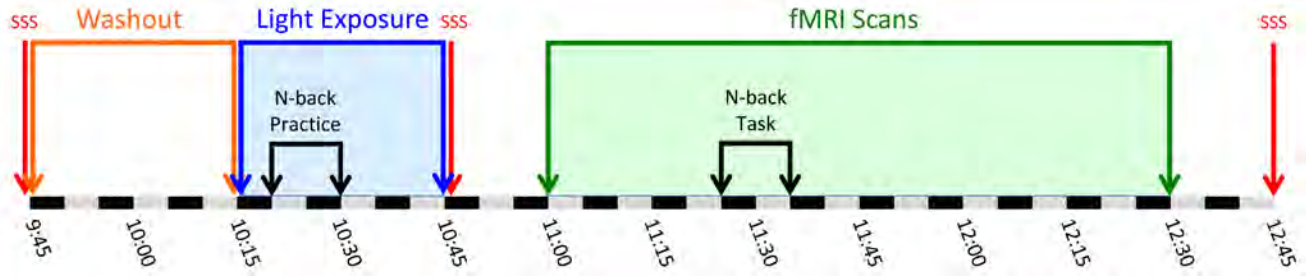


Figure 2—Timeline detailing the study procedure. Between 09:45 and 10:15, participants underwent 30 minutes of "washout" amber light exposure. Immediately following the washout period, participants either received 30 minutes of amber placebo light or blue light exposure (i.e., between 10:15 and 10:45). During this time, at 10:20, participants received instructions on the *N*-back task and completed one practice run, lasting 10 minutes in total. At 11:00, participants began the fMRI scan, and the *N*-back task was initiated at 11:25 and ended at 11:33. The scan ended at 12:30. Participants completed the Stanford Sleepiness Scale (SSS) 3 times during the procedure, including just before the start of the washout period, immediately after the light exposure, and at 12:45 after exiting the fMRI scanner.

glasses (to minimize extraneous blue light exposure) and were escorted to the neuroimaging center at the University of Arizona Department of Medical Imaging. At 09:45, participants then completed the SSS and immediately underwent a "blue light washout" period for 30 min to ensure that residual effects of outdoor and ambient lighting had dissipated before the beginning of the light exposure period. During this washout period, participants were seated comfortably in a darkened room and then removed the light-blocking glasses. Ambient lighting was provided by 2 amber light devices (see Materials), which were activated on the desk in front of the participant and located 45° to the left and right of center, approximately 80 cm from the participant's nasion (see Figure 1A). The amount of light exposure was measured and the lights were adjusted for each participant to ensure that 20 lux of amber light was registered on each side of the nose. Participants were instructed not to look directly at the light devices, and to relax with their eyes open and maintain a generally forward gaze. At 10:15, the 2 Washout Period light devices were replaced with the 4 Exposure Period devices (see Figure 1B). Then the 30-min Exposure Period was initiated by engaging the 2 pairs of light devices (either blue or amber, depending on condition), with each pair mounted side by side on the desk in front of the participant, centered at the same location as the Washout Period amber lights. During the 30-min Exposure and Washout Periods, participants maintained a forward gaze and completed several computerized practice tasks to prepare them for their time in the scanner. The laptop monitors were shielded by an amber colored Plexiglas panel, which was acquired from www.lowbluelights.com, to block blue wavelength light. These computerized practice tasks ranged from 5 to 10 min each and were interspersed with 5-min rest breaks that involved sitting silently and maintaining a forward gaze at a crosshair on the wall facing the participant. At the completion of the Exposure Period (10:45), participants again donned their blue light-blocking glasses, were escorted to the MRI scanner, and again completed the SSS. Once in the scanner, the scanner room lights were dimmed and the glasses were removed. While we have no measurement of the lux levels in the scanner due to the incompatibility of lux meters within the magnetic field of the scanner, the light conditions were held constant across participants. The scanning sequence was initiated at 11:00, and the *N*-back task was started at approximately 11:25, and the scan was completed by 12:30. At the conclusion of the scan, participants exited the scanner and completed one last SSS (10:45) and were released. Figure 2 details the timeline of the study procedure.

Ethical Considerations

The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office.

Neuroimaging Methods

Participants underwent fMRI immediately after completion of the 30-min exposure to either blue or amber light. Neuroimaging scans were collected on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR / TE / flip angle = 2.1 s / 2.33 ms / 12 degree) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR / TE / flip angle = 2.0 s / 25.0 ms / 90 degree) with 239 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

Image Processing

Processing and analysis of neuroimaging scans was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Raw functional images were first preprocessed by realigning and unwarping the functional images, and then co-registering the newly created mean functional image to each subject's structural T1 scan. Forward deformation fields were used to normalize the images from subject native space to Montreal Neurological Institute (MNI) coordinate space. Finally, the images were spatially smoothed (6 mm full-width at half maximum), and resliced to 2 × 2 × 2 mm voxels. A high pass

Table 1—Sample characteristics.

	Blue group (n = 17) Mean (SD)	Amber group (n = 18) Mean (SD)	Statistic
Age	21.71 (2.58)	22.22 (4.06)	$t_{33} = 0.63$, P = 0.53
Gender	47% female	55% female	$\chi^2 = 0.25$, P = 0.62
Years of Education	12.71 (3.58)	12.44 (3.34)	$t_{33} = 0.22$, P = 0.26
Mean hours of sleep on a weeknight	7.25 (0.97)	7.22 (0.94)	$t_{33} = 0.09$, P = 0.93
Hours of sleep the night before the assessment	6.88 (0.54)	6.86 (0.87)	$t_{33} = -0.09$, P = 0.93
Mean number of caffeinated products per day	0.78 (0.81)	1.08 (0.97)	$t_{33} = -0.97$, P = 0.34
Typical wake time on weeknights	07:52 (0:56)	07:24 (1:05)	$t_{33} = -0.13$, P = 0.19
Typical bed time on weeknights	23:40 (1:12)	23:25 (0:56)	$t_{33} = -0.70$, P = 0.48
SSS pre-washout	1.69 (0.87)	1.89 (0.58)	$F_{2, 32} = 0.63$, P = 0.43
SSS post-exposure	2.38 (1.25)	2.78 (1.14)	$F_{2, 32} = 0.98$, P = 0.33
SSS post-fMRI scan	1.94 (1.12)	2.11 (1.27)	$F_{2, 32} = 0.17$, P = 0.67

SSS, Stanford Sleepiness Scale.

filter with a 128-s cutoff period was used to remove low frequency confounds. The standard canonical hemodynamic response function in SPM was employed, and serial autocorrelation was corrected with an autoregressive model of 1 (+white noise). Motion artifacts exceeding 3 SD in mean global intensity and scan-to-scan motion that exceed 1.0 mm were regressed out using the Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect/).

Statistical Analysis

On an individual basis, a general linear model (GLM) was specified to contrast activation between the two-back > zero-back condition. These contrast images were entered into a second-level independent samples t-test analysis with light group (blue versus amber) as the independent variable. Based on our *a priori* hypotheses and previous findings from a large meta-analysis of normative functional neuroimaging studies using the *N*-back task,[16] spheres of a 10 mm radius centered on stereotaxic coordinates derived from the previous meta-analysis were placed in areas of the DLPFC and VLPFC. The Talairach coordinates reported in Owen et al.[16] were transformed to MNI coordinates using the MNI2TAL online program from Lacadie et al.[24] (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). The following MNI coordinates were used: DLPFC (x = 41, y = 31, z = 30; x = −37, y = 45, z = 21; x = −46, y = 19, z = 22), and VLPFC (x = −31, y = 21, z = 4; x = 34, y = 23, z = 1). Analyses were thresholded at P < 0.001 (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, family wise error (FWE) corrected at P < 0.05, and *k* (extent) ≥ 10 contiguous voxels.

In addition to the primary analysis of our hypothesized effects, we also conducted an exploratory whole brain analysis to provide complete data for future hypothesis generation. Here, we used a slightly more liberal height threshold of P < 0.005, while protecting against type I error through a cluster-corrected extent threshold of 201 voxels, which represents an FWE correction of P < 0.05.[25] Because this analysis was exploratory, we had no *a priori* hypothesis and merely present these supplemental findings for completeness and to obviate bias in reporting.

RESULTS

Descriptive Statistics

According to self-report, participants slept on average 7.2 h (SD 0.94) per night, and obtained 6.8 h (SD 0.72) of sleep the night before the assessment. Participants reported going to bed on average at 23:32 (SD 1 h 4 min) and waking at 07:37 (SD 1 h 2 min) on weekdays. Participants reported drinking an average of 0.93 (SD 0.89) caffeinated products per day, and 8 participants (4 in each group) reported having had one caffeinated product prior to the assessment, which was consistent with their normal morning consumption patterns. Groups did not differ on age, gender, years of education, mean number of hours slept on weeknights, number of hours slept the previous night, mean number of caffeinated products per day, and waking and bed times (see Table 1).

Behavioral Results

A repeated-measures ANOVA of the SSS scores showed no interaction between light color and session (pre-washout, post light exposure, and post-fMRI) ($F_{2, 31} = 0.12$, P = 0.88). An analysis of simple effects showed no difference between light color groups at each of the 3 sessions (see Table 1).

There was no difference in accuracy and response time between the blue and amber groups for the zero-back condition, but participants in the blue group responded faster during the one- ($t_{33} = -2.26$, P = 0.03) and two-back conditions ($t_{33} = -1.98$, P = 0.05) than participants in the control group (see Table 2).

Neuroimaging Results

Hypothesis Testing

For the two-back > zero-back contrast, individuals in the blue light group showed significantly greater activation in a cluster within the left DLPFC ($k = 29$; $P_{FWE} = 0.03$; $t = 4.12$; x = −50, y = 14, z = 22, small volume corrected) and a cluster within the right VLPFC ($k = 17$, $P_{FWE} = 0.006$, $t = 4.83$; x = 34, y = 20, z = −6, small volume corrected) than individuals who were exposed to the amber control light (see Figure 3). There were no regions within the brain where amber light exposure was

Table 2—Mean accuracy and reaction times for the *N*-back task.

	Accuracy (SD) in %	Total Reaction Time (SD) in milliseconds	Reaction Time for Correct Responses (SD) in milliseconds
Zero-back			
Blue	96.05 (0.39)	410.72 (97.04)	407.81 (91.55)
Amber	97.43 (0.25)	457.05 (94.07)	458.64 (93.03)
One-back			
Blue	87.31 (0.71)	485.09 (133.81)[a]	485.09 (133.81)[c]
Amber	88.49 (0.82)	601.97 (168.77)[a]	601.97 (168.77)[c]
Two-back			
Blue	88.60 (0.91)	556.00 (196.87)[b]	553.00 (192.05)[†]
Amber	88.74 (1.03)	691.01 (205.59)[b]	682.62 (204.16)[†]

[a], [b], and [c], denote groups that significantly differ at P < 0.05; [†] marginal difference (P = 0.06).

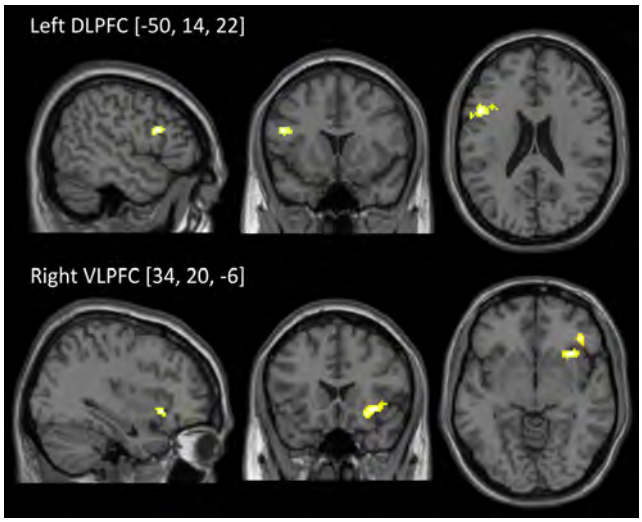


Figure 3—SPM images showing the clusters of significant activation where Blue > Amber for the *N*-Back task (two-back > zero-back). Based on the a priori regions of interest, this comparison revealed that the blue light condition was associated with significantly greater activation within the left dorsolateral prefrontal cortex (DLPFC) and the right ventrolateral prefrontal cortex (VLPFC) when compared to the amber light condition during complex working memory. Clusters are significant at P < 0.05, FWE corrected, but are displayed at P < 0.005 for ease of visualization.

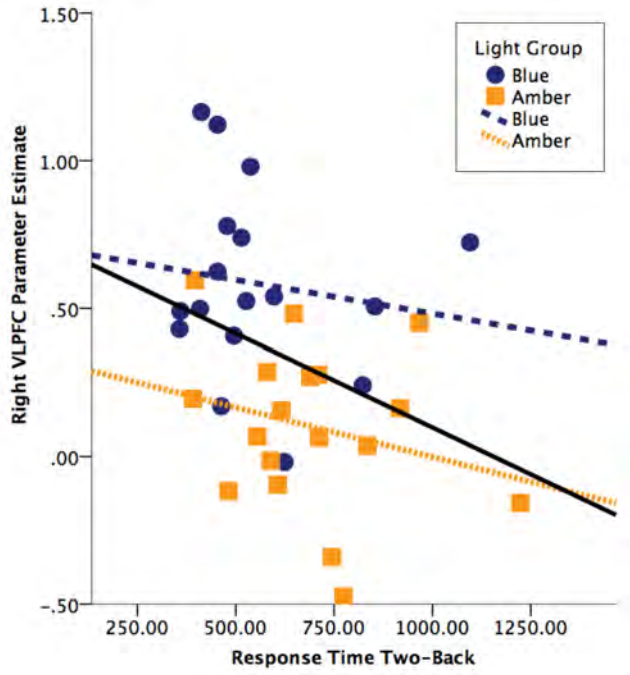


Figure 4—The scatterplots illustrate the association between the activation within the right ventrolateral prefrontal cortex (VLPFC) and reaction time during the two-back condition for the blue and amber light groups, and the sample as a whole.

associated with greater functional brain responses than blue light exposure.

In order to investigate the association between regional activation and behavioral responses, we extracted the activation for the unadjusted cluster eigenvariate for both brain regions and conducted Pearson correlations between the eigenvariate and response time and performance metrics during the two-back condition. There was a negative correlation between VLPFC activation and response time ($r = -0.35$, P = 0.04). This correlation was present among the sample as a whole and was not driven by one group in particular (Figure 4). No significant associations with accuracy were found. In addition, no significant associations were found between activation within the DLPFC and performance on the working memory task.

To investigate whether participants were more "efficient" with increases in working memory (i.e., the number of correct responses per second), a measure of cognitive throughput was calculated ([Accuracy × (1 / RT) * 1,000]).[26] Throughput provides a quantitative metric of the speed versus accuracy tradeoff. While there was no difference in throughput between the 2 groups in the zero-back condition ($t_{33} = -1.60$, P = 0.19), participants in the blue group showed enhanced throughput in the one-back ($t_{33} = -2.57$, P = 0.01), and marginally higher throughput in the two-back condition ($t_{33} = -1.92$, P = 0.06). In other words, participants in the blue light group provided a greater number of correct responses per unit of time than participants in the amber control group (Figure 5). Given that the groups were essentially equivalent with regard to accuracy, this difference suggests that exposure to blue light led to faster response times with no loss in accuracy.

Exploratory Analysis

Finally, exploratory whole brain analysis was undertaken for the purpose of facilitating future hypothesis generation, with a peak height threshold of $P < 0.005$, and cluster-corrected extent threshold of $P < 0.05$ (FWE corrected). Again comparing the two-back > zero-back contrast, we found that the blue-wavelength light exposure group showed significantly greater activation than the amber control group within several distributed regions including left and right VLPFC (i.e., inferior frontal gyrus/insula), left and right middle temporal gyrus, right posterior cingulate gyrus, left middle occipital cortex, brainstem, and thalamus (Figure 6). Table 3 lists the cluster maxima for these exploratory analyses. There were no regions in the brain showing greater activation for the amber control light group compared to blue light group during the working memory task.

DISCUSSION

The goal of the present study was to examine the effects of 30 minutes of controlled blue wavelength (469 nm) light exposure compared to amber placebo light (578 nm) exposure on subsequent functional brain responses and performance during an *N*-back working memory task among healthy non-sleep deprived individuals. We found that exposure to 30 minutes of blue wavelength light produced greater activation within regions of the DLPFC and VLPFC and faster response times during a subsequent working memory task than exposure to amber wavelength light under otherwise identical conditions. Moreover, greater activation in the VLPFC for both groups combined was significantly correlated with faster response times during the working memory task, consistent with this region's role in executive functioning. Finally, while blue light effects were observed for brain activation and response time, there were no group differences in accuracy on the working memory task. Together, these findings suggest that a relatively brief exposure to blue light has an enhancing effect on speeded cognition and brain function that may persist for at least 40 minutes after cessation of the light.

It is well established that both the DLPFC and VLPFC are critically involved in the encoding, retention, and retrieval of information during working memory tasks.[16,27,28] Our findings suggest that a single, relatively short exposure to blue wavelength light of only 30 minutes can increase neural activation over the subsequent 40-minute period within those prefrontal areas most critical for successful working memory performance. Prior work has shown that even short bursts of blue light for periods lasting from 50 seconds to 20 minutes are effective at activating similar regions of the DLPFC and VLPFC during auditory working memory tasks.[15,19,29] While previous studies have found increases within the prefrontal regions *during* exposure,[15,19] this study shows that brain activation and improved working memory task performance as a result of light exposure can substantially endure well beyond the exposure period and adds to emerging work suggesting that prolonged blue light exposure (30 minutes or more) may continue to affect brain function even after termination of the light.[30] Although previous studies suggest that light-induced changes in functional brain responses may decline within 10 minutes after the end of the exposure period,[20] it is important to consider that the duration of the light exposure was considerably shorter, roughly 10 to 29 minutes less time than in the present study.[15,19,20] It is therefore possible that the longer light exposure may have contributed to these differences in findings. However, it should be also pointed out that some of these previous studies may have employed shorter periods of light exposure (e.g., 50 second bursts of exposure[15]) in order to prevent the confounding effects of variations in alertness and performance on the *N*-back task. Future studies comparing varying durations of light exposure, and employing different tasks, will therefore be necessary to determine the

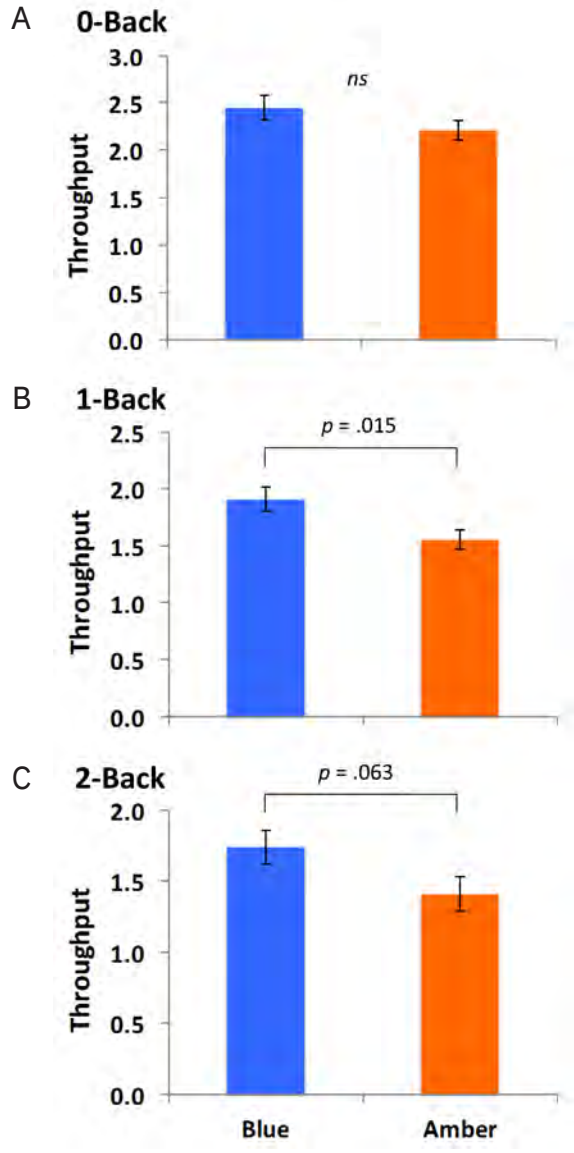


Figure 5—The figure shows group differences in working memory cognitive throughput (Accuracy × [1 / RT] * 1,000), which is a measure of the speed × accuracy trade-off. (A) There was no difference between the blue and amber groups with regard to throughput performance on the zero-back task. (B) On the one-back task, the blue light group showed significantly enhanced throughput performance compared to the amber control group. (C) On the two-back task, there was a marginally significant trend toward greater throughput for the blue compared to the amber control group.

Table 3—Cluster maxima for whole brain exploratory analysis of blue > amber light conditions.

Region	Cluster Size	x	y	z	T	Cluster P (FWE corrected)
Right Middle Temporal Gyrus	262	60	−24	−6	5.41	0.007
Right Posterior Cingulate Gyrus	611	12	−46	26	5.00	< 0.001
Left Middle Occipital Gyrus	306	−36	−74	4	4.90	0.002
Right Inferior Frontal Gyrus/Insula	210	34	20	−6	4.83	0.009
Left Inferior Parietal Cortex	201	−44	−46	60	4.76	0.010
Left Inferior Frontal Gyrus	277	−44	34	−10	4.37	0.002
Brainstem/Thalamus	553	−4	−28	−8	4.13	< 0.001
Left Middle Temporal Gyrus	284	−54	−32	8	3.90	0.002

Exploratory whole brain analyses were conducted using a height threshold of P < 0.005 (uncorrected) and a cluster-extent correction of P < 0.05, family-wise error (FWE) corrected.

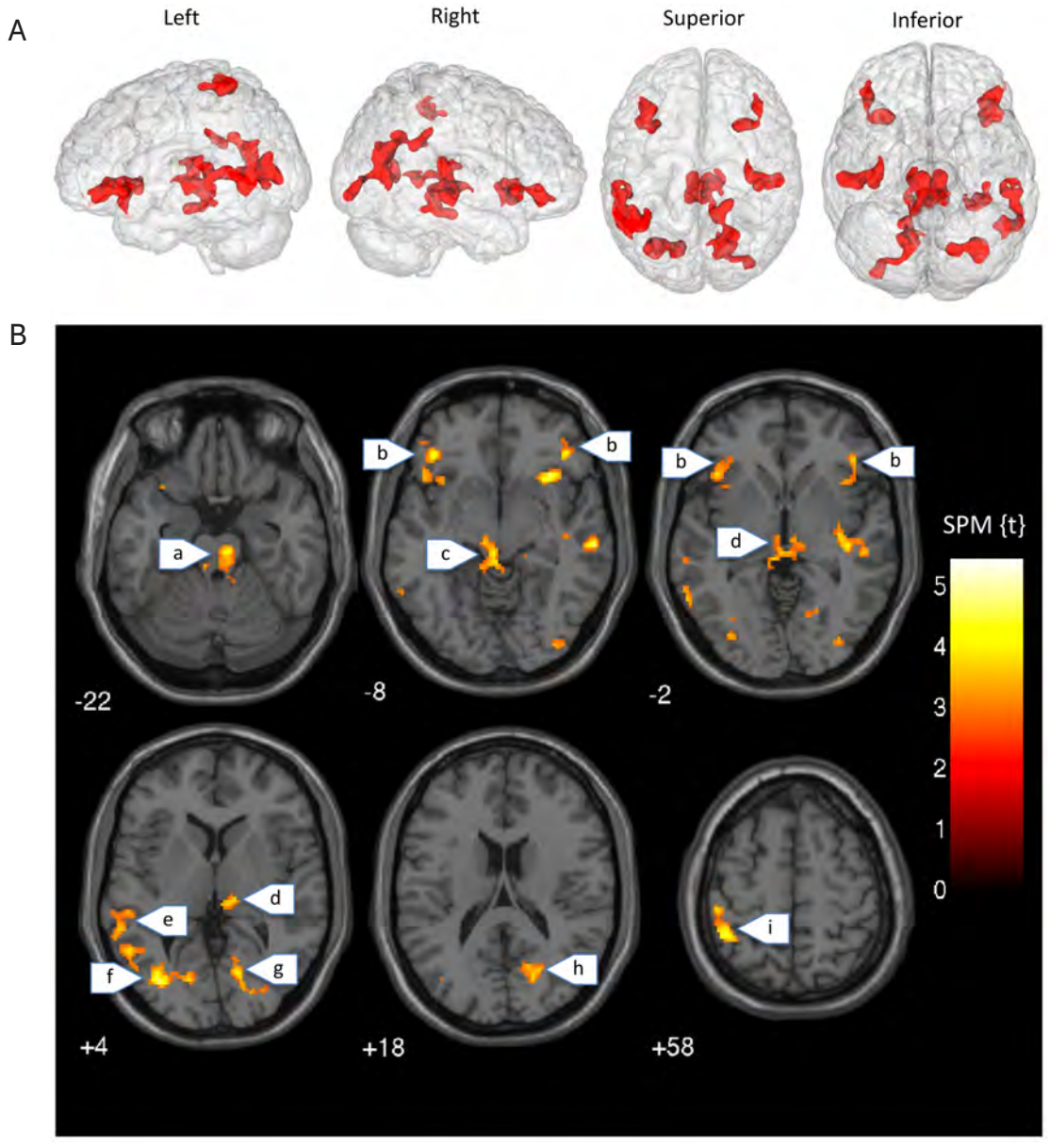


Figure 6—Whole brain exploratory analysis (height P < 0.005, cluster corrected P < 0.05, FWE). (A) The "glass brain" figures show the location of significant clusters of brain activation where Blue > Amber for the *N*-Back Task (two-back > zero-back). (B) The axial slices show the aforementioned clusters in greater anatomical detail. Blue light was associated with greater activation than amber control within: (a) pons, (b) inferior frontal gyrus, (c) superior brainstem, (d) thalamus, (e) middle temporal gyrus, (f) middle occipital gyrus, (g) lingual gyrus, (h) calcarine cortex, (i) inferior parietal lobule.

extent of the persisting effects of light on subsequent performance. It is conceivable that this prolonged effect may be a result of sustained noradrenergic activation. Prior research has shown that blue light exposure leads to greater activation within the LC, which in turn releases norepinephrine throughout the cortex.[13] If blue light exposure in our study promoted increased noradrenergic influence within the PFC (leading to an increase in baseline regional activation), this could plausibly explain the increased prefrontal BOLD responses and improved response times that we observed.

It is important to note that performance on the *N*-back task, in terms of faster response times, correlated positively with activation within the mid VLPFC. This finding is consistent with previous studies suggesting that an increase in baseline lateral prefrontal activation leads to faster decision-making.[31] Neurocomputational models suggest that the higher the baseline activity within a cortical area, the lower the activation needed to reach a response threshold, which can lead to faster response times.[18] This increase in baseline activation may in turn be explained by increased release of norepinephrine throughout the frontal cortex, due to stimulation of the LC[14] as a result of blue light exposure. It is also notable that blue light improved the speed of responses to the working memory task relative to amber control, but did not lead to an overall improvement in accuracy. Consideration of these data in light of the throughput metric, which quantifies the speed-accuracy tradeoff, suggests that while blue light was associated with an increase in the speed of responding to the working memory items, there was no corresponding loss of accuracy. Thus, blue light exposure was associated with the ability to make a greater number of correct responses per unit of time compared to the amber control light.

While previous studies that investigated the alerting effects of blue light have often employed study designs during nighttime,[5] or during prolonged (i.e., 4 hours) daytime exposure to blue light,[8] the present findings may have a broader application. Together with findings from previous studies, the results suggest that a relatively short duration (i.e., 30 minutes) of blue light exposure during the day can have a measurable effect on brain functioning and cognitive performance, not only acutely during the period of exposure, but that the effects may also endure for some time after termination of the light. This may have implications for the kind of light that is being used in office spaces, cockpits, and hospitals, in particular for individuals who have to perform their duties during sleep-deprived conditions. While the present study only examined the effects of light exposure under normally rested conditions, it is likely that these effects on brain activation and performance might be even more robust during periods of insufficient sleep. Prior work has suggested that blue wavelength light may be effective at improving some aspects of alertness and cognitive performance during nocturnal sleep loss,[32] but this has not been explored using neuroimaging techniques. It should also be pointed out that participants did not report any subjective differences in sleepiness/alertness depending on light condition. It is possible that longer light exposure is necessary to produce subjectively alerting effects of blue light exposure.

While the present findings suggest that blue wavelength light has meaningful effects on brain function and performance that persist beyond the exposure period, there are a number of limitations to be borne in mind. First, we present data on only a single cognitive task in a relatively artificial neuroimaging environment. Light exposure in the "real world" rarely follows these constraints. Further work with more ecologically valid tasks and environments will be necessary to establish the effectiveness of blue or blue-enriched white light in a variety of occupational settings. Some work has demonstrated increases in subjective alertness and performance after four weeks of blue-enriched white light exposure in offices,[9] but additional research will be necessary to determine the most effective parameters for administering light for the purpose of enhancing or sustaining performance in occupational settings. In addition, previous neuroimaging studies have employed an auditory, and not a visually presented letter variant of the *N*-back task as in the present study. It is unclear the extent to which the different variants of the *N*-back task might have contributed to some of the differences in findings across studies. It has been shown that an auditory *N*-back task may be more difficult than a visual variant of the *N*-back task. However, these differences in task type were only apparent at the three-back level.[33] The present study and previous fMRI studies investigating the effects of blue light on functional brain responses[15,19] have thus far been restricted to the two-back level. Nevertheless, future work that includes both visual and auditory *N*-back tasks that are more cognitively demanding will be necessary to establish whether blue wavelength light has a differential effect on these separate working memory systems. Furthermore, our sample sizes, while consistent with current practice in much of the neuroimaging literature, remain modest and limited in power, necessitating further replication to establish the reliability of the findings. Our sample was also relatively young and homogeneous in terms of background and health. Some evidence suggests that the effects of blue light on alertness may be attenuated among older individuals.[34] It has also been suggested that the effects of light on performance and brain responses may differ depending on genotype and circadian phase of testing.[35] Although participants were included if habitual bed and wake times fit within the pre-determined range to reduce variability due to circadian differences, the laboratory experiment started relatively early at 07:45 which may have led to elevated melatonin levels in some participants with later waking times. In addition, we did not collect genetic material in this sample, so examination of the role of genetics on the observed effects will require further study. Lastly, it should be pointed out that participants practiced the *N*-back task during either the blue light or amber light exposure (depending on condition). During the practice session participants received detailed instructions, were able to ask questions, and completed one trial of each condition (zero-back, one-back, and two-back) with feedback while undergoing light exposure. It is therefore possible that blue light exposure during the practice session influenced participants' ability to learn the task in such a way that they were able to perform better during the actual task. This potential role of light in learning is indeed an intriguing possibility. While the effects of blue light on immediate learning versus its persistent effects on subsequent performance cannot be disentangled here, this will likely be a fruitful question for further research.

CONCLUSIONS

The present findings suggest that daytime exposure to 30 minutes of blue wavelength light in non-sleep-deprived individuals has a beneficial impact on working memory performance and elicits measurable functional brain responses within prefrontal regions associated with executive functions. These results extend previous work by showing that exposure to blue light leads to persistent changes within the brain and performance during the post-exposure period (40 minutes). Additional research is necessary to identify the duration and breadth of these effects and how they may interact with individual difference factors such as gender, age, genotype, and other factors such as sleep debt and circadian influences.

REFERENCES

1. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002;295:1070–3.
2. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. PLoS Biol 2009;7:1221.
3. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert. PloS One 2011;6:e16429.
4. Cajochen C, Munch M, Kobialka S, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab 2005;90:1311–6.
5. Phipps-Nelson J, Redman JR, Schlangen LJ, Rajaratnam SM. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. Chronobiol Int 2009;26:891–912.
6. Lockley SW, Evans EE, Scheer F, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep 2006;29:161–8.
7. Wright HR, Lack LC, Kennaway DJ. Differential effects of light wavelength in phase advancing the melatonin rhythm. J Pineal Res 2004;36:140–4.
8. Rüger M, Gordijn MC, Beersma DG, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. Am J Physiol Regul Integr Comp Physiol 2006;290:R1413–20.
9. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J Work Environ Health 2008:297–306.
10. Beaven CM, Ekström J. A comparison of blue light and caffeine effects on cognitive function and alertness in humans. PloS One 2013;8:e76707.
11. Rautkyä E, Puolakka M, Halonen L. Alerting effects of daytime light exposure-a proposed link between light exposure and brain mechanisms. Light Res Technol 2012;44:238–52.
12. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nat Neurosci 2001;4:732–8.
13. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. Brain Res 1996;742:89–97.
14. Foote S, Berridge C, Adams L, Pineda J. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Progr Brain Res 1991;88:521–32.
15. Vandewalle G, Schmidt C, Albouy G, et al. Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. PLoS One 2007;2:e1247.
16. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005;25:46–59.
17. Kane MJ, Engle RW. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. J Exp Psychol Gen 2003;132:47.
18. Bogacz R, Wagenmakers E-J, Forstmann BU, Nieuwenhuis S. The neural basis of the speed–accuracy tradeoff. Trend Neurosci 2010;33:10–6.
19. Vandewalle G, Gais S, Schabus M, et al. Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. Cereb Cortex 2007;17:2788–95.
20. Vandewalle G, Balteau E, Phillips C, et al. Daytime light exposure dynamically enhances brain responses. Curr Biol 2006;16:1616–21.
21. Vandewalle G, Maquet P, Dijk D-J. Light as a modulator of cognitive brain function. Trend Cogn Sci 2009;13:429–38.
22. Gevins A, Cutillo B. Neuroelectric evidence for distributed processing in human working memory. Electroencephalogr Clin Neurophysiol 1993;87:128–43.
23. Hoddes E, Zarcone V, Dement W. Development and use of Stanford Sleepiness scale (SSS). In: Psychophysiology. New York, NY: Cambridge University Press, 1972.
24. Lacadie CM, Fulbright RK, Rajeevan N, Constable RT, Papademetris X. More accurate Talairach coordinates for neuroimaging using non-linear registration. Neuroimage 2008;42:717–25.
25. Woo CW, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. Neuroimage 2014;91:412–9.
26. Thorne DR. Throughput: a simple performance index with desirable characteristics. Behav Res Methods 2006;38:569–73.
27. D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res 2000;133:3–11.
28. Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 2003;7:415–23.
29. Vandewalle G, Archer SN, Wuillaume C, et al. Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. J Biol Rhythms 2011;26:249–59.
30. Alkozei A, Smith R, Killgore WD. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. Neurosci Lett 2016;616:5–10.
31. van Veen V, Krug MK, Carter CS. The neural and computational basis of controlled speed-accuracy tradeoff during task performance. J Cogn Neurosci 2008;20:1952–65.
32. Taillard J, Capelli A, Sagaspe P, Anund A, Akerstedt T, Philip P. In-car nocturnal blue light exposure improves motorway driving: a randomized controlled trial. PLoS One 2012;7:e46750.
33. Jaeggi SM, Buschkuehl M, Perrig WJ, Meier B. The concurrent validity of the N-back task as a working memory measure. Memory 2010;18:394–412.
34. Daneault V, Hebert M, Albouy G, et al. Aging reduces the stimulating effect of blue light on cognitive brain functions. Sleep 2014;37:85–96.
35. Gaggioni G, Maquet P, Schmidt C, Dijk DJ, Vandewalle G. Neuroimaging, cognition, light and circadian rhythms. Front Syst Neurosci 2014;8:126.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2015
Submitted in final revised form April, 2016
Accepted for publication April, 2016

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DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by a U.S. Army US Army MOMRP Grant as well as by an Arizona Health Education Centers (AHEC) Research Grant. The authors have no other conflict of interest. The authors have indicated no financial conflicts of interest.

Neuroscience Letters 616 (2016) 5–10

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli

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HIGHLIGHTS

- We compared the effects of thirty minutes of blue versus amber light exposure.
- Participants completed an emotional anticipation task after the light exposure.
- 'Uncertain event' > 'certain reward' led to lower activation for blue vs. amber.
- Blue light may improve adaptive learning-related synaptic processing within the ACC.

ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form 13 January 2016
Accepted 19 January 2016
Available online 22 January 2016

Keywords:
Blue light
fMRI
Emotional anticipation
Anterior cingulate cortex

ABSTRACT

Blue wavelength light has been used as an effective treatment for some types of mood disorders and circadian rhythm related sleep problems. We hypothesized that acute exposure to blue wavelength light would directly affect the functioning of neurocircuity implicated in emotion regulation (i.e., ventromedial prefrontal cortex, amygdala, insula, and anterior cingulate cortex [ACC]) during 'certain' and 'uncertain' anticipation of negative and positive stimuli. Thirty-five healthy adults were randomized to receive a thirty-minute exposure to either blue (active) or amber (placebo) light, immediately followed by an emotional anticipation task during functional magnetic resonance imaging (fMRI). In contrast to placebo, participants in the blue light group showed significantly reduced activation within the rostral ACC during 'uncertain' anticipation (i.e., uncertainty regarding whether a positive or negative stimulus would be shown) in comparison to 'certain' anticipation of a positive stimulus. These findings may be explicable in terms of interactions between blue light exposure and the influence of specific neuromodulators on ACC-mediated decision-making mechanisms.

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1. Introduction

Daily exposure to bright blue wavelength (≈480 nm) light has been used as a successful treatment for individuals with depression and seasonal affective disorder (SAD) [1]. The mechanisms underlying this effect of blue light on cognition/emotion remain poorly understood but likely include the well known indirect effects of light on the regulation of sleep and circadian rhythms, as well as more direct effects on neurological and neuroendocrine systems [2]. Considerable evidence suggests that the retina contains unique melanopsin photosensitive receptors that respond specifically to the blue wavelengths of light and that these neurons project predominantly to the suprachiasmatic nucleus of the hypothalamus, the primary regulator of circadian rhythms in the brain [3]. However, in addition to the circadian effects of light, some preliminary evidence suggests that light exposure may produce direct and immediate changes in the functioning of neural systems implicated in emotion-related functions. For example, it has been shown that direct exposure to a single dose of blue wavelength light for two hours not only led to improvements in alertness and cognitive performance, but also to increases in subjective wellbeing [4]. This may be explained by the fact that the melanopsin photosensitive ganglion cells also project to brain regions other than the hypothalamus. For example, blue light exposure has been shown to activate

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http://dx.doi.org/10.1016/j.neulet.2016.01.034
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the locus coeruleus (LC), which in turn releases norephinephrine throughout the cerebral cortex and influences a variety of brain functions as a result [5,6]. Several functional MRI studies have also suggested that blue light has an effect on emotion-related brain regions. For example, a 3-week daily white light intervention with peaks in the blue spectrum was associated with brain activation changes during perception of angry and fearful faces, including decreased activation within the amygdala and medial prefrontal cortex (mPFC), brain areas critical for the regulation of emotional responses [7]. Another study instead showed that short alternating periods of exposure (i.e., forty seconds) of blue versus green wavelength light were associated with increased activation within the temporal cortex and hippocampus during exposure to threatening versus neutral auditory stimuli [8], and such alternating light exposure produced greater activation within the hypothalamus in patients with SAD in comparison to healthy controls [9]. The inconsistencies in prior research require further exploration but may be due to differences in exposure time, the specific wavelengths used, the visual versus auditory nature of the tasks, differences in the populations or spatial location of the brain regions under investigation. Specifically, it is possible that prolonged daily exposure to blue light has distinct effects on functional brain responses when compared to short bursts of blue light exposure acutely during fMRI scanning, and that blue light has a differential effect in different regions of the brain, as well as in healthy versus clinical populations. However, the limited data on the effects of blue light on functional brain responses currently makes it impossible to draw firm conclusions and further research is necessary to clarify the effects of acute blue light exposure on emotional task responses.

The goal of the present study was to examine the effects of acute exposure to blue wavelength light on immediate post-exposure responses within neural systems implicated in affective regulation. Such systems, which include the amygdala, insula, anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC), among others, have been shown to be dysregulated in individuals with depression and anxiety, particularly when perceiving threatening stimuli [10,11] and when anticipating aversive stimuli [12–14]. For most people, uncertainty and unpredictability about the affective nature of future events is aversive, and has been shown to lead to hyperactivation of the insula, amygdala, and ACC relative to expectations about events with high certainty or predictability [15,16]. The ACC in particular appears to play an important regulatory role in decision-making within affective situations; recent models suggest that it does so by integrating information about uncertainty and reward expectations (in part, via dopaminergic reward prediction-error signals it receives from the ventral tegmental area [VTA]), and predicted cost/effort associated with perceptual cues and potential actions [17,18]. These decision-making functions also appear to be optimized via reward prediction-error based learning mechanisms. For example, it has been shown that in anticipation of reward, firing of neurons within the ACC increases as reward approaches [19]; interestingly, depressed individuals show reduced activation of the ACC during reward anticipation [20], and this resolves with successful treatment [21]. Further, synaptic plasticity within the ACC (which may underlie the learning rate within the aforementioned decision-making functions) appears to be facilitated by greater norepinephrine release under conditions of 'certain reward' anticipation [18,22,23]; as blue light is known to increase norepinephrine release from the LC (which itself has extensive projections to the ACC), this suggests that, under such conditions, blue light should increase the synaptic activation within the ACC associated with the integration of reward prediction-error and related learning mechanisms [5,6].

Considering that abnormalities in the processing of reward and uncertainty are implicated in multiple emotion-related psychiatric disorders, and that one major source of unpleasant emotion is uncertainty with respect to affectively significant future outcomes, the aim of this study was to investigate whether the effects of blue wavelength light discussed above might have a modulatory influence on brain responses during the anticipation of 'uncertain events' (i.e., a positive or a negative stimulus) versus 'certain threat' or 'certain reward' events. Specifically, we measured functional brain responses during three conditions of anticipation ('certain threat' cues, 'certain reward' cues, or 'uncertain event' cues) in healthy adults following a single dose of thirty minutes of blue wavelength versus an equal exposure to an amber wavelength light condition. We aimed to explore how exposure to thirty minutes of blue wavelength light would lead to functional brain changes within the amygdala, insula, ACC and mPFC during anticipation of 'certain threat', 'certain reward' and 'uncertain event' stimuli, in comparison to an equal dose of placebo (amber) light.

2. Methods

2.1. Participants

Thirty-five healthy adults who were free from psychiatric, neurological or substance use disorders, and reported a regular sleep schedule of going to bed between 10pm and 1am and waking between 6am and 9am participated in the study. Participants reported sleeping on average 7.2 h (SD = 0.93) per night, and obtained 6.8 (SD = 0.89) h of sleep the night before the assessment. Seventeen participants were randomized to receive thirty minutes of blue wavelength light exposure and eighteen participants were randomized to receive thirty minutes of placebo light exposure (see below). Groups did not differ regarding age, sex, BDI-II scores, number of hours slept on weeknights, and number of hours slept the night prior to assessment (see Table 1). All participants provided written informed consent. The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office.

2.2. Materials

2.2.1. Light exposure

Participants were randomized to receive either thirty minutes of blue wavelength light or placebo amber wavelength light while sitting a darkened room. Blue light was administered by four commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT), mounted on a desk at a distance of 80 cm, with each light centered at a 45° angle from midline. Each device consisted of a plastic table-mounted device with a 10 × 6 array of light emitting diodes (LEDs), encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and panel irradiance (mW/cm^2) = 1.23 at 20 cm). The amber placebo devices were provided by the manufacturer for research purposes and were essentially identical to the goLite BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and total irradiance (mW/cm^2) = 0.35).

2.2.2. Emotional anticipation task

The Emotional Anticipation Task (EAT) was designed to evaluate the brain activation associated with anticipating a positive, negative, or uncertain stimulus. The task was adapted from Aupperle et al.'s [24] study design and lasted a total of 460 s. Participants completed the task in the MRI scanner by viewing images on a translucent projection screen and viewed through the mirror mounted on the head coil. For each trial, participants were presented with a grey background with a black arrow that alternated

Table 1
Participant Characteristics.

	Blue group (n = 17) Mean (SD)	Amber group (n = 18) Mean (SD)	Statistic
Age	21.59 (2.59)	21.78 (3.54)	t (33) = 0.17 p = 0.86
Sex	47% female	55% female	χ^2 = 0.25, p = 0.61
BDI-II	2.82 (3.45)	3.39 (4.04)	t (33) = 0.44, p = 0.66
Number of hours slept on weeknights	7.13 (0.86)	7.27 (1.01)	t (33) = 0.45, p = 0.65
Number of hours slept the night prior to the assessment	6.92 (0.91)	6.71 (0.88)	t (33) = 0.69, p = 0.49

randomly pointing either left or right (baseline condition). For each image, participants were instructed to indicate via button press the direction the arrow was pointing. Participants were told that occasionally the screen color would change to signify that another type of image was to follow. Specifically, when the screen turned yellow, a negative picture would soon appear ('certain threat' anticipation). If the screen turned blue, a positive picture would soon appear ('certain reward' anticipation), and if the screen turned green, either a positive *or* a negative picture would soon appear ('uncertain event' anticipation). The anticipation period always lasted 6 s, and the baseline period varied in duration from 4 s to 8 s. Each anticipation condition was presented 9 times in pseudorandom order and each anticipation period was preceded by a baseline condition. The picture stimuli were presented for 2 s each and consisted of positive and negative pictures from the International Affective Picture System (IAPS). The most unpleasant (e.g., mutilated bodies) (mean valence = 1.62, SD = 1.09, mean arousal = 6.87, SD = 2.14) as well as the most pleasant (e.g., animals) pictures (mean valence ratings = 7.48, SD = 1.53 mean arousal = 5.42, SD = 2.29) were chosen from the picture set.

2.2.3. Beck depression inventory (BDI-II)

The Beck Depression Inventory (BDI-II; [25]) is a 21-item self-report questionnaire to assess depressive symptoms within the last 2 weeks.

2.3. Procedure

Participants completed the study on an individual basis, but each participant was run at the same time each day to minimize circadian effects. Participants arrived for the study at 0745 and were escorted to the laboratory. For the next 1.5 h, participants completed the informed consent process, filled out some basic information questionnaires, and completed the BDI-II. At approximately 0915, participants were then fitted with blue light blocking glasses (to minimize extraneous blue light exposure) and escorted to the neuroimaging center at the University of Arizona Department of Medical Imaging. To ensure that residual effects of outdoor and ambient lighting had dissipated before the beginning of the light exposure period, all participants underwent a "blue-light washout" period for thirty minutes, beginning at 0945. During this period, participants were seated comfortably in a darkened room, without the light blocking glasses, with two amber lights activated on the desk in front of them at 45° to the left and right of center. Participants were instructed not to look directly at the lights, but to relax with their eyes open. At 1015, the thirty-minute active light condition was initiated by engaging four light devices (either blue or amber, depending on condition), which were mounted on the desk in front of the participant. At the completion of the active light condition, participants again donned their blue blocking glasses and were escorted to the MRI scanner. Once in the scanner, the glasses were removed. The scanning sequence, including the EAT was initiated at 1100 and completed by 1200. At the conclusion of the scan, participants completed a few more questionnaires and were released.

2.4. Neuroimaging methods

Participants underwent neuroimaging on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/2.33 ms/12°) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/25.0 ms/90°) with 230 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

2.5. Image processing

Processing and analysis of neuroimaging scans was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Raw functional images were first realigned and unwarped. The mean functional images was then coregistered to each subject's MRPAGE image in accordance with standard algorithms. Images were then normalized from native space to Montreal Neurological Institute (MNI) coordinate space using forward deformation fields. Finally, images were spatially smoothed (6 mm full-width at half maximum), and resliced to 2 × 2 × 2 mm voxels. The standard canonical hemodynamic response function in SPM was employed, serial autocorrelation was corrected with the AR(1) function, and low-frequency confounds were minimized with a 128-second high-pass filter. The Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect/) was used to regress out scans exceeding 3 SD in mean global intensity and scan-to-scan motion that exceeded 1.0 mm.

2.6. Statistical analysis

On an individual basis, a general linear model was specified to contrast activation between all anticipation periods and baseline periods, as well as between the anticipation periods themselves. These contrast images were entered into a second-level independent samples t-test analysis with light group as the independent variable. Based on our a priori hypotheses, bilateral search territories were created using the Wake Forest University PickAtlas Utility [26] and the boundaries defined by the Automated Anatomical Labeling Atlas [27], focusing on the vmPFC, amygdala, insula, and ACC bilaterally. Analyses were thresholded at $p < 0.001$ (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, false discovery rate (FDR) corrected at the cluster level at $p < 0.05$, and k (extent) ≥ 10 contiguous voxels. In order to ensure that the results were not explained by participant's depression scores, which may have an impact on functional brain responses within these areas, analyses were re-run controlling for BDI-II scores.

3. Results

3.1. Anticipation > baseline

There were no significant differences in activation within the a priori ROIs between the two light groups for the following contrasts: 'certain threat' > baseline, 'certain reward' > baseline or 'uncertain event' > baseline.

3.2. Anticipation condition contrasts

There were no significant differences in activation within the ROIs between the two groups for the following contrasts: 'certain threat' > 'certain reward', and 'certain threat' > 'uncertain event'.

3.2.1. 'Uncertain event' > 'certain reward'

For the 'uncertain event' > 'certain reward' contrast, an independent samples *t*-test between the placebo (amber) > blue light group focusing on the a priori ROIs showed a significant difference in activation comprising two large clusters within the left rostral ACC (238 voxels, $p < 0.001$, $t = 4.72$, $x = -6$, $y = 42$, $z = 10$; and 108 voxels, $t = 4.35$, $x = -4$, $y = 42$, $z = -4$). Participants in the blue light condition showed reduced activation within those areas in comparison to participants in the placebo light condition (see Fig. 1).

When controlling for BDI-II scores in the analysis, the difference between the amber versus the blue light group was particularly pronounced for a large cluster within the rostral ACC (560 voxels, $p < 0.001$, cluster-level FDR corrected, and peak-level FWE-corrected at $p = 0.03$; $t = 5.10$, $x = -6$, $y = 42$, $z = 10$).

4. Discussion

In this study we found that a single dose of thirty minutes of blue light exposure immediately preceding the scanning session was associated with a reduced activation difference (relative to amber light exposure) within the left rostral ACC between 'uncertain' anticipation of negative or positive stimuli ('uncertain event' anticipation) and 'certain' anticipation of positive stimuli ('certain reward' anticipation). That is to say, the degree to which left rostral ACC activation was stronger during 'uncertain' than 'certain' anticipation was significantly greater in the amber light condition than the blue light condition. We suggest that this result may be explicable in terms of the known role of the ACC in the integration of uncertainty and valence-related information in decision-making and reinforcement learning.

In particular, we suggest these findings might be explained by the effects of blue light exposure on norepinephrine-mediated increases in learning-related synaptic plasticity within the ACC. The ACC has direct connections with the brainstem, including dopaminergic afferents from the VTA, as well as reciprocal connections with the LC [for a review see Ref. [18]], which releases norepinephrine in response to blue light exposure [5,6]. When exposed to a cue that predicts 'certain reward', dopaminergic neurons will increase their firing rate (i.e., positive reward prediction-error signaling), plausibly leading to an increase in BOLD response within the ACC regions that receive these signals [18]. In the case of the 'certain reward' condition in the present study, participants were told, and would learn quickly, that a blue screen predicts 'reward' in terms of a positive picture. This means that when the reward-predicting blue screen unexpectedly appeared, dopaminergic neuron firing rates in the VTA (signaling positive prediction-error) would increase, leading to a downstream influence on the ACC regions that receive these signals. However, synaptic plasticity (and associated learning rates) in response to such prediction-error signals have also been shown to be facilitated by norephinephrine, which has in turn been shown to be released by the LC in response to blue light exposure [5,22,23]. Thus, blue light, by increasing norepinephrine release in the ACC, may cause an increased 'learning rate' in response to dopaminergic positive reward prediction-error signals (reflected in greater synaptic activation/plasticity), leading to a greater BOLD response within the ACC. This would not be true of the uncertain condition, in which no reward prediction-error signal would be generated (and hence no learning signal would be present for norepinephrine to modulate). In summary, these considerations jointly suggest that individuals in the blue light condition should have exhibited greater synaptic activation (associated with a faster learning rate) when anticipating 'certain reward', due to the increase in norepinephrine, leading to greater BOLD response within the ACC, in comparison to the amber light group. As this increased activation in the certain condition would reduce the difference between the uncertain and certain condition in the blue light group, this would explain why ACC activation in the 'uncertain' > 'certain' contrast is greater in the amber light condition than in the blue light condition. The upshot of this interpretation is that it suggests that blue light may improve adaptive learning-related synaptic processing within the ACC during conditions of expected reward, which could in turn lead to more adaptive decision-making. In contrast, blue light would not be expected to have an effect of this kind in the uncertain condition, as the 'uncertain' cues do not generate prediction-error signal capable of driving learning (i.e., because they do not predict anything reliably about future positive or negative outcomes). However, future research will be necessary to establish whether these findings can be explained by differences in noradrenergic influence, for example, with the use of PET scans.

If blue light does, via its effects on norepinephrine release in the ACC, increase the adaptive use of reward prediction-error signals during learning and decision-making, this could help explain why depression is reduced after continued daily exposure to blue light over time. In particular, it would suggest that blue light exposure could help depressed individuals to become better able to learn from unexpected rewards (and reward-related cues). This may be particularly important in relation to the findings we report here, as the ACC has been identified as an important cortical region that predicts treatment response in mood disorders. For instance, greater ACC activation in anticipation of reward has been shown as a result of successful treatment of depression [21], and greater ACC activation at baseline has been shown to be a predictor of successful treatment response [28]. In the present study, our sample consisted of a healthy, nonclinical population. How these findings might apply to individuals with clinical symptoms of depression remains to be determined. In addition, our study lacks pre- and post-light exposure mood ratings or behavioral responses, it is therefore unclear how the functional brain changes correspond to differences in behavior. However, our findings complement those of previous studies in highlighting the potential of light treatment to improve depressive mood, possibly by changing individuals' internal responses to, and ability to learn from, reward-related processing.

Our results are also consistent with previous findings that showed that a 3-week daily bright light intervention led to reductions in activation within an overlapping medial prefrontal area in response to aversive stimuli [7]. However, as our study included only 30 min of light exposure on a single occasion, this suggests that the effect of blue light may be more immediate than previously thought, and the fact that our study design included positive as well as aversive conditions extends those findings further. This previous study suggested that these findings may reflect increases in emotion regulation abilities, possibly due to differences in neuromodulatory signaling, but proposed that other processes, in particular those involving reward, might also be involved. Our results may therefore compliment those of previous studies, and it should also be noted that the explanation we propose for our

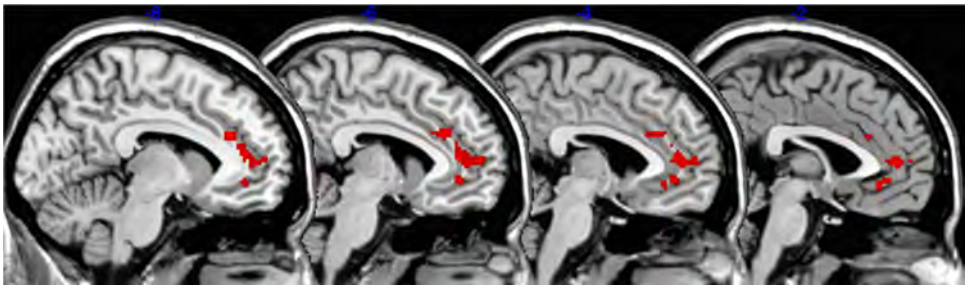


Fig. 1. There was a significantly greater activation difference between 'uncertain event' anticipation > 'certain reward' anticipation in the amber versus the blue light group after 30 min of light exposure within two clusters in the left ACC (MNI: x = −6, y = 42, z = 10, and x = −4, y = 42, z = −4).

results could also relate to emotion regulation. That is, if blue light improves the influence of reward cues on learning and decision-making within the ACC, then it is plausible that this would lead to better emotion regulation-related cognitive/behavior responses. However, as we did not gather behavioral data relevant to decision-making, these ideas will need to be tested in future work. It is also important to highlight that alternative explanations of our results cannot be ruled out. For example, considering the ACC has been shown to be recruited during conditions of unpredictable aversive stimuli [16,29], our results could also reflect a suppression of ACC activation during the 'uncertain event' condition, perhaps suggesting decreased emotional reactivity. Therefore, future research will be necessary to investigate the effects of blue light on ACC activation during emotional tasks in greater detail.

Contrary to our hypotheses, we did not find differences in activation between the two groups within the amygdala or insula during emotional anticipation, although some of these regions have been implicated in previous studies [7,30]. It is possible that the ACC is particularly responsive to the effects of blue wavelength light, because of the immediate increases in norepinephrine due to activation of the LC, whereas other structures require more prolonged daily exposure before functional changes become apparent. Future studies will therefore also need to establish whether this can explain the differences between the present findings and those of previous studies.

5. Conclusion

A single thirty-minute exposure to blue wavelength light versus exposure to a placebo amber wavelength light was associated with a reduced activation difference within the ACC during conditions of 'uncertain event' versus 'certain reward' anticipation. The findings suggest that blue wavelength light has the potential to enhance activation within the ACC during 'certain reward' anticipation, possibly due to an increase in norepinephrine, leading to an increase in the effectiveness of dopaminergic reward prediction-error signals. This increase in the learning rate during reward anticipation may partly explain the beneficial effect of blue light as a treatment for individuals with depression. Future neuroimaging studies including different brain imaging methods (e.g., PET), different functional tasks, and the inclusion of clinical populations will be necessary to illuminate these issues further.

Acknowledgment

This research was funded by a USAMRMC/CDMRP grant to WDSK (W81XWH-14-1-0571).

References

[1] R.N. Golden, et al., The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence, Am. J. Psychiatry 162 (4) (2005) 656–662.
[2] T.A. LeGates, D.C. Fernandez, S. Hattar, Light as a central modulator of circadian rhythms, sleep and affect, Nat. Rev. Neurosci. 15 (2014) 443–454.
[3] G.C. Brainard, et al., Sensitivity of the human circadian system to short-wavelength (420-nm) light, J. Biol. Rhythms 23 (5) (2008) 379–386.
[4] S.L. Chellappa, et al., Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? PLoS One 6 (1) (2011) pe16429.
[5] S.M. Florin-Lechner, et al., Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus, Brain Res. 742 (1) (1996) 89–97.
[6] G. Aston-Jones, et al., A neural circuit for circadian regulation of arousal, Nat. Neurosci. 4 (7) (2001) 732–738.
[7] P.M. Fisher, et al., Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling, Biol. Psychiatry 76 (4) (2014) 332–339.
[8] G. Vandewalle, et al., Spectral quality of light modulates emotional brain responses in humans, Proc. Natl. Acad. Sci. U. S. A. 107 (45) (2010) 19549–19554.
[9] G. Vandewalle, et al., Abnormal hypothalamic response to light in seasonal affective disorder, Biol. Psychiatry 70 (10) (2011) 954–961.
[10] B.-T. Lee, et al., The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (7) (2007) 1487–1492.
[11] M.B. Stein, et al., Increased amygdala and insula activation during emotion processing in anxiety-prone subjects, Am. J. Psychiatry 164 (2) (2007) 318–327.
[12] I.A. Strigo, et al., Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain, Arch. Gen. Psychiatry 65 (11) (2008) 1275–1284.
[13] T. Straube, H.-J. Mentzel, W.H. Miltner, Waiting for spiders: brain activation during anticipatory anxiety in spider phobics, Neuroimage 37 (4) (2007) 1427–1436.
[14] J.B. Nitschke, et al., Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response, Am. J. Psychiatry 166 (3) (2009) 302–310.
[15] C. Herry, et al., Processing of temporal unpredictability in human and animal amygdala, J. Neurosci. 27 (22) (2007) 5958–5966.
[16] I. Sarinopoulos, et al., Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala, Cereb. Cortex (2009) pbhp155.
[17] G. Bush, et al., Dorsal anterior cingulate cortex: a role in reward-based decision making, Proc. Natl. Acad. Sci. U. S. A. 99 (1) (2002) 523–528.
[18] M. Silvetti, et al., From conflict management to reward-based decision making: actors and critics in primate medial frontal cortex, Neurosci. Biobehav. Rev. 46 (2014) 44–57.
[19] M. Shidara, B.J. Richmond, Anterior cingulate: single neuronal signals related to degree of reward expectancy, Science 296 (5573) (2002) 1709–1711.
[20] M.J. Smoski, et al., fMRI of alterations in reward selection: anticipation, and feedback in major depressive disorder, J. Affect. Disord. 118 (1) (2009) 69–78.
[21] G.S. Dichter, et al., The effects of psychotherapy on neural responses to rewards in major depression, Biol. Psychiatry 66 (9) (2009) 886–897.
[22] Y. Izumi, C.F. Zorumski, Norepinephrine promotes long-term potentiation in the adult rat hippocampus in vitro, Synapse 31 (3) (1999) 196–202.
[23] H. Katsuki, Y. Izumi, C.F. Zorumski, Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region, J. Neurophysiol. 77 (6) (1997) 3013–3020.
[24] R.L. Aupperle, et al., Neural responses during emotional processing before and after cognitive trauma therapy for battered women, Psychiatry Res.: Neuroimaging 214 (1) (2013) 48–55.

[25] A.T. Beck, R.A. Steer, G.K. Brown, BDI-II: Beck Depression Inventory Manual, 2nd ed., Psychologial Corporation, San Antonio, TX, 1996.
[26] J.A. Maldjian, et al., An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets, Neuroimage 19 (3) (2003) 1233–1239.
[27] N. Tzourio-Mazoyer, et al., Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain, Neuroimage 15 (1) (2002) 273–289.
[28] R.J. Davidson, et al., The neural substrates of affective processing in depressed patients treated with venlafaxine, Am. J. Psychiatry 160 (1) (2014) 64–75.
[29] C. Grillon, et al., Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder, Am. J. Psychiatry 165 (7) (2008) 898–904.
[30] G. Vandewalle, et al., Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem, PLoS One 2 (11) (2007) 1247.

Neurobiology of Disease 134 (2020) 104679

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury

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ARTICLE INFO

Keywords:
mTBI
Concussion
Light therapy
Blue light
Sleep
Circadian rhythm
Neuroimaging
DTI
VBM
Connectivity

ABSTRACT

Sleep and circadian rhythms are among the most powerful but least understood contributors to cognitive performance and brain health. Here we capitalize on the circadian resetting effect of blue-wavelength light to phase shift the sleep patterns of adult patients (aged 18–48 years) recovering from mild traumatic brain injury (mTBI), with the aim of facilitating recovery of brain structure, connectivity, and cognitive performance. During a randomized, double-blind, placebo-controlled trial of 32 adults with a recent mTBI, we compared 6-weeks of daily 30-min pulses of blue light (peak λ = 469 nm) each morning versus amber placebo light (peak λ = 578 nm) on neurocognitive and neuroimaging outcomes, including gray matter volume (GMV), resting-state functional connectivity, directed connectivity using Granger causality, and white matter integrity using diffusion tensor imaging (DTI). Relative to placebo, morning blue light led to phase-advanced sleep timing, reduced daytime sleepiness, and improved executive functioning, and was associated with increased volume of the posterior thalamus (i.e., pulvinar), greater thalamo-cortical functional connectivity, and increased axonal integrity of these pathways. These findings provide insight into the contributions of the circadian and sleep systems in brain repair and lay the groundwork for interventions targeting the retinohypothalamic system to facilitate injury recovery.

1. Introduction

Sleep and circadian rhythms have potent effects on human health, neurobiology, and cognitive functioning. Without the benefit of restorative sleep, elementary cognitive performance declines rapidly and is accompanied by unpredictable lapses of attention (Durmer and Dinges, 2005), and impairments in higher-order cognitive capacities such as judgment, decision-making, and executive functions (Killgore et al., 2006; Killgore et al., 2007; Tucker et al., 2010). At the neural level, sleep is critical for processes that facilitate physiological maintenance and repair, including flushing out accumulated neurotoxins (Xie et al., 2013), restoration of damaged DNA in neurons (Bellesi et al., 2016), production of oligodendrocyte precursor cells involved in myelin formation (Bellesi et al., 2013), sustainment of myelin sheath thickness (Bellesi et al., 2018), and maintaining the structural plasticity and homeostasis of synaptic connections (de Vivo et al., 2017; Tononi and Cirelli, 2014). Animal models demonstrate that sleep plays a vital role in recovery from brain injury (Gao et al., 2010; Zunzunegui et al., 2011), presumably through many of the mechanisms just described. Clearly, one of the many functions of sleep is to facilitate repair and restoration of brain systems that have been damaged, depleted, or degraded. Sleep, however, is not driven solely by homeostatic forces; our propensity for sleep is inextricably linked with the diurnal circadian rhythm of melatonin secretion by the pineal gland and the attendant fluctuations in alertness. Because retinal light exposure suppresses melatonin, circulating levels of this hormone are nearly absent throughout the circadian day, but typically rise dramatically as light levels decline in the evening (Cajochen et al., 2003). For humans, the most efficient, restful, and restorative sleep occurs when the sleep cycle is closely aligned with the circadian night (Arendt, 2006; Lavie, 2001).

Circadian rhythms are demonstrated by almost every cell within the human body, comprising a hierarchical multi-oscillator system that is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus (Honma, 2018). The near 24-hour rhythm of this system is maintained by a molecular entrainment process that resets the circadian clock each period via retinal exposure to light. When light strikes the retina, it

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https://doi.org/10.1016/j.nbd.2019.104679
Received 10 July 2019; Received in revised form 20 October 2019; Accepted 15 November 2019
Available online 18 November 2019
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stimulates melanopsin-based intrinsically photosensitive retinal ganglion cells (ipRGCs) that are uniquely sensitive to wavelengths in the blue range of the light spectrum (Panda et al., 2005; Provencio et al., 2000; Qiu et al., 2005). These ipRGCs project extensively, via the retinohypothalamic tract (RHT), to the SCN (Hattar et al., 2002; Panda et al., 2002), which in turn, suppresses the production of melatonin by the pineal gland (Sapede and Cau, 2013). Thus, exposure to blue wavelength light in the morning suppresses melatonin and phase advances the circadian rhythm (i.e., sleep onset occurs earlier in the next period) while similar exposure in the evening leads to a phase delay (i.e., sleep onset will be pushed back later in the next period). This modifiability of the circadian rhythm by light exposure has led to recent efforts to use targeted phototherapy to treat circadian-related sleep problems.

While many types of sleep difficulties could potentially benefit from light exposure interventions, one disorder where sleep may play a key role in brain repair and recovery is mild traumatic brain injury (mTBI) (Raikes and Killgore, 2018). Approximately 50% of patients with an mTBI experience chronic sleep disruption and associated cognitive decrements following injury (Orff et al., 2009; Rao et al., 2008; Verma et al., 2007). Critically, mTBI is associated with disturbances in the normal rhythm of melatonin production (Grima et al., 2016; Shekleton et al., 2010). As melatonin production in the evening plays a crucial role in regulating sleep onset, disruptions in this cycle can have pronounced effects on sleep quality (Grima et al., 2016; Shekleton et al., 2010). Moreover, sleep problems following an mTBI are associated with worse cognitive recovery and greater neuropsychiatric complications (Gilbert et al., 2015; Sullivan et al., 2016). Based on the aforementioned role of sleep in neural maintenance and repair, sleep disturbance in mTBI may hinder normal brain recovery following an injury. We, therefore, proposed to facilitate recovery from an mTBI by optimizing the timing and quality of sleep via targeted light exposure, which has not been directly assessed through experimental research. Sinclair and colleagues first demonstrated that morning blue-wavelength light exposure was effective at reducing subjective fatigue and daytime sleepiness in patients recovering from TBI (Sinclair et al., 2014), however, objective outcomes were not measured. More recently, our team reported preliminary evidence that morning blue light exposure may be helpful in changing the water diffusion patterns of cerebral white matter in patients recovering from mTBI (Bajaj et al., 2017). However, full examination of the combined effects of blue light treatment on circadian timing, neurocognitive performance, and multimodal assessment of neural mechanisms has not been undertaken.

Here, we identified the cognitive and neurobiological changes produced by a 6-week intervention of daily morning blue-wavelength light exposure in individuals recovering from a non-complicated mTBI. In a randomized, double-blind, placebo-controlled trial, adults with a documented mTBI in the preceding 18 months used an LED lightbox each morning for 30-min. Each device was fitted with either BLUE or AMBER LEDs (see Fig. 1). Sleep/wake activity was monitored with wrist actigraphy and on-line sleep diaries for one week before treatment, and throughout the 6-week intervention period. Participants also completed a comprehensive neuropsychological assessment battery, a series of objective multiple sleep latency tests (MSLTs), and functional and structural magnetic resonance imaging (MRI) scans on the day preceding the treatment period and immediately upon completion of the intervention. We hypothesized that the blue light intervention would lead to a greater phase advance in the circadian rhythm, improved sleep, and enhanced daytime alertness relative to amber placebo. Further, we hypothesized that compared to the placebo condition, the blue light would produce greater improvement in neurocognitive performance and symptom reduction, which would correspond to increased functional and structural connectivity within brain networks involved in visual attention.

2. Methods

2.1. Participants

Individuals with a documented history of an mTBI in the preceding 18 months were recruited from the greater Boston Metropolitan area to participate. Interested volunteers first underwent a rigorous telephone screening interview, followed by a detailed in-person interview to determine eligibility. Volunteers were between the ages of 18 and 50 and had experienced a “concussion” or non-complicated mTBI within the preceding 18 months, but no sooner than 4 weeks prior to their initial assessment. Before participation, all individuals were required to provide written documentation by a medical or other relevant professional (e.g., physician, nurse, emergency medical technician, coach, physical trainer, police officer, security guard) who either witnessed or was involved in the immediate response to the injury. Eligible volunteers were required to meet the definition of an mTBI as specified by the VA/DoD practice guidelines (VA/DoD Management of Concussion/mTBI Working Group, 2009), which define an mTBI as a traumatically induced structural injury and/or physiological disruption caused by an external force (e.g., head impact, blast wave) leading to an alteration in mental status (e.g., confusion, disorientation, retrograde or anterograde amnesia), consciousness (i.e., loss of consciousness < 30 min; alteration of consciousness up to 24 h), or post-traumatic amnesia up to 24 h, and/or a Glasgow Coma Scale ≥ 13. For this study, all participants were also required to have reported the onset of significant sleep-related problems that emerged or worsened following the injury. Only primary English speakers (i.e., those who began speaking English as their primary language in the home by 3 years of age), and those who were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) were included. Potential volunteers were also excluded for any history of neurological, mood, or psychotic disorder that was present before the index traumatic injury, as well as abnormal visual acuity not correctable by contact lenses, metal within the body, pregnancy, or other contraindications for MRI. Other exclusionary criteria included current or anticipated shift work, intent to leave the time zone during the course of the study, use of contraindicated medications (i.e., sleep medications; medications that affect neuroimaging), or use of illicit substances, including recent or long-term marijuana use, or excessive alcohol use (as defined by CDC criteria). Prior to enrollment, all participants completed written informed consent, and were compensated for their time in the study. The protocol for this experiment was approved by the Institutional Review Boards (IRB) of Partners Health Care, McLean Hospital, and the U.S. Army Human Use Protections Office.

Primary endpoints for this study, collected at baseline and post-treatment, included 1) actigraphically measured sleep (minutes per night), 2) actigraphically measured circadian phase shift (i.e., shift in sleep onset time, wake time, and midpoint of the sleep period), and 3) subjective sleepiness, and 4) objective sleepiness. Secondary endpoints included 1) cognitive performance (i.e., psychomotor vigilance, neuropsychological performance, and executive functioning), 2) brain volumetrics, 3) functional connectivity, and 4) white matter axonal integrity. Each of these was assessed at the baseline week or visit and again during the final week or follow-up visit. A total of 38 participants met full criteria for initial enrollment in the study. However, due to participant non-compliance ($n = 2$), disqualifying psychopathology ($n = 1$), and claustrophobia upon entering the scanner ($n = 1$), 34 participants were ultimately randomized to one of the treatment groups (Fig. 2). Two participants in the BLUE condition failed to complete required study procedures during the course of treatment, yielding complete data for most outcome measures from 32 participants (15 male; 17 female) ranging in age from 18 to 48 years ($M = 23.27$; $SD = 7.14$). Of these participants, $n = 16$ (50%) received the active BLUE light condition and $n = 16$ (50%) received the placebo AMBER placebo light condition. Table 1 presents the demographic data for the

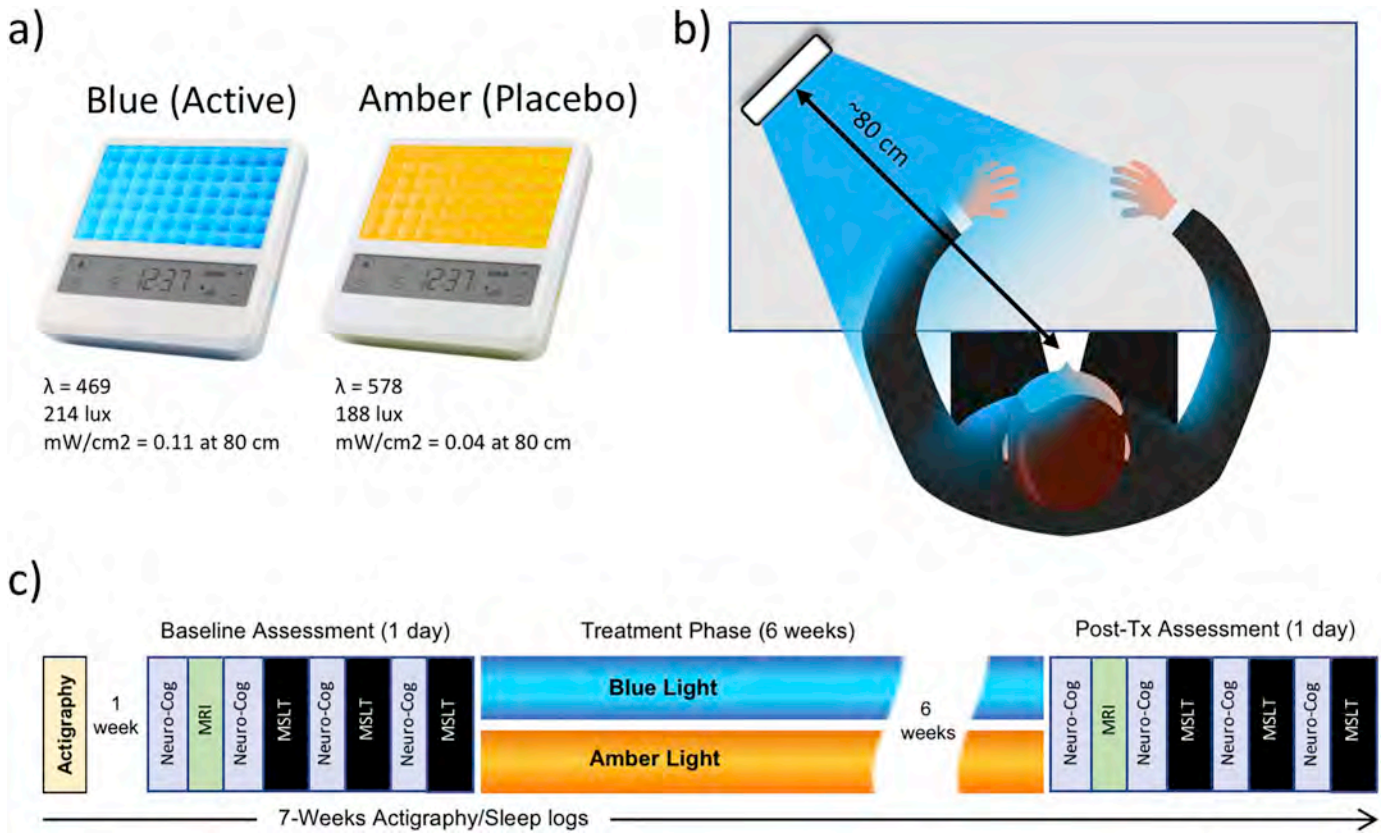


Fig. 1. Light therapy conditions and experimental design. (a) Participants received either a blue (active condition) or amber (placebo condition) light box fitted with light-emitting diodes. (b) The participant was instructed to place the device at arm"s length on a table at an approximately 45-degree angle and bathe their face with the light for 30-minutesmin each morning. (c) The study lasted for 7-weeks. The figure shows that the participant wore an actigraph sleep monitor for the entire study period. After one week of baseline actigraphy, the participant completed a full day of neurocognitive assessments, magnetic resonance imaging (MRI) scans, and multiple sleep latency tests (MSLTs). Participants were then randomized to one of the two light treatment conditions (blue versus amber), during which time they used the lightbox each morning. At the end of 6-weeks, participants returned to complete another day-long assesses session with the same measures collected at baseline. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

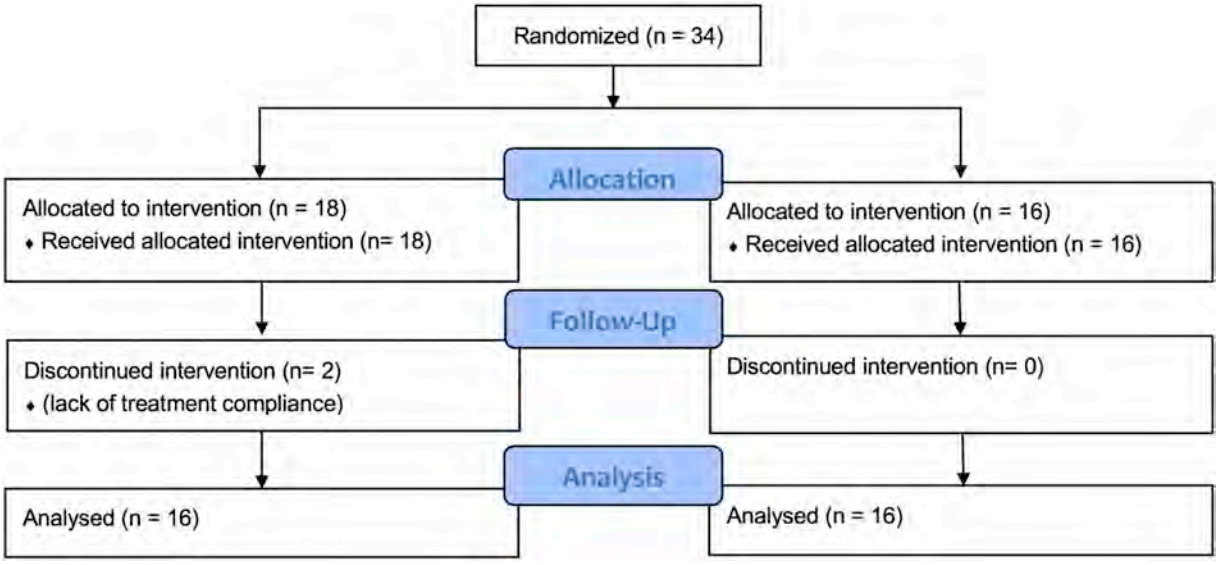


Fig. 2. Participant flow diagram. The figure shows that 3 participants were randomly assigned to either the active blue light condition or placebo amber light condition. Two participants from the blue group were excluded due to non-compliance, yielding 16 participants per group in the final analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Baseline demographics for blue and amber groups.

	Blue	Amber	Test	p-value
N	16 (50%)	16 (50%)		
Female	9 (56.2%)	8 (50%)	χ^2 (1) = 0.125	0.72
Male	7 (43.8%)	8 (50%)		
Age	23.2 (7.1)	23.3 (7.4)	$t(30) = 0.037$	0.97
Education	15.0 (2.4)	14.6 (2.2)	$t(30) = 0.466$	0.65
# Concussions	2.4 (1.8)	2.2 (1.6)	$t(30) = 0.368$	0.72
Months Since Injury	6.8 (4.4)	6.7 (3.6)	$t(30) = 0.066$	0.95
RPCSQ Total	13.6 (11.1)	16.7 (8.3)	$t(30) = 0.883$	0.38
NSI	18.4 (19.4)	16.9 (10.5)	$t(30) = 0.260$	0.80
BDI	7.3 (6.6)	7.1 (3.4)	$t(30) = 0.134$	0.89
FOSQ	16.1 (2.9)	16.5 (2.1)	$t(30) = 0.38$	0.71
MEQ	51.8 (4.3)	50.8 (6.5)	$t(30) = 0.514$	0.61

samples.

2.2. General procedure

Over seven weeks, participants completed three laboratory visits, including two full-day neurocognitive assessments plus neuroimaging scans, and were randomly assigned to complete a 6-week at-home light treatment regimen with either daily BLUE or AMBER light therapy each morning.

2.2.1. Visit 1: Intake

Upon arrival, each eligible participant completed the informed consent process followed by the Neurobehavioral Symptom Inventory (NSI) (King et al., 2012), and the MINI International Neuropsychological Interview (MINI) (Sheehan et al., 1998) to screen for psychopathology. Each participant was then fitted with an actigraphic sleep monitor wristwatch (Actiwatch Spectrum, Philips Respironics, OR, USA) and shown how to log onto a secure web-based sleep diary to complete daily questions about sleep and activity. Participants were instructed to wear the actigraph watch continuously for the duration of the study and return to the lab for a baseline neurocognitive assessment and MRI scan in one week.

2.2.2. Visit 2: Baseline neurocognitive assessment/MRI scan

After one week of at-home baseline actigraphic sleep assessment, participants returned for a baseline neurocognitive and neuroimaging assessment. Participants arrived at the lab at 8:00 a.m. to complete pre-scan procedures, including a pregnancy test for females and brief practice tasks for the functional portion of the scan. Beginning at 9:00 a.m., participants underwent a 60-min neuroimaging scan that included standard structural MRI (MPRAGE), resting-state functional MRI, and diffusion tensor imaging (DTI). After leaving the scanner at 10:00 a.m., participants completed a half-hour neurocognitive assessment with the Repeatable Battery of Neuropsychological Status (RBANS). Between 10:30–11:00 a.m., polysomnographic electrodes were applied, and the participant underwent the first of three trials of the Multiple Sleep Latency Test (MSLT) at 11:50 a.m. After the MSLT, a break for lunch occurred, followed by administration of a measure of balance and stance stability at 1:15 p.m. A second MSLT occurred at 1:50 p.m. Multiple sleep and symptom questionnaires were administered, followed by the Tower of London at 3:15 p.m., and a third MSLT at 3:50 p.m. After testing, electrodes were removed and the participant was provided with a light therapy device with a full demonstration on its use, as well as a printed instruction brochure that provided detailed information about the use of the device.

2.2.3. 6-week light therapy

Based on a pre-established computer-generated randomization scheme, participants were provided either a BLUE or AMBER light device (described in greater detail below) in a double-blind manner (i.e., participants were not informed that there were different colours of lights and all study staff with direct participant contact were blind to the colour of light device assigned to each participant). Participants were instructed to activate the light device every morning within two hours of awakening, but no later than 11:00 a.m., and use the device continuously for 30 min. When using the device, participants were instructed to place the lightbox at approximately arm's length (20–30 in. distance from the face) at a slight angle (20–40°), so that the light would bathe both sides of the face, and were encouraged to avoid looking directly at the diodes to avoid visual discomfort. The device was programmed to turn off automatically after 30 min of continuous use. Additionally, participants were instructed to log onto a secure website to complete a sleep and light use diary each morning after the completion of light exposure.

2.2.4. Visit 3: Post-treatment neurocognitive assessment/MRI scan

Upon completion of the 6-weeks of daily morning light treatment, participants returned to the lab for a final assessment session, which was virtually identical to the baseline session (Visit 2). At the end of the day, participants returned all equipment and were released from the study.

2.3. Assessment measures

The following assessment measures and devices were used:

2.3.1. Personality and psychodiagnostic assessment

At Visit 1, a trained technician administered the Mini-International Neuropsychiatric Interview (M.I.N.I.), a psychometrically validated scale for assessing psychopathology (Sheehan et al., 1998), and the VA National Traumatic Brain Injury Neurobehavioral Symptom Inventory (NSI) (King et al., 2012). At Visit 2, participants completed several self-report assessment scales including the Beck Depression Inventory (BDI-II) (Beck et al., 1996), Rivermead Postconcussion Symptom Questionaire (RPCSQ) and basic questionnaires regarding sleep history, injury history, caffeine use, and demographics.

2.3.2. Actigraphy

Participants wore an Actiwatch Spectrum (Philips Respironics) wristwatch actigraph to monitor activity and sleep. The device collected wrist activity movement counts and accumulated light exposure every 60 s throughout the duration of the study. After each participant's study run, the activity data were downloaded from the watch.

2.3.3. Sleepiness and subjective sleep need assessment

At each visit, participants completed the Epworth Sleepiness Scale (ESS)(Johns, 1991), a measure of typical daytime sleepiness. Additionally, at seven times during each visit day (8:55 a.m., 10:05 a.m., 11:40 a.m., 1:05 p.m., 1:35 p.m., 2:35 p.m., 3:35 p.m.), participants completed a rapid single-item 7-point Likert assessment of immediate sleepiness with the Stanford Sleepiness Scale (SSS)(Herscovitch and Broughton, 1981). Additionally, as an indicator of perceived sleep need, we also asked participants to indicate “how many hours do you need to sleep to feel your best.”

2.3.4. MSLT

Following the MRI procedure, each participant underwent a polysomnography (PSG) hook-up following standard procedures using the 10–20 system. A total of 14 leads were connected (i.e., A1, A2, O1, O2, Cz, C3, C4, F3, F4, LEOG, REOG, P3, Pz, P4). At three times during the assessment session (i.e., 11:50 a.m., 1:50 p.m., 3:50 p.m.), participants were escorted to a private, infrared video-monitored, sleep chamber to complete the multiple sleep latency test (MSLT). The participant laid supine on a bed and was connected to a Nihon Kohden Polysmith system (software version 11.0), with an amplifier (JE-912AK) and

remote headbox (JE-915A). After standard biocalibration, the participant was instructed to lie quietly and try to relax. The lights were then turned off. PSG recording continued for 20 min and was monitored continuously by a trained technician in real time. The procedure was terminated after 20 min or was ended early if there were three consecutive 30-s epochs of sleep stage N1 or one continuous epoch of any other sleep stage. Each recording was then independently scored by a trained and certified polysomnographic technician to determine the number of minutes of wakefulness before entering into stage N1 or deeper sleep. A score of 20 indicated no sleep was measured.

2.3.5. Psychomotor vigilance test (PVT)

At three times during the course of each assessment session (11:30 a.m., 1:25 p.m., 3:25 p.m.), participants completed a 10-min assessment of attention and vigilance with the psychomotor vigilance test (PVT) (Dinges and Powell, 1985) on a desktop computer. During the task, participants were required to monitor a black screen and press a response key as quickly as possible whenever a target stimulus appeared in the center of the screen. Response time feedback was provided for each response. Each stimulus was presented in a pseudo-random fashion with an inter-stimulus interval that ranged randomly without replacement from 2 to 10 s.

2.3.6. Neurocognitive assessment

From approximately 10:05–10:35 a.m., participants completed the RBANS, a brief battery of well-normed neuropsychological tests that is commonly used for assessing individuals with traumatic brain injury. The test provides several index scores, including: Immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory, and Total Score. Two alternate forms were counterbalanced across the two groups for each administration. Additionally, at approximately 3:15 p.m., participants completed a 10-trial computerized version of the TOL as a measure of executive functioning (i.e., planning and sequencing ability) (Colorado Assessment Tests, http://www.catstests.com). On each trial, the participant began with a starting "tower" that consisted of three "pegs" of differing lengths, each with an arrangement of three different coloured "beads" in various configurations upon the pegs. To solve the puzzle, the examinee must rearrange the beads to match a pre-specified goal pattern as quickly and in as few moves as possible. Dependent variables from this task included the number of moves required to match the goal arrangement, the average total move time, and an index of throughput that accounted for both speed and accuracy (i.e., [(proportion of correct moves)/(average total move time in seconds)] x 0.60).

2.3.7. Light exposure devices

At the conclusion of Visit 2, participants were provided with either a BLUE or AMBER a light therapy device to be used each morning. The devices were manufactured by Philips Electronics (Stamford, CT). All units were identical in design, with the exception of the colour wavelength of the LEDs. Each device consisted of a 13.5 × 14 cm plastic encased table-mounted device with a 10 × 6 array of light emitting diodes (LEDs). Each LED was encased in a 1 × 1 cm cubical projection element covered by a translucent plastic window. For the active BLUE condition, participants were provided with a commercially available Philips goLITE BLU® Energy Light device (Model HF3321/60). The goLITE BLU Energy Light has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm). The AMBER placebo devices were provided on loan by the manufacturer. The AMBER devices were essentially identical in design to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm). Participants were instructed to use the device on its highest setting, and the device was set to deactivate after 30 min of continuous use.

2.4. Neuroimaging methods

Data were collected at baseline and post-treatment using a 3.0 T magnetic resonance imaging scanner (Siemens Tim Trio, Erlangen, Germany) using a 32-channel head coil. All scans occurred between 9:00–10:00 a.m.

2.4.1. Structural neuroimaging

Volumetric data were collected using a T1 weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) that consisted of 176 sagittal slices (256 × 256 matrix) with a slice thickness of 1 mm and a voxel size of 1 × 1 × 1 mm^3. T1 weighted structural images were preprocessed using the Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat/) in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were realigned to the anterior-posterior commissure axis and then segmented using the longitudinal pipeline into gray matter, white matter, and cerebrospinal fluid using VBM12, a fully automated algorithm in SPM12. Segmented images were used to create a custom DARTEL template and then the images were normalized to Montreal Neurological Institute (MNI) space. Smoothing of normalized images was performed with a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

2.4.2. Functional neuroimaging

Resting-state functional MRI images were acquired for 6 min using a gradient echo T2*-weighted sequence (TR/TE/flip angle = 2 s/30 ms/90°) and a 224 mm FOV. The resting functional images were collected in the same plane with 34 coronal slices and a voxel size of 3.5 × 3.5 × 3.5 mm^3, in an interleaved excitation order, with foot-to-head phase encoding. At the beginning of each scan, four images were acquired and discarded to allow for T1-equilibrium effects. Head movement was restricted using expandable foam cushions, and subjects were asked to remain awake with eyes open while lying still during the scans. Participants were simply instructed to allow their mind to wander during the scan. Resting-state fMRI data were preprocessed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were slice-time corrected, co-registered to their anatomical images, realigned and resliced to 2 × 2 × 2 mm^3 isotropic voxels, unwarped to correct for field inhomogeneity, normalized to the standard three-dimensional space of the Montreal Neurological Institute (MNI), and spatially smoothed using a 6 mm isotropic Gaussian kernel. Outliers from motion and global signal intensity were identified using the *ART* toolbox https://www.nitrc.org/projects/artifact_detect/. Images with movement from a preceding image exceeding 0.5 mm or a global mean intensity > 3 standard deviations were regressed out of the first level general linear models.

2.4.3. Diffusion tensor imaging (DTI)

DTI scans were acquired using a Siemens Tim Trio 3 T scanner (Erlangen, Germany) at McLean Hospital Imaging Center. Diffusion-weighted imaging (DWI) data were acquired along 72 directions with a b-value of 1000 s/mm^2 and following parameters: voxel size = 1.75 × 1.75 × 3.5 mm^3, TR = 6340 ms, TE = 99 ms, flip angle = 90° and 40 axial slices with thickness = 3.5 mm, encompassing the whole brain. A set of 8 images with no diffusion weighting (b0 images) was also acquired. Using dcm2nii toolbox (part of MRIcron (Rorden et al., 2007)), we converted DWI data from DICOM into NIFTI format. A b-value and b-vector file was generated during this step. The raw data were imported into the DSI Studio (http://dsi-studio.labsolver.org) and converted into SRC format. Each SRC file underwent standard eddy current and subject movement correction, followed by a thorough examination using quality control (QC) procedure to ensure the quality and integrity of data. Neighboring DWI correlation (NDC) values for the current data set were > 0.95. No outlier in NDC values (> 3 median absolute deviation) was identified.

2.5. Data analysis

Data analysis followed a sequential process. First sleep and performance measures were compared between pre- and post-treatment. Second, we compared gray matter volume (GMV) in the brain between pre- and post-treatment using voxel-based morphometry (VBM). As discussed in detail below, two separate clusters within the left and right thalamus demonstrated significant increases in volume following treatment with BLUE light. Third, the resulting significant GMV clusters were used as seed regions of interest (ROIs) in a subsequent resting state functional connectivity (rsFC) analysis. Significant functional connectivity values between the seed ROIs and associated cortical clusters (ROIs) were extracted for further analysis. Fourth, the functional connectivity data were also analyzed using Granger causality (GC) analysis to determine the directional nature of the connectivity patterns. Areas which were not found to be structurally connected were not analyzed using GC. Lastly, the seed and target ROIs resulting from the rsFC analysis were implemented as endpoint regions in a fiber tractography analysis using the diffusion tensor imaging scan data. Once fiber tracts were defined for each individual, standard DTI metrics of fiber pathway integrity were extracted and compared between pre-and post-treatment for each light condition. The resulting metrics from each region were extracted for further analysis with relevant behavioral outcome metrics.

2.5.1. Actigraphic sleep analysis

Actigraphic data were downloaded and then processed and scored in Actiware® 6 (Philips Respironics) according to standardized procedures. For the present analysis, we averaged the minutes of sleep obtained for each overnight sleep opportunity for the first six nights of the baseline week (i.e., between Visit 1 and 2) and the final six nights preceding the post-treatment visit (Visit 3). For each participant, sleep onset time, wake time, sleep duration, sleep efficiency, and wake after sleep onset (WASO) was calculated. A 2 between (light colour: blue vs amber) x 2 within (time: baseline vs post-treatment) mixed analysis of variance (ANOVA) was conducted on each of these variables separately. For all behavioral analyses, we controlled for a set of variables likely to affect sleep, including concussion severity (RPCSQ and occurrence of loss of consciousness (LOC) from the most recent concussion), depression (BDI), and participant age. As appropriate, for select sleep measures, change metrics were also examined as dichotomous outcome variables (i.e., improvement vs. no-improvement) to allow determination of odds ratios (OR).

2.5.2. Cognitive/behavioral performance analysis

To assess the effects of light treatment group on cognitive and behavioral measures, data from self-report questionnaires (e.g., ESS) and cognitive metrics (e.g., TOL) were computed as a change from baseline. These change scores were then compared using one-way ANCOVA, controlling for RPCSQ, LOC, BDI, and age. As appropriate, for select behavioral measures, change metrics were also examined as dichotomous outcome variables (i.e., improvement vs. no-improvement) to allow determination of odds ratios (OR).

2.5.3. GMV statistical analysis

Statistical analyses were conducted in several stages. First, processed GMV data from CAT12 were analyzed in SPM12. A 2 between (blue vs. amber) x 2 within (baseline vs. post-treatment) mixed analysis of variance (ANOVA) was conducted within SPM12 using the flexible factorial option, controlling for age, intracranial volume, and the number of days the light device was used (according to online sleep logs). Maps were cluster corrected for family-wise error (FWE, $p < .05$) at the whole brain level. Resulting clusters were then compared from pre-to post-treatment using paired *t*-tests in SPM12 for the BLUE light group, with age, intracranial volume, and the number of total days in the study during which participants reported using the light device entered as nuisance covariates. To increase precision, separate search territories were placed for the left and right thalamus using the automated anatomic labeling atlas (AAL; (Tzourio-Mazoyer et al., 2002)). We used a cluster-extent based thresholding, following the recommended approach suggested by Woo, Krishnan, and Wager (Woo et al., 2014), applying a primary significance threshold of $p < .001$, uncorrected, as the default lower limit. Based on this primary height threshold, SPM12 provided the critical cluster size for cluster-extent correction with family-wise error (FWE) maintained at $p < .05$ for the search territory. Between group *t*-tests were conducted for the BLUE group and resulting significant clusters were used a regions of interest (ROIs) that were then compared for the AMBER group to constrain for multiple comparisons. Using the Region Extraction Tool (REX), the mean GMV estimates were extracted for each cluster for the BLUE and AMBER groups separately and exported to IBM SPSS Statistics 25 for further analyses.

We were interested in the associations between the change metrics for each neuroimaging parameter and several cognitive/behavioral outcome variables. Here, the volumetric change values for each cluster were extracted for each individual for correlation with cognitive/behavioral measures of interest. A hierarchical multiple regression procedure was employed, including covariates for age, intracranial volume, and the number of days the light was used (as determined from online sleep logs) in the first block of the analysis, followed by the specific change values for GMV in the second block. After controlling for covariates, the partial correlation coefficient calculated between GMV change and the cognitive/behavioral metrics.

2.5.4. Functional connectivity analysis

A single subject was removed from each group from subsequent fMRI analyses, as > 20% of their scans were identified as outliers. An independent samples *t*-test indicated no significant difference between groups in the number of outliers identified and incorporated into subsequent first level models at baseline ($p = .09$) and post-treatment ($p = .54$).

Here, we used the two GMV clusters identified in the previous analysis (i.e., left pulvinar (LPul) and right pulvinar (RPul)) as seed regions for resting state functional connectivity (rsFC) analyses. Functional connectivity analyses were performed with a seed-to-voxel driven approach within the CONN toolbox V17.f (Whitfield-Gabrieli and Nieto-Castanon, 2012). Preprocessed structural and resting state data had physiological and other noise sources identified as nuisance covariates using a component-based noise correction method (CompCor). The first acquisition image, images identified as outliers, nuisance covariates, as well as white matter and cerebrospinal fluid masks, were regressed out of the first level general linear models. The BOLD time series was then band pass filtered at 0.01–0.1 Hz. Individual subject seed-to-voxel whole-brain connectivity maps were created for the LPul and RPul seeds with the mean time series from each seed used as a predictor in a multiple regression General Linear Model (GLM). The resulting individual bivariate correlation coefficients were Fisher transformed into *Z*-scores for subsequent second level analyses.

2.5.4.1. Seed-to-voxel analysis. Two analyses were performed at the second level to create statistical parametric maps (SPMs) representing associated changes in functional connectivity for each seed region. Repeated measures two-way ANCOVAs were used to investigate the main effect on functional connectivity associated with BLT, with mean-centered age and mean-centered days light used as covariates within the models. SPMs for each seed were defined with a cluster-forming threshold (voxel-level uncorrected $P < .001$) and a cluster-level extent threshold (Family Wise Error (FWE) corrected $P < .05$), using a positive contrast, to identify clusters of voxels associated with significant increases in connectivity to the seed region. No clusters were identified using the RPul seed, and three clusters were identified using the LPul seed. A mask was created for each cluster identified containing voxels that correlated with the LPul seed, in order to further

investigate Regions of Interest (ROIs) that contained voxels associated with significant change for the treatment group.

2.5.4.2. Seed-to-ROI analysis. To determine the extent of connectivity change observed for either treatment group, the BOLD time-series was extracted from each cluster identified in the seed-to-voxel analyses. Seed-to-ROI within group connectivity analyses were performed using paired *t*-tests with the identified ROIs (i.e. Left Parietal Cortex: LParC, Left Agranular Frontal Area: LAFA, and the Right Parietal Cortex: RParC), and the LPul seed. Mean-centered age and mean-centered days light used were included in the models as covariates and results were corrected for multiple comparisons ($p < .05$, seed-level FDR-correction).

The functional connectivity values for each connection were extracted for each individual for further correlation with cognitive/behavioral measures of interest. We applied hierarchical multiple regression procedures, including covariates for age and the number of days the light was used (as determined from online sleep logs) in the first block of the analysis, followed by the specific functional connectivity parameter of interest in the second block. After controlling for covariates, the partial correlation was determined for the parameters of interest.

2.6. Directed functional connectivity (DFC) analysis: Granger causality (GC)

Raw time-series data were band pass filtered using the Butterworth filter design using higher cutoff frequency of 0.0028 Hz (f_1) and a lower cutoff frequency of 0.1 Hz (f_2). Higher cutoff frequency was determined from time-series length ($n = 180$ time-points) and repetition time (TR = 2 s) as following:

$$f_1 = \frac{1}{n * TR} = 0.0028\text{Hz}$$

The lower cutoff frequency of 0.1 Hz was selected because low frequency (< 0.1 Hz) BOLD fluctuations often show strong correlations at rest (Cordes et al., 2001). The ensemble means from the time-series for each node were removed to make the zero-mean process for GC analysis. Moreover, these steps helped to remove slow trends and physiological noise associated with respiratory and cardiac activities.

A spectral interdependency method (Dhamala, 2013) was used to estimate the DFC between ROIs by quantifying the inter-relationships between their corresponding oscillatory mechanisms as a function of frequency (f) of oscillations. Directional influences between two regions, say a and b, are estimated from a spectral density matrix (S). Matrix S is constructed parametrically from the time-series of systems a and b using autoregressive (AR) modeling as following:

$$GC_{a\to b} = \ln \frac{S_{bb}(f)}{\widetilde{H}_{aa}(f)\sum_{aa}\widetilde{H}^{*}_{aa}(f)}$$

$$GC_{b\to a} = \ln \frac{S_{aa}(f)}{\widetilde{H}_{bb}(f)\sum_{bb}\widetilde{H}^{*}_{bb}(f)}$$

Here, $\widetilde{H}_{aa} = H_{aa} + \frac{\sum_{ab}}{\sum_{aa}}H_{ab}$ and $\widetilde{H}_{bb} = H_{bb} + \frac{\sum_{ab}}{\sum_{bb}}H_{ba}$ represent new transfer function matrices for a and b respectively in terms of noise covariance matrix, Σ and transfer function matrix *H*. Here, * denotes matrix adjoint. Mathematical details of these estimations are documented previously (Dhamala, 2013).

GC measures can be computed by either parametric or non-parametric methods (Dhamala et al., 2008a; Dhamala et al., 2008b). In this study, we used the parametric approach. The optimal model order for parametric approach was calculated by comparing power spectra from the parametric and non-parametric approaches (Dhamala et al., 2008a). Different model orders from 1 to 10 were tested, and the model order, which yielded the lowest power difference, was selected. The threshold level for statistically significant directed functional connection was estimated from surrogated data by using permutation test ($n = 1000$) and a gamma function under a null hypothesis of no interdependence at the significance level of $p < 10^{-4}$ (Blair and Karniski, 1993; Brovelli et al., 2004) ($p = 10^{-4}/16$, corrected for multiple comparisons). Previously, the GC technique has been shown to have consistent results with the dynamic causal modeling technique, in terms of directional connectivity from resting-state fMRI data (Bajaj et al., 2016).

For the present analyses, the range of GC metrics was extracted for each individual and correlated with cognitive/behavioral measures of interest. Using hierarchical multiple regression procedures, covariates including age, intracranial volume, and the number of days the light was used were entered at a first block, followed by the specific GC range parameter of interest at the second block, and the partial correlation was determined for the parameters of interest.

2.7. Anatomical connectivity analysis: DTI

Diffusion MRI connectometry (Yeh et al., 2016) was performed to compare longitudinal pair-wise scans between pre and post-treatment conditions for both amber-light treatment (ALT) and blue-light treatment (BLT) groups. The connectometry approach, which is implemented in DSI Studio, uses a permutation test to perform the longitudinal pairwise comparison between white-matter pathways. Tracts, which showed significant longitudinal differences along axonal fiber directions, were identified using a deterministic tractography algorithm (Yeh et al., 2013). Group averages of local connectome were quantified in terms of their differences in density and diffusivity measurements of water diffusion, *including* fractional anisotropy (FA) as well as isotropic (ISO) diffusion. Here, FA is one of the most common *diffusivity* measures, which is defined for each voxel and represents how fast water diffuses, whereas ISO is a *density* measure and represents how much water diffuses in an isotropic fashion. Both FA and ISO components were estimated using the Q-space diffeormophic reconstruction (QSDR) (Yeh and Tseng, 2011) approach implemented in DSI Studio. QSDR is a model-free approach, which calculates the distribution of water diffusion using a high-resolution standard brain atlas constructed from 90-diffusion spectrum imaging datasets in the ICBM-152 space. Automated registration to standard template space was used for each subject. All the regions of interest (ROIs) were transformed into MNI space in order to perform diffusion MRI connectometry in QSDR-space. A seed-count of 5000 sub-voxels for each region (LPul, LParC and LAFA) was used for connectometry analysis. All the ROIs were dilated to 3 mm to extend to white matter. Tracts with differences in FA and ISO diffusion were identified for all the connections, which showed significant involvement in functional connectivity analysis i.e., between LPul and LParC and between LPul and LAFA. To limit the tracts between LPul and LAFA, LPul was used as a seed region as well as an end region and LAFA was used as an end region. A lower T-value threshold of 0.5 was used to identify tracts which were more sensitive to light treatment. Track pruning was conducted using 10 iterations, and tract length threshold was 30 voxels. A total of 10,000 permutations and false discovery rate (FDR) of 0.05 were used to obtain the null distribution of the tract length. Subject-wise differences for the tracts that showed differences (at FDR between 0 and 0.2) in either FA or ISO diffusion measures were extracted for further correlation analysis with behavioral parameters. Using hierarchical multiple regression procedures, covariates including age, intracranial volume, and the number of days the light was used (as determined from online sleep logs) were entered at a first block, followed by the specific ISO diffusion parameter of interest at the second block, and the partial correlation was determined for the parameters of interest.

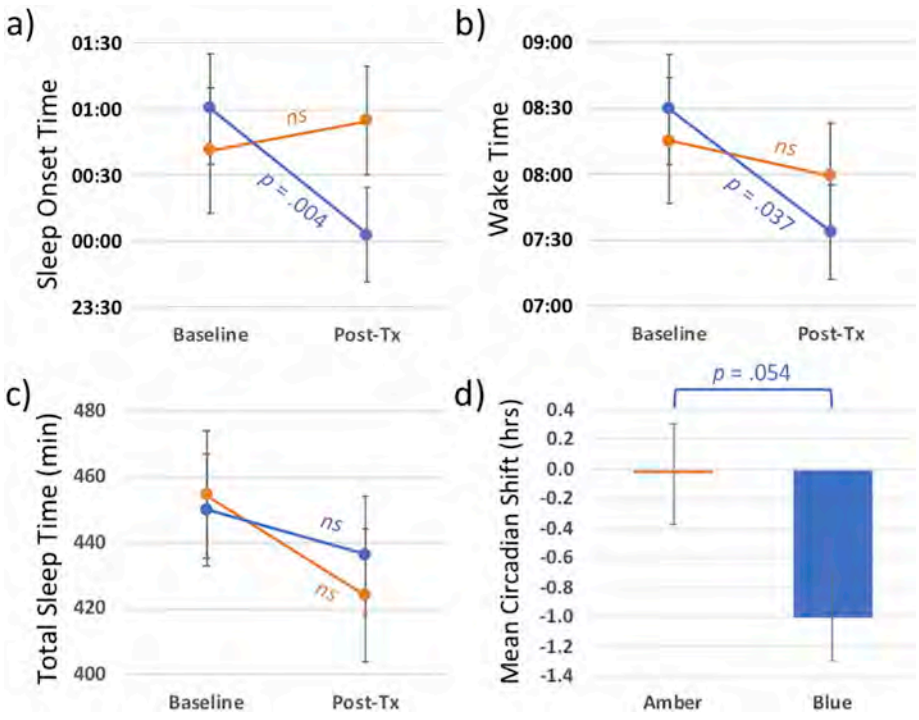


Fig. 3. Effects of light treatment on actigraphic sleep measures. (a) Blue light shifted sleep onset time by 57.5 min earlier by the end of treatment, versus no change for the amber group. (b) Blue light shifted wake time by 55.9 min earlier by the end of treatment, but there was no difference for amber light. (c) There was no significant effect of light condition for change in total sleep time (TST) from pre- to post-treatment. (d) A comparison of the midpoint of sleep onset and wake time for each light group showed that blue light was associated with a non-significant trend toward a circadian phase advancement in the sleep period of 60.1 min by the end of treatment. Error bars represent 1 SE. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Baseline metrics

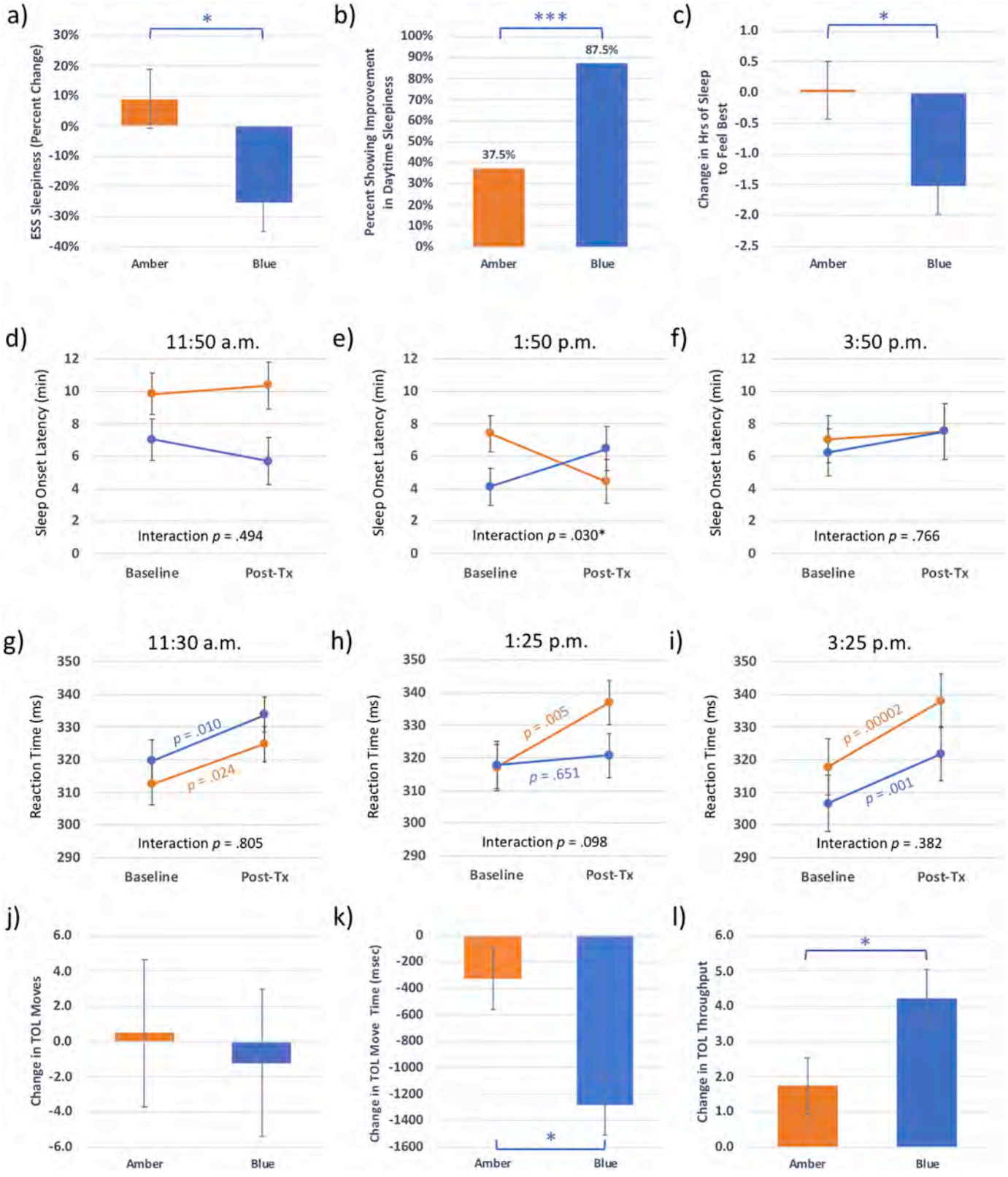
As evident in Table 1, light condition groups were similar on key variables at baseline, including sex, age, years of education, number of previous concussions, months since injury, concussion severity, depression, functional outcomes of sleep, chronotype, and days of compliance with light treatment (determined from daily time-stamped website diary completion). Half of participants (n = 16) reported only one concussion, while half reported more than one lifetime concussion (range 1 to 7 total). Of those reporting more than one concussion, the modal response (i.e., endorsed by 5 participants) was 2 head injuries.

3.2. Actigraphic sleep

BLUE light produced a significant phase advance in sleep onset and offset times relative to AMBER light. After accounting for covariates (baseline concussion symptoms, loss of consciousness (LOC) from the most recent concussion, depression (BDI), age), there was a significant light-condition x time interaction, $F(1, 21) = 6.16$, $p = .022$ (Fig. 3a). Over the course of treatment, planned comparisons showed that participants in the BLUE condition were phase advanced in sleep onset times, generally falling asleep 57.5 min earlier in the final week of the study compared to baseline ($p = .004$), while those in the AMBER condition fell asleep 13.8 min later compared to baseline ($p = .508$). Overall, 80% of participants in the BLUE condition showed some evidence of earlier sleep onset, while 58.3% of those in the AMBER group did ($\chi^2 = 1.50$, $p = .221$). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 13.04 (95% CI: 0.84 to 202.52; $p = .066$. Further, planned comparisons showed that participants in the BLUE condition were awakening 55.9 min earlier by the final week of treatment compared to baseline ($p = .037$), whereas the AMBER condition was awakening only 16.1 min earlier after treatment ($p = .576$; see Fig. 3b). Overall, 66.7% of participants in the BLUE condition showed some evidence of earlier wake times, while 50% of those in the AMBER group did ($\chi^2 = 0.77$, $p = .38$). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 3.68 (95% CI: 0.55 to 24.74; $p = .18$. There were no significant changes in mean total sleep time (TST) per night between pre- and post-treatment assessments, regardless of light-condition (all p-values > .05; see Fig. 3c). There was a nonsignificant trending difference between light-condition groups in the extent of circadian phase shift (CPS; i.e., taking the midpoint between sleep onset and offset for each participant) from baseline, $F(1, 21) = 4.18$, $p = .054$ (see Fig. 3d), such that those in the BLUE light condition showed an average circadian phase advance in the midpoint of the sleep period of 60.1 min, whereas those in the AMBER light condition shifted earlier by only 1.9 min on average. Overall, while 73.3% of participants who received BLUE light showed at least some evidence of phase advancement, 58.3% of those in the AMBER group also showed at least some phase advancement ($\chi^2 = 0.675$, $p = .411$). After accounting for covariates (described above), the odds ratio (OR) for showing any phase advancement with BLUE light compared to AMBER was 7.34 (95% CI: 0.59 to 90.71; $p = .12$.

3.3. Sleepiness and subjective sleep need

Relative to placebo, the BLUE light intervention led to reduced typical daytime sleepiness $F(1,26) = 5.49$, $p = .027$ (see Fig. 4a). Moreover, we found that 87.5% of the participants in the BLUE light condition showed reduced sleepiness scores from pre- to post-treatment, whereas only 37.5% of those in the AMBER placebo condition showed any measurable reduction in sleepiness over the same time frame (($\chi^2 = 8.53$, $p = .003$; see Fig. 4b). After controlling for covariates (described above), the odds ratio (OR) for showing any improvement in daytime sleepiness was 25.63 (95% CI: 2.76 to 237.84; $p = .004$; Nagelkerke $R^2 = 0.446$). We also found that the number of hours necessary to subjectively "feel best" was reduced for the BLUE light condition ($M = -1.51$, $SE = 0.47$) relative to AMBER ($M = 0.043$, SE = 0.47), $F(1,26) = 4.99$, $p = .034$ (see Fig. 4c).



(caption on next page)

Fig. 4. Effects of light treatment on behavioral variables. (a) Blue light led to a significant reduction in daytime sleepiness scores on the Epworth Sleepiness Scale (ESS), with (b) a significantly greater percentage of blue light participants showing some improvement in daytime sleepiness relative to amber participants. (c) Blue light was associated with a significant reduction in the number of nightly hours of sleep that participants reported needing to feel their best, relative to the amber group. (d-f) Sleep onset latency on the multiple sleep latency test (MSLT) was unaffected by light condition in the late morning (11:50 a.m.) or late afternoon (3:50 p.m.), but showed a significant interaction for the early afternoon "post-lunch dip" period. Similarly, (g-i) psychomotor vigilance test reaction time did not differ between groups during the late morning (11:30 a.m.) or late afternoon (3:25 p.m.), but was affected by blue light only in the early afternoon. Although there was (j) no effect of light condition on the total number of moves from the Tower of London (TOL) test, (k) blue light was associated with a significant improvement in average bead movement times relative to amber light, and (l) when speed and accuracy were combined as a metric of "throughput", blue light was associated with significantly more correct moves per minute than the amber placebo group. (*$p < .05$), **$p < .01$, ***$p < .005$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

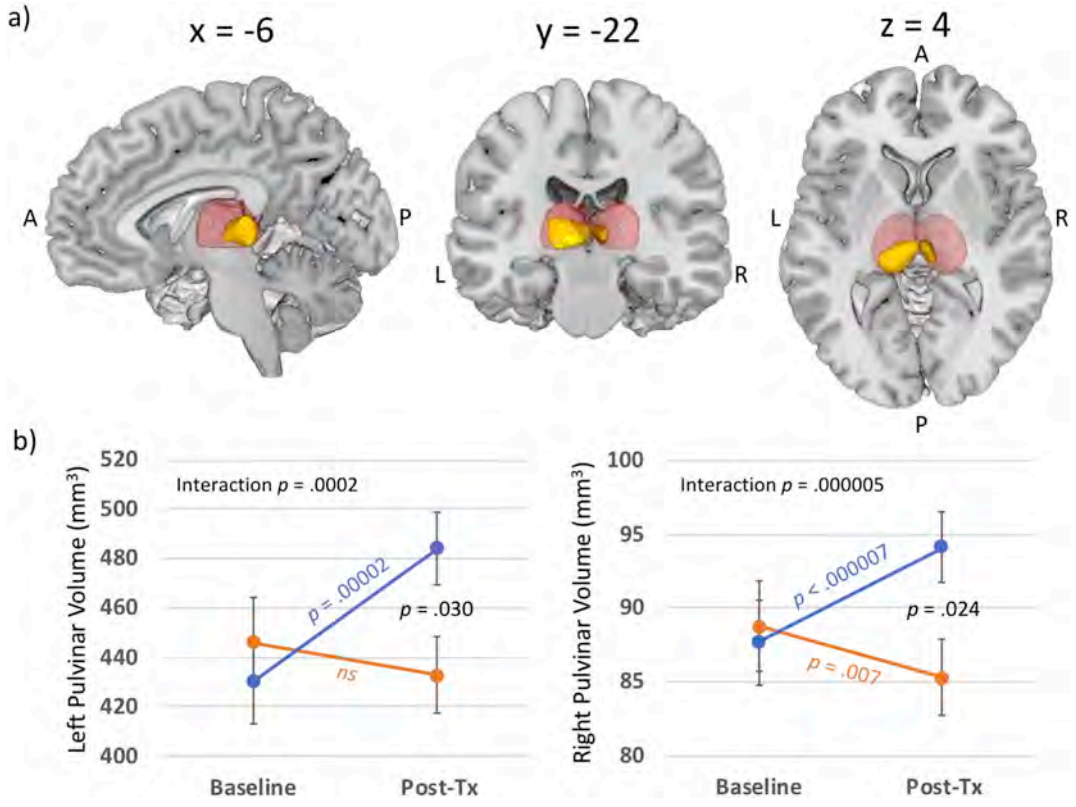


Fig. 5. Voxel-based morphometry results for blue versus amber light treatment. Results of a whole brain voxel-based morphometry (VBM) analysis comparing baseline and post-treatment changes for those receiving the blue light condition. (a) The figure shows the sagittal (left) coronal (middle) and axial (right) orientations. This analysis showed significant increases in gray matter volume (GMV) within the left (567 voxels; MNI: x = −3, y = −22, z = 3) and right (119 voxels; MNI: x = 3, y = −22, z = 3) posterior thalamic volume for those receiving the BLUE light intervention ($p_{FWE} < 0.05$). (b) Extracted volumes from each of these clusters are plotted in the figures for visualization for the left and the right thalamic regions for the BLUE and AMBER groups separately. The location of the left and right thalami are represented by the red wire mesh areas of the figure. It is clear that BLUE light was associated with significant increases in the volume of both the left and right posterior regions, but this was not evident for the same regions in the AMBER group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. MSLT

As an objective measure of daytime sleepiness/alertness, participants completed a modified version of the MSLT over three time points at baseline and post-treatment. Notably, it was only the second MSLT, occurring in the early afternoon (1:50 p.m.) proximal the "post-lunch dip" (Monk, 2005), that showed a significant light-condition x time interaction, $F(1, 26) = 5.26$, $p = .030$ (see Fig. 4d–f), suggesting that from pre- to post-treatment, participants in the BLUE light condition showed increased latency to fall asleep during the mid-day (i.e., were more alert). There were no significant light-condition x time interactions for the early morning or late afternoon MSLT sessions.

3.5. Cognitive/behavioral performance

Participants completed multiple cognitive and behavioral tasks at baseline and after 6-weeks of intervention with either the BLUE or AMBER light.

3.5.1. Psychomotor vigilance

At the first psychomotor vigilance test (PVT), which occurred in the late morning (11:30 a.m.), there was no significant light-condition x time interaction, $F(1, 22) = 0.062$, $p = .805$ (see Fig. 4g), with both groups slowing in reaction time (RT) during the post-treatment session relative to baseline, and no group differences. By the second PVT, in the early afternoon (1:25 p.m.), near the "post-lunch dip", there was a non-significant light-condition x time interaction, $F(1, 22) = 2.985$, $p = .098$ (see Fig. 4h), with post-hoc tests indicating that from pre- to post-treatment, participants in the AMBER light condition showed significant slowing of RT ($p < .005$), while those participants in the BLUE light condition sustained RT from pre- to post-treatment. Finally, by late afternoon (3:25 p.m.), the light-condition x time interaction remained non-significant $F(1, 22) = 0.797$, $p = .382$ (see Fig. 4i).

3.5.2. Neuropsychological performance

Contrary to predictions, light condition had no significant effect on mean performances on a brief neurocognitive performance battery (RBANS), which included immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory, and RBANS Total Score.

3.5.3. Executive functioning

On the Tower of London (TOL), a classic executive function planning task, the light condition did not affect the number of moves required to solve the puzzles between pre- and post-treatment, $F(1,26) = 0.08$, $p = .79$ (see Fig. 4j). However, the light-condition did affect the time taken to solve the puzzles, $F(1,26) = 7.45$, $p = .01$ (see Fig. 4k). On average, participants who underwent the BLUE wavelength light condition were 1280 (SE = 234) ms faster in completing each move following treatment, while those in the AMBER placebo condition improved by only 325 (SE = 234) ms per move. When speed and accuracy were combined as a measure of "throughput," there was a significant effect of light condition, $F(1,26) = 4.26$, $p = .049$. As shown in Fig. 4l, participants in the BLUE light condition showed an increase in the number of correct bead placements of 4.23 (SE = 0.83) per minute, whereas those in the AMBER condition increased by only 1.73 (SE = 0.83) per minute after treatment. Overall, most participants showed at least some improvement in TOL performance, regardless of condition, with 93.8% of participants in the BLUE group and 81.3% of participants in the AMBER group showing greater throughput after 6-weeks ($\chi^2 = 1.143$, $p = .285$). After accounting for covariates (described above), the odds ratio (OR) for showing any improvement in throughput with BLUE light compared to AMBER was 6.50 (95% CI: 0.41 to 102.15; $p = .183$.

3.6. Gray matter volume (GMV)

To examine morphometric volume changes in the brain, the anatomical brain images obtained during the MRI scan were analyzed in SPM12 with a 2 between (BLUE vs. AMBER) x 2 within (baseline vs. post-treatment) mixed analysis of covariance (ANCOVA), controlling for age, intracranial volume, and the number of days the light device was used. The ANCOVA yielded a large bilateral cluster (807 voxels, $p_{FWE} < 0.05$; MNI: x = 0, y = −21, z = 3) reflecting a significant light dependent change in volume from pre- to post-treatment. This region was constrained to the pulvinar regions of the left (LPul) and right (RPul) thalamus (Fig. 5a). Given the significant interaction, we examined the effects of each light condition individually. As shown in Fig. 5b, a pre- to post-treatment *t*-test for those receiving the BLUE light condition showed that this effect was driven primarily by an increase in thalamic GMV (bilateral) ($p_{FWE} < 0.05$), but this was not evident for the AMBER light condition.

Multiple regression was used to determine the partial correlations between changes in pulvinar volume and performance metrics. As shown in Fig. 6a–c, after controlling for age, intracranial volume, and the number of days of light device use, greater volume increases in the pulvinar region of the left thalamus were associated with faster bead pickup time, faster total move time on the TOL, and with a slight increase in subjective ratings of sleepiness at post-treatment, measured using the SSS. Right thalamic volume changes were not associated with any measured changes in cognitive/behavioral scores.

3.7. Functional connectivity

Building on the GMV findings above, we used the two previously identified thalamic clusters (i.e., LPul and RPul) as seed regions in a seed-to-voxel and seed-to-ROI resting state functional connectivity (rsFC) analysis. Repeated measures two-way ANCOVAs were used to investigate the main effect of light-condition on rsFC from pre- to post-treatment.

3.7.1. Seed-to-voxel analysis

Relative to the AMBER light condition, individuals in the BLUE light condition showed increased rsFC from pre- to post-treatment between the LPul seed and voxels comprising three separate areas (Fig. 7a), including a region in the left parietal cortex (LParC; $\beta = 0.34$, $p = .001$), the right parietal cortex (RParC; $\beta = 0.31$, $p < .001$), and left agranular frontal area (LAFA; $\beta = 0.34$, $p < .001$). In contrast, the RPul seed region did not show any significant increase in connectivity with other voxel clusters in the brain.

3.7.2. Seed-to-ROI analysis

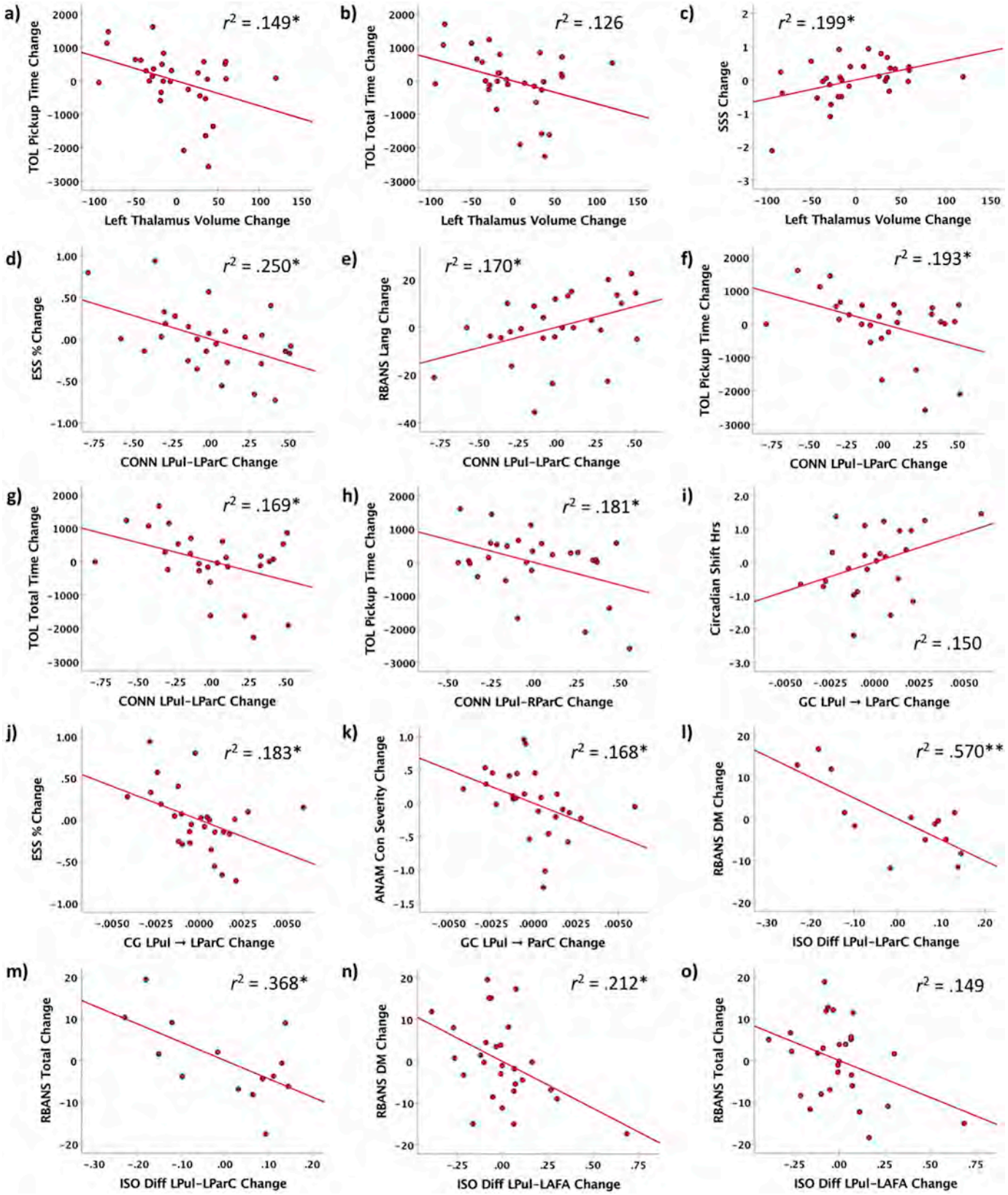
Within each light-condition, we examined the ROI-to-ROI connectivity. Consistent with the seed-to-voxel analysis, mean rsFC was significantly increased for the BLUE light condition over the course of treatment between the LPul and the three ROIs, including the LParC, $t(25) = 2.38$, $p = .03$, RParC, $t(25) = 2.26$, $p = .03$, and LAFA, $t(25) = 2.33$, $p = .03$). For the AMBER light condition, significant decreases in connectivity over the course of treatment between the LPul and ROIs were found for all three ROIs, including the LParC, $t(25) = -3.58$, $p = .002$, RParC, $t(25) = -3.65$, $p = .001$, and LAFA, $t(25) = -4.16$, $p < .001$ (Fig. 7b).

As shown in Fig. 6d–g, after controlling for standard covariates, increased rsFC between LPul and LParC ROIs from pre- to post-treatment was associated with a significant reduction in daytime sleepiness on the ESS ($r(23) = -0.50$, $p = .011$), increased scores on RBANS Language ($r(23) = 0.418$, $p = .038$), TOL average bead pickup time ($r(23) = -0.439$, $p = .028$), and TOL Average total move time ($r(23) = -0.411$, $p = .041$). Similarly, increased rsFC between the LPul and RParC was also associated with faster bead pickup time on the TOL ($r(23) = -0.425$, $p = .034$; Fig. 6h).

3.8. Granger causality (GC)

To determine if the rsFC connectivity change was "bottom-up" (i.e., increased thalamocortical connectivity) or "top-down" (i.e., increased corticothalamic connectivity), we next employed GC to determine the directional influence between the previously identified areas of interest. The previous analysis revealed that FC was only evident for the left pulvinar connections (i.e., LPul—LParC, LPul—LAFA, and LPul—RParC). However, we did not find structural connectivity between LPul and RParC for any subject/condition; therefore only four connections (C1: LPul to LParC, C2: LParC to LPul, C3: LPul to LAFA, and C4: LAFA to LPul) were further interrogated using GC.

GC-frequency spectra for all four directional connections (C1, C2, C3, and C4) were computed. The estimated threshold level of GC strength used to identify significant connections was 0.0142 at $p < 10^{-4}$ (permutation method; corrected for multiple comparisons). In Fig. 7c–f, it is evident that GC-frequency spectra for all four connections and for all four conditions (AMBER: APre-T (Amber-light pre-treatment), APost-T (Amber-light post-treatment); BLUE: BPre-T (Blue-light pre-treatment) and BPost-T (Blue-light post-treatment)) had peaks at frequency < 0.1 Hz, and showing the connectivity patterns for APost-T (Fig. 7d) and BPost-T (Fig. 7f). Within the AMBER group, we found that the C1 connection exceeded threshold only at baseline (APre-T), but that connection did not exceed the threshold at APost-T (Fig. 7c). By contrast, in the BLUE group, this same connection did not reach the threshold at BPre-T, but exceeded the threshold at BPost-T (Fig. 7e–f). Connection C2 did not exceed the threshold for either BLUE or AMBER conditions (Fig. 7c and e). In addition, two connections (C3 and C4) exceeded the threshold for connectivity at pre- and post-treatment for both the AMBER and BLUE groups, suggesting that these connections were not meaningfully affected by light condition. In sum, the findings suggest that connection C1 (LPul to LParC) was significantly affected by light condition, showing a decrease in directed bottom-up connectivity in the AMBER group and an increase in this bottom-up connectivity within the BLUE group. Other connections



(caption on next page)

Fig. 6. Association of changes in behavioral measures with changes in voxel-based morphometry, directed connectivity strength, and isotropic diffusion (ISO). Greater increases in the volume of the left pulvinar region of the thalamus was associated with (a) faster pickup speed, (b) a trend toward faster total move time on the Tower of London (TOL), and (c) slight increases in subjective sleepiness on the Stanford Sleepiness Scale (SSS). Changes in functional connectivity strength from pre- to post-treatment for the Left Pulvinar (LPul) and Left Parietal Cortex (LParC) were associated with (d) decreases in daytime sleepiness on the Epworth Sleepiness Scale (ESS), (e) improvements in language processing on the Repeatable Battery for Neuropsychological Assessment (RBANS), (f) faster average bead pickup time on the TOL, (g) faster total move time on the TOL. Similarly, increased functional connectivity between the LPul and Right Parietal Cortex (RParC) was associated with (h) faster total move time on the TOL. We found a significant positive association between changes in directed connectivity strength (LPul to LParC) and (i) changes in circadian shifts, and significant negative associations with (j) changes in daytime sleepiness, and (k) scores on the concussion severity scale. We also found a significant negative association between changes in ISO for fibers connecting LPul and LParC and (l) changes in delayed memory scores, as well as (m) total scores on RBANS battery. ISO for fibers connecting LPul and LAFA also showed a significant negative association with (n) changes in delayed memory scores and (o) total scores on RBANS battery.

either remained below the threshold or were essentially unchanged by light condition.

As in the previous analyses, we also examined the cognitive/behavioral correlates associated with changes in causal flow. As shown in Fig. 6i–k, after controlling for age, intracranial volume, and the number of days of light device use, increased causal influence of LPul on LParC from pre- to post-treatment was not significantly associated with change in circadian phase (r (19) = 0.387, p = .083), but was associated with a significant reduction in typical daytime sleepiness on the ESS (r (23) = −0.427, p = .033), and a significant reduction in concussion severity scores on the ANAM (r (23) = −0.409, p = .042).

3.9. Anatomical connectivity

We next examined whether the connectivity changes reported above would be associated with corresponding changes within axonal tracts connecting the identified regions.

We found that there were no tracts with significant differences between pre- and post-treatment for fractional anisotropy (FA) (FDR > 0.05) in either AMBER or BLUE light conditions (Fig. 8a). However, we found tracts connecting LPul and LParC with a significant reduction in isotropic diffusion (ISO) (a measure of white matter disintegrity) following treatment for the BLUE (Fig. 8b) (FDR < 0.05), but not for the AMBER light condition (FDR > 0.05). Furthermore, we found that tracts connecting LPul and LAFA showing reduced ISO diffusion following treatment for the BLUE light condition at a less stringent threshold (FDR = 0.11) (Fig. 8b) and a significant increase in ISO following treatment for AMBER light condition (FDR < 0.05) (Fig. 8c).

We examined the cognitive/behavioral correlates of changes in ISO diffusion within specific white matter tracts discussed above. For the BLUE light condition, subject-wise differences for the tracts connecting LPul and LParC, and LPul and LAFA, were extracted. For the AMBER light condition, subject-wise differences for the tracts connecting LPul and LAFA were extracted. As shown in Fig. 6l–o, only changes in RBANS measures showed significant associations with changes in white matter integrity. Specifically, after controlling for age, intracranial volume, and the number of days the light device was used, decreases in ISO diffusion from pre- to post-treatment for the BLUE light condition were associated with improved visual construction (RBANS VC) performance (r (9) = −0.714, p = .014), improved delayed memory (RBANS DM) performance (r (9) = −0.755, p = .007), and improved total neuropsychological (RBANS Total) performance (r (9) = −0.607, p = .048). For the sample as a whole, decreases in ISO diffusion between LPul and LAFA were associated with improved delayed memory (RBANS DM) performance (r (23) = −0.460, p = .021), and a trend toward greater total neuropsychological (RBANS Total) performance (r (23) = −0.386, p = .057).

4. Discussion

During a 6-week randomized placebo-controlled trial of daily light exposure, we found that 30-min of morning blue-wavelength light was more effective than amber-wavelength placebo light at shifting sleep-wake periods, reducing subjective and objective sleepiness, and improving cognitive performance among participants recovering from mTBI. Moreover, compared to amber light, the blue light intervention was associated with increases in gray matter volume within the posterior thalamus and greater structural and functional thalamocortical connectivity, as well as multiple associations between improvements in cognitive performance and the observed physiological changes. These findings are consistent with the hypothesized role of morning blue-wavelength light in phase advancing the circadian rhythm of sleep and alertness, and the postulated role of sleep in accelerating neural repair processes. Together, these findings point to the ipRGC-SCN-mediated circadian system as a critical contributor to brain repair processes and suggest a potential target mechanism for intervention to facilitate recovery following brain injury.

Our findings are consistent with well-established evidence that blue light exposure affects the timing of sleep-wake cycles through stimulation of the retinohypothalamic system (Geerdink et al., 2016), as we found that the BLUE light condition showed a trend toward phase-advancement of the midpoint of participants' sleep periods by just over one hour by the end of treatment, with no meaningful change observed for the AMBER light condition. Notably, this alteration in sleep timing was not associated with a measurable change in total sleep time based on actigraphy. While light treatment has shown robust effects for shifting sleep timing (Geerdink et al., 2016; Rosa et al., 2018; Tahkamo et al., 2018), prior research demonstrates mixed outcomes in terms of modifying total sleep time (TST) or subjective perception of time spent asleep (Figueiro et al., 2014; Richardson et al., 2018; Saxvig et al., 2014; Wu et al., 2018). It should be borne in mind, however, that our primary measure of TST was based entirely on wrist-actigraphy, which has a satisfactory accuracy level (> 80%) (Marino et al., 2013), but may not be sensitive enough to detect the subtler effects of light treatment on sleep architecture.

Recent work demonstrates that daily morning blue light therapy improves subjective fatigue and daytime sleepiness in patients with TBI (Sinclair et al., 2014). Our results extend these earlier findings, as our BLUE light condition led to a significant decline in subjective daytime sleepiness and a reduction in self-perceived sleep requirement relative to the AMBER placebo condition. Thus, even though BLUE light did not lead to an increase in total sleep time after treatment, participants treated with BLUE light reported a reduced tendency to “doze” off throughout the day, as well as a decrease in the total time asleep necessary to feel their best. Moreover, BLUE light use was also associated with objectively greater daytime alertness, as evidenced by extended latencies to fall asleep during the early afternoon post-lunch dip, compared to the placebo condition, when measured using polysomnography. The blue-wavelength light intervention was also associated with sustained psychomotor vigilance performance in the early afternoon. Thus, the treatment is associated with improvements in both subjective and objective daytime alertness for individuals recovering from mTBI during times when drowsiness is particularly likely to occur.

When directly comparing the groups on neurocognitive performance, we found a clear superiority in blue-wavelength treatment compared to a placebo light treatment on performance during the TOL, a classic test of visual planning and sequencing ability. Relative to AMBER light, daily exposure to BLUE light in the morning was

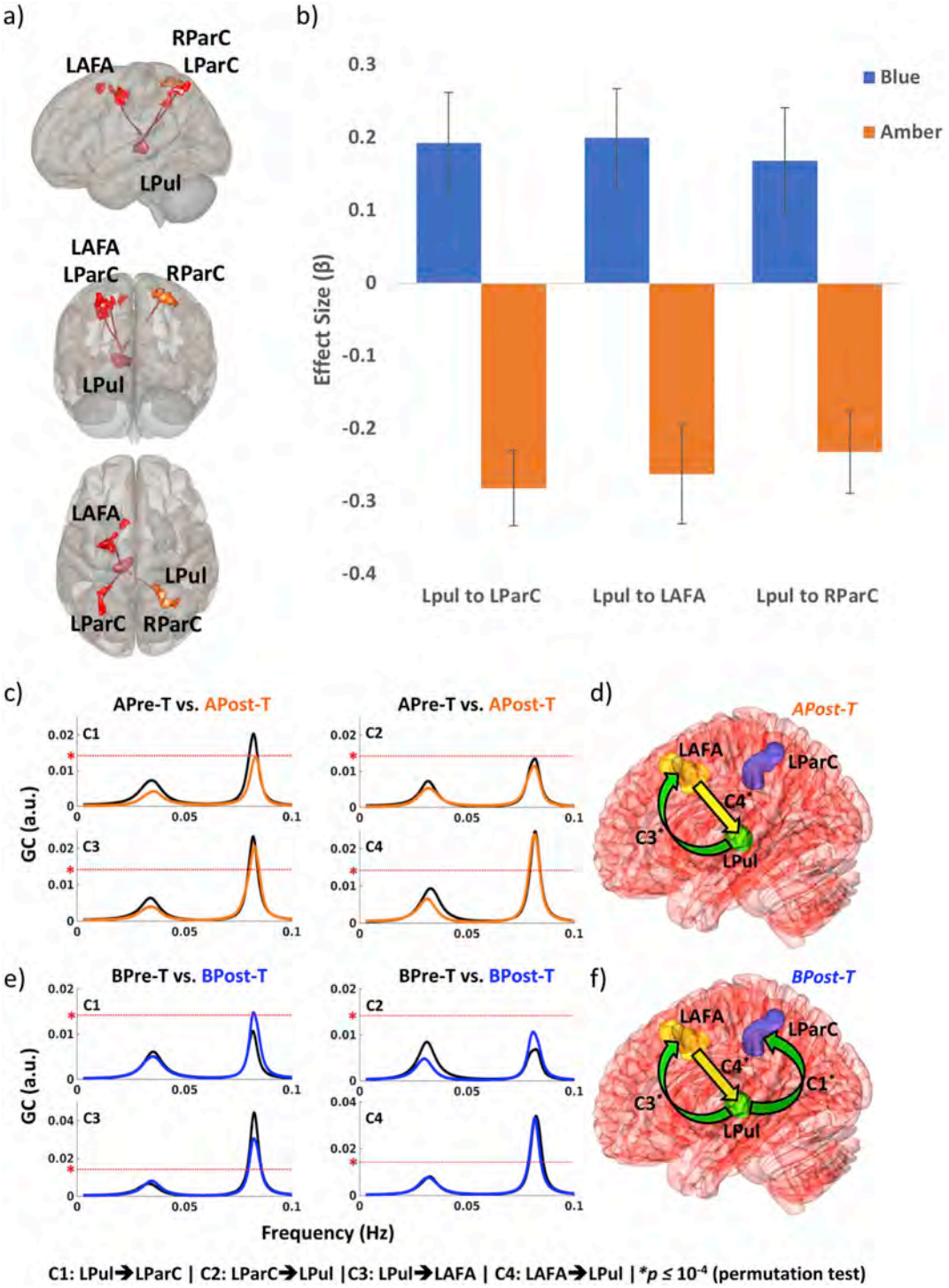


Fig. 7. Functional Connectivity (FC) and Granger causality measures. (a) The extracted volumes from the VBM analysis were used to investigate the main effect on FC associated with the observed structural changes in the left thalamic (LPul) and right thalamic (RPul) regions. Individual subject seed-to-voxel whole brain connectivity maps identified three clusters of voxels associated with significant increases in connectivity to the LPul. The extracted clusters (i.e. Left Parietal Cortex: LParC, Left Agranular Frontal Area: LAFA, and the Right Parietal Cortex: RParC), are plotted in the figures for visualization with the strength of the correlation represented by the colour of the line. (b) The resting-state correlations for FC between the LPul and ROIs were extracted as beta weights for each participant and the correlation is plotted for the BLUE and AMBER groups separately with error bars representing the within-group standard errors. (c-f) Next we show that the peaks from GC-frequency spectra are at frequency $<$ 0.1 Hz for the directed connectivity from the LPul to LParC (C1), LParC to LPul (C2), LPul to LAFA (C3), and LAFA to LPul (C4) for both ALT group (c-d) (Pre-treatment: APre-T and Post-treatment: APost-T), and BLT group (e-f) (Pre-treatment: BPre-T and Post-treatment: BPost-T). Dotted lines represent the threshold value of GC estimated from the permutation test at p £10^{-4}. Overall, GC measures between LPul and LAFA (C3 and C4) for APost-T (e) and between LPul and LAFA (C3 and C4) as well as from LPul to LParC (C1) for BPost-T (f) showed significant directional influence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

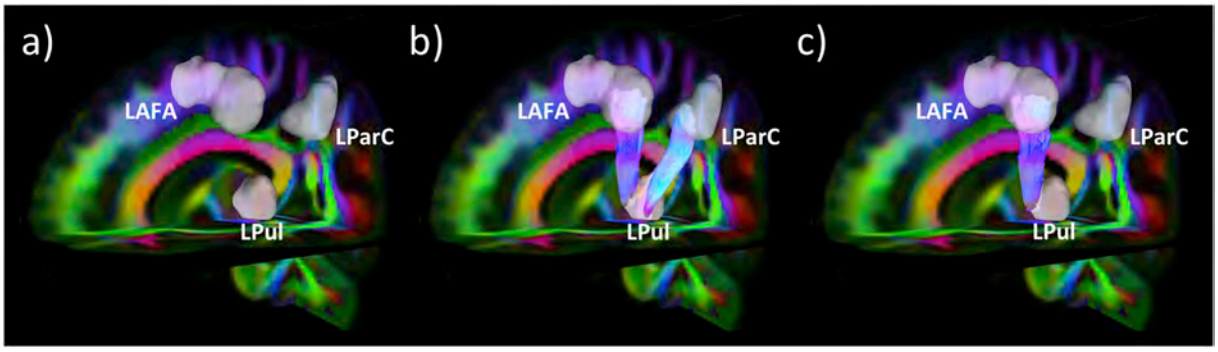


Fig. 8. Diffusion connectometry analysis for amber-light treatment (ALT) and blue-light treatment (BLT) groups. We found that there were no tracts with significant differences between pre- and post-treatment conditions for fractional anisotropy (FA) (FDR $>$ 0.05) in either ALT or BLT group (a). However, we found tracts connecting LPul and LParC with significant reduction in isotropic diffusion (ISO) following treatment for BLT group (b) (FDR $<$ 0.05), but not for ALT group (FDR $>$ 0.05). Also, there were tracts connecting LPul and LAFA with reduced ISO following treatment for BLT group (FDR = 0.11) (c) and a significant increase in ISO following treatment for ALT group (FDR $<$ 0.05) (c). Here, identified tracts are colour-coded in transverse (right-left: red), longitudinal (anterior-posterior: green) and horizontal (foot-head: blue) directions and overlaid on colour-coded FA image. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associated with a significant improvement in the completion speed of each move. Moreover, participants in the BLUE light condition also made more correct moves per unit of time, suggesting greater efficiency in planning and execution when compared to those in the placebo group. To our knowledge, this is the first study to examine the effects of daily blue-wavelength light exposure on executive function tasks that incorporate planning and sequencing ability. Further research will be necessary to determine the extent and nature of neurocognitive changes produced by daily exposure to blue light in the morning.

While prior research suggests an association between regular exposure to blue light in the early waking hours and reduced fatigue and sleepiness in patients with TBI (Sinclair et al., 2014), the underlying neurobiological mechanisms contributing to these effects have remained unclear. Recently, Clark and colleagues demonstrated that fatigue following mTBI was explicitly associated with reduced thalamic volume (Clark et al., 2018). We found that the BLUE light intervention was associated with a significant increase in GMV of the mediodorsal and pulvinar regions of the thalamus bilaterally compared to the AMBER light condition. Some studies suggest that the thalamus is particularly vulnerable to the disruptive effects of mTBI (Bolzenius et al., 2018; Naess-Schmidt et al., 2017), perhaps due to its centralized location and extensive anatomical/functional connectivity. Furthermore, increases in mean thalamic volume correlate with the recovery of cognitive performance in individuals with mTBI (Munivenkatappa et al., 2016). Sleep loss is associated with decreased thalamic volumes, suggesting a potential role for sleep in modulating the volume of the thalamus (Dai et al., 2018; Liu et al., 2014). Our findings suggest that alterations in circadian rhythms or improvements in sleep secondary to daily blue light exposure may contribute to the observed structural changes and associated performance outcomes in this study.

The BLUE light condition was associated with increased functional connectivity between the left thalamus and cortical regions in the frontal and parietal cortex, relative to the AMBER condition, and this change correlated with improvements in daytime sleepiness, language performance, and executive functioning. This effect is consistent with prior research showing negative correlations in thalamocortical functional connectivity and fatigue in patients with mTBI (Nordin et al., 2016). Compared to non-injured controls, patients with mTBI have decreased functional connectivity between the thalamus and cortical regions including the dorsal attention network and the frontoparietal control network (Banks et al., 2016). Moreover, these patterns of disrupted connectivity tend to attenuate throughout recovery, with positive associations between symptom improvement and increases in connectivity across these networks (Banks et al., 2016). Our findings suggest that daily morning exposure to blue-wavelength light may help facilitate the dynamic relationship between the restoration of connectivity with cognitive and symptom recovery.

Finally, we examined whether the increases in the structural connectivity of axonal pathways secondary to the intervention were associated with changes in neurocognitive performance. Prior research in patients with mTBI demonstrates reductions in white matter anisotropy between the left thalamus and prefrontal regions in patients with mTBI (Aoki and Inokuchi, 2016). Our findings suggest that blue light treatment may facilitate the reversal of some of these deficits, as we found increased structural integrity in axonal tracts connecting the left thalamus to the left prefrontal and left parietal cortex after blue light treatment. Moreover, the magnitude of increases in the structural integrity of these pathways correlated with improved neuropsychological performances, particularly those involving visual construction and delayed memory abilities. We propose that the post-treatment decreases in isotropic diffusion for these tracts may reflect increased myelination, due to the proliferation of oligodendrocyte precursor cells that have been previously shown to be enhanced by sleep (Bellesi et al., 2013). Future research will be necessary to verify this assertion.

Several methodological limitations should be kept in mind. These include modest capacity to monitor treatment compliance, lack of experimental control over the direction of gaze when using the light device, and the use of wrist actigraphy as a proxy for gold-standard nightly polysomnographic sleep recordings. Further, we also found that half of the participants reported experiencing more than one lifetime concussion. Unfortunately, we did not collect data on the time frame between multiple concussions, which is also a limitation. Finally, the present analysis only focused on primary outcome variables collected at baseline and after 6-weeks of treatment. Forthcoming work will explore actigraphic variables in depth at each week to determine whether sleep outcomes reach their peak before 6-weeks. With due consideration to these limitations, we believe that the present findings provide compelling evidence for the role of sleep and circadian systems in brain repair and suggest that stimulation of the ipRGC-SCN system, via daily exposure to morning blue-wavelength light, may offer an effective method for re-entraining the circadian system and facilitating recovery among individuals with a recent mTBI.

Acknowledgments

This study was funded by a grant from the U.S. Army Medical Research and Development Command (W81XWH-11-1-0056) to W.D.S.K.

References

Aoki, Y., Inokuchi, R., 2016. A voxel-based meta-analysis of diffusion tensor imaging in mild traumatic brain injury. Neurosci. Biobehav. Rev. 66, 119–126.
Arendt, J., 2006. Melatonin and human rhythms. Chronobiol. Int. 23, 21–37.
Bajaj, S., et al., 2016. Bridging the gap: dynamic causal modeling and granger causality analysis of resting state functional magnetic resonance imaging. Brain Connect. 6, 652–661.
Bajaj, S., et al., 2017. Blue-light therapy following mild traumatic brain injury: effects on white matter water diffusion in the brain. Front. Neurol. 8, 616.
Banks, S.D., et al., 2016. Thalamic functional connectivity in mild traumatic brain injury: longitudinal associations with patient-reported outcomes and neuropsychological tests. Arch. Phys. Med. Rehabil. 97, 1254–1261.
Beck, A.T., et al., 1996. BDI-II: Beck Depression Inventory Manual. Psychological Corporation, San Antonio, TX.
Bellesi, M., et al., 2013. Effects of sleep and wake on oligodendrocytes and their precursors. J. Neurosci. 33, 14288–14300.
Bellesi, M., et al., 2016. Contribution of sleep to the repair of neuronal DNA double-strand breaks: evidence from flies and mice. Sci. Rep. 6, 36804.
Bellesi, M., et al., 2018. Myelin modifications after chronic sleep loss in adolescent mice. Sleep. 41.
Blair, R.C., Karniski, W., 1993. An alternative method for significance testing of waveform difference potentials. Psychophysiology. 30, 518–524.
Bolzenius, J.D., et al., 2018. Relationships between subcortical shape measures and subjective symptom reporting in US Service members with mild traumatic brain injury. J. Head Trauma Rehabil. 33, 113–122.
Brovelli, A., et al., 2004. Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by granger causality. Proc. Natl. Acad. Sci. U. S. A. 101, 9849–9854.
Cajochen, C., et al., 2003. Role of melatonin in the regulation of human circadian rhythms and sleep. J. Neuroendocrinol. 15, 432–437.
Clark, A.L., et al., 2018. Fatigue is associated with global and regional thalamic morphometry in veterans with a history of mild traumatic brain injury. J. Head Trauma Rehabil. 33, 382–392.
Cordes, D., et al., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am. J. Neuroradiol. 22, 1326–1333.
Dai, X.J., et al., 2018. Plasticity and susceptibility of brain morphometry alterations to insufficient sleep. Front Psychiatry. 9, 266.
de Vivo, L., et al., 2017. Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. Science. 355, 507–510.
Dhamala, M., 2013. Spectral interdependency methods. In: Jaeger, D., Jung, R. (Eds.), Encyclopedia of Computational Neuroscience. Springer New York, New York, NY.
Dhamala, M., et al., 2008a. Analyzing information flow in brain networks with nonparametric granger causality. Neuroimage. 41, 354–362.
Dhamala, M., et al., 2008b. Estimating granger causality from fourier and wavelet transforms of time series data. Phys. Rev. Lett. 100, 018701.
Dinges, D.F., Powell, J.W., 1985. Microcomputer analyses of performance on a portable, simple, visual RT task during sustained operations. Behav. Res. Methods Instrum. Comput. 17, 652–655.
Durmer, J.S., Dinges, D.F., 2005. Neurocognitive consequences of sleep deprivation. Semin. Neurol. 25, 117–129.
Figueiro, M.G., et al., 2014. Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. Clin. Interv. Aging 9, 1527–1537.
Gao, B., et al., 2010. Sleep disruption aggravates focal cerebral ischemia in the rat. Sleep. 33, 879–887.
Geerdink, M., et al., 2016. Short blue light pulses (30 min) in the morning support a sleep-advancing protocol in a home setting. J. Biol. Rhythm. 31, 483–497.
Gilbert, K.S., et al., 2015. Sleep disturbances, TBI and PTSD: implications for treatment and recovery. Clin. Psychol. Rev. 40, 195–212.
Grima, N.A., et al., 2016. Circadian melatonin rhythm following traumatic brain injury. Neurorehabil. Neural Repair 30, 972–977.
VA/DoD Management of Concussion/mTBI Working Group, 2009. VA/DoD clinical practice guidelines for maagement of concussion/mild traumatic brain injury. J. Rehabil. Res. Dev. 46, CP1–68.
Hattar, S., et al., 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science. 295, 1065–1070.
Herscovitch, J., Broughton, R., 1981. Sensitivity of the stanford sleepiness scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. Sleep. 4, 83–91.
Honma, S., 2018. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J. Physiol. Sci. 68, 207–219.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 14, 540–545.
Killgore, W.D.S., et al., 2006. Impaired decision-making following 49 hours of sleep deprivation. J. Sleep Res. 15, 7–13.
Killgore, W.D.S., et al., 2007. The effects of 53 hours of sleep deprivation on moral judgment. Sleep. 30, 345–352.
King, P.R., et al., 2012. Psychometric study of the neurobehavioral symptom inventory. J. Rehabil. Res. Dev. 49, 879–888.
Lavie, P., 2001. Sleep-wake as a biological rhythm. Annu. Rev. Psychol. 52, 277–303.
Liu, C., et al., 2014. Long-term total sleep deprivation reduces thalamic gray matter volume in healthy men. Neuroreport. 25, 320–323.
Marino, M., et al., 2013. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep. 36, 1747–1755.
Monk, T.H., 2005. The post-lunch dip in performance. Clin. Sports Med. 24 (e15–23), xi–xii.
Munivenkatappa, A., et al., 2016. Role of the thalamus in natural recovery of cognitive impairment in patients with mild traumatic brain injury. Brain Inj. 30, 388–392.
Naess-Schmidt, E.T., et al., 2017. Microstructural changes in the thalamus after mild traumatic brain injury: a longitudinal diffusion and mean kurtosis tensor MRI study. Brain Inj. 31, 230–236.
Nordin, L.E., et al., 2016. Post mTBI fatigue is associated with abnormal brain functional connectivity. Sci. Rep. 6, 21183.
Oldfield, R.C., 1971. The assessment of handedness: the Edinburgh inventory. Neuropsychologia. 9, 97–111.
Orff, H.J., et al., 2009. Traumatic brain injury and sleep disturbance: a review of current research. J. Head Trauma Rehabil. 24, 155–165.
Panda, S., et al., 2002. Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. Science. 298, 2213–2216.
Panda, S., et al., 2005. Illumination of the melanopsin signaling pathway. Science. 307, 600–604.
Provencio, I., et al., 2000. A novel human opsin in the inner retina. J. Neurosci. 20, 600–605.
Qiu, X., et al., 2005. Induction of photosensitivity by heterologous expression of melanopsin. Nature. 433, 745–749.
Raikes, A.C., Killgore, W.D., 2018. Potential for the development of light therapies in mild traumatic brain injury. Concussion. 3, CNC57.
Rao, V., et al., 2008. Prevalence and types of sleep disturbances acutely after traumatic brain injury. Brain Inj. 22, 381–386.
Richardson, C., et al., 2018. A randomised controlled trial of bright light therapy and morning activity for adolescents and young adults with delayed sleep-wake phase disorder. Sleep Med. 45, 114–123.
Rorden, C., et al., 2007. Improving lesion-symptom mapping. J. Cogn. Neurosci. 19, 1081–1088.
Rosa, J.P.P., et al., 2018. Effect of bright light therapy on delayed sleep/wake cycle and reaction time of athletes participating in the Rio 2016 Olympic games. Chronobiol. Int. 35, 1095–1103.
Sapede, D., Cau, E., 2013. The pineal gland from development to function. Curr. Top. Dev. Biol. 106, 171–215.
Saxvig, I.W., et al., 2014. A randomized controlled trial with bright light and melatonin for delayed sleep phase disorder: effects on subjective and objective sleep. Chronobiol. Int. 31, 72–86.
Sheehan, D.V., et al., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33 (quiz 34–57).
Shekleton, J.A., et al., 2010. Sleep disturbance and melatonin levels following traumatic brain injury. Neurology. 74, 1732–1738.
Sinclair, K.L., et al., 2014. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. Neurorehabil. Neural Repair 28, 303–313.
Sullivan, K.A., et al., 2016. Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. Appl Neuropsychol. Adult. 23, 426–435.
Tahkamo, L., et al., 2018. Systematic review of light exposure impact on human circadian rhythm. Chronobiol. Int. 1–20.
Tononi, G., Cirelli, C., 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron. 81, 12–34.
Tucker, A.M., et al., 2010. Effects of sleep deprivation on dissociated components of executive functioning. Sleep. 33, 47–57.
Tzourio-Mazoyer, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 15, 273–289.
Verma, A., et al., 2007. Sleep disorders in chronic traumatic brain injury. J. Clin. Sleep Med. 3, 357–362.
Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connectivity. 2, 125–141.
Woo, C.W., et al., 2014. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. Neuroimage. 91, 412–419.
Wu, L.M., et al., 2018. The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. J. Clin. Sleep Med. 14, 31–39.
Xie, L., et al., 2013. Sleep drives metabolite clearance from the adult brain. Science. 342, 373–377.
Yeh, F.C., Tseng, W.Y., 2011. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage. 58, 91–99.
Yeh, F.C., et al., 2013. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One 8, e80713.
Yeh, F.C., et al., 2016. Connectometry: a statistical approach harnessing the analytical potential of the local connectome. Neuroimage. 125, 162–171.
Zunzunegui, C., et al., 2011. Sleep disturbance impairs stroke recovery in the rat. Sleep. 34, 1261–1269.

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ORIGINAL RESEARCH
published: 22 November 2017
doi: 10.3389/fneur.2017.00616

Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain

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Mild traumatic brain injury (mTBI) is a common and often inconspicuous wound that is frequently associated with chronic low-grade symptoms and cognitive dysfunction. Previous evidence suggests that daily blue wavelength light therapy may be effective at reducing fatigue and improving sleep in patients recovering from mTBI. However, the effects of light therapy on recovering brain structure remain unexplored. In this study, we analyzed white matter diffusion properties, including generalized fractional anisotropy, and the quantity of water diffusion in isotropic (i.e., isotropic diffusion) and anisotropic fashion (i.e., quantitative anisotropy, QA) for fibers crossing 11 brain areas known to be significantly affected following mTBI. Specifically, we investigated how 6 weeks of daily morning blue light exposure therapy (compared to an amber-light placebo condition) impacted changes in white matter diffusion in individuals with mTBI. We observed a significant impact of the blue light treatment (relative to the placebo) on the amount of water diffusion (QA) for multiple brain areas, including the corpus callosum, anterior corona radiata, and thalamus. Moreover, many of these changes were associated with improvements in sleep latency and delayed memory. These findings suggest that blue wavelength light exposure may serve as one of the potential non-pharmacological treatments for facilitating structural and functional recovery following mTBI; they also support the use of QA as a reliable neuro-biomarker for mTBI therapies.

Keywords: concussion, diffusion tensor imaging, fractional isotropy, isotropic diffusion, neuropsychological function, quantitative anisotropy, sleep, structural recovery

OPEN ACCESS

Edited by:
Stefania Mondello, University of Messina, Italy

Reviewed by:
Rao P. Gullapalli, University of Maryland Medical Center, United States
Shoji Yokobori, Nippon Medical School, Japan

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Specialty section:
This article was submitted to Neurotrauma, a section of the journal Frontiers in Neurology

Received: *03 September 2017*
Accepted: *06 November 2017*
Published: *22 November 2017*

Citation:
Bajaj S, Vanuk JR, Smith R, Dailey NS and Killgore WDS (2017) Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. Front. Neurol. 8:616. doi: 10.3389/fneur.2017.00616

INTRODUCTION

Mild traumatic brain injury (mTBI) is a common and often unobtrusive wound that occurs when kinetic energy is transferred to the brain through some form of traumatic event, such as a fall, blow to the head, or blast wave. While there are typically no exceptionally conspicuous physical or neuroimaging signs of mTBI, the mechanical trauma to the brain leads to a mild temporary disruption of consciousness or other alteration of ongoing cognition. Also commonly known as "concussion," mTBI can further lead to persistent alterations in neuropsychological functions, including changes in mood (e.g., depression), poor attention and concentration, and memory problems (1, 2). Importantly, sleep deprivation is also known to produce many of these same symptoms (3, 4).

It is therefore possible that sleep disturbances following mTBI may cause, or at least exacerbate, ongoing post-concussion symptoms. However, the nature of these complaints and their contribution to the experience of daytime sleepiness is not well understood (5). An objective measure of daytime sleepiness is the multiple sleep latency test (MSLT), which is used to determine the time it takes an individual to fall asleep (sleep onset latency) when given the opportunity to take a nap. Following a head trauma, symptoms are believed to result from neuronal damage in the form of diffuse axonal injury (6, 7), leading to the release of specific proteins that in turn promote maladaptive functional and structural changes within the brain (8). Identifying neuro-markers of these changes remains an important challenge in ongoing attempts to understand and treat mTBI and post-concussive symptoms.

A very limited number of treatment options for mTBI have been proposed and experimentally validated. Available treatments include cognitive behavior therapy (9), neuropsychological rehabilitation (10), educational intervention (11), and pharmacological intervention (12). Although the effects are small, some intervention studies report reliable reductions in post-concussion symptoms, including sleep problems, following successful treatment (13). Considering a range of post-concussion symptoms can also occur as the result of sleep loss, it is likely that improving sleep quality in particular would also lead to improvements of other post-concussion symptoms, such as attention, concentration, memory, and mood disturbances. While improving sleep makes sense, this is often easier said than done. A natural and potentially powerful method for regulating the sleep–wake cycle is through targeted exposure to bright light in the morning hours. Exposure to short wavelength light (~430–475 nm; blue wavelength light) has been demonstrated as an alternative to pharmacological treatment methods that focus on improving alertness, concentration, daytime sleepiness, as well as sleep quality (14, 15). Intrinsically photosensitive retinal ganglion cells are particularly responsive to light within the short wavelengths. These cells transmit signals to hypothalamic nuclei, which in turn regulate the production of melatonin (16, 17). Morning exposure to blue wavelength light leads to a suppression of melatonin production, which contributes to a phase delay and stabilization of the circadian rhythm (18), increases daytime alertness and vigilance, and earlier onset of evening sleep (19, 20). Interestingly, a recent clinical trial showed that 4 weeks of 45 min of morning blue-light therapy (BLT) in comparison to longer wavelength placebo light was effective at reducing self-rated fatigue and daytime sleepiness among individuals recovering from TBI (21). However, the extent to which these behavioral changes correspond to structural changes within the brain has not been explored.

When considering the potential influences of BLT on mTBI, it is important to consider that mTBI is associated with microscopic changes in brain structure, particularly within the white matter axonal tracts. Abnormalities in fractional anisotropy (FA) in the brain following an mTBI have been studied extensively using diffusion tensor imaging (DTI), a method that allows high-resolution imaging of the directional movement of water molecules along axonal fiber tracts (i.e., how fast water molecules move along fiber tracts). Abnormalities in FA in individuals with an mTBI are reported in areas such as uncinate fasciculus (UF) (22), superior longitudinal fasciculus (SLF) (23), anterior corona radiata (ACR) (22), corpus callosum (CC) (24), and thalamus (25). Alterations in FA within (a) UF are reported to be associated with changes in Mini-Mental State Examination (MMSE) scores (cognitive function) and specifi ally, memory performance (22, 26); (b) SLF and CC are reported to be associated with executive function (attention and memory) (27); (c) ACR changes are correlated with changes in attention (22); and (d) anterior thalamic nucleus changes are also linked to changes in executive function, memory, and attention (25). In addition, studies have found that individuals with mTBI show alterations in white matter within the frontal lobe (frontal cortex/dorsolateral prefrontal cortex, DLPFC), and that these alterations are correlated with lower executive control and related cognitive functions (28). Also, compared to healthy controls (HCs), there are multiple studies that have reported abnormally high FA values in individuals with mTBI within several areas, including the genu and splenium of CC, ACR (bilaterally), lUF, and internal capsule (IC; bilaterally) (29, 30). Recently, new diffusion measures—quantitative anisotropy (QA), isotropic diffusion (ISO), and generalized fractional anisotropy (GFA)—were introduced to the fi ld of DTI for the analysis of diffusion properties of white matter (31). QA and ISO represent *how much* water diffuses (i.e., density) in a specific/restricted direction and in an isotropic fashion (i.e., total isotropic component), respectively. In contrast, GFA, which is calculated from an orientation distribution function, is a measure of *how fast* water diffuses (i.e., diffusivity) in an anisotropic fashion, i.e., it represents degree to which diffusion is anisotropic (31, 32). Highly signifi ant correlations between FA and GFA were reported in the past (33). In addition, the difference between QA and GFA pertains to the fact that QA is a measure of water diffusion along each fiber orientation, whereas GFA/FA is defi ed for each voxel. Compared to GFA/FA, QA is also reported to have lower susceptibility to partial volume effects of crossing-fibers, free-water diffusion in ventricles, and non-diffusive particles (31). Moreover, normalization of QA helps to stabilize the spin-density measurement across subjects. In this study, we investigated multiple diffusion measures (i.e., diffusivity as well as density measures) simultaneously to better characterize the white matter properties; therefore, in conjunction with GFA, we also estimated normalized QA (NQA) and ISO measures. To the best of our knowledge, no study to date has used these metrics simultaneously to examine the effect of light exposure treatment on the brain following mTBI.

In individuals with mTBI, how changes in post-concussion symptoms following an exposure to BLT may correspond to structural changes within the brain has not yet been explored. Recent evidence suggests that sleep is important for clearing the neurotoxins that build up throughout the day (34) and increases the production of oligodendrocyte progenitor cells that contribute to myelin formation (35), which could conceivably facilitate repair of axonal damage. Based on this, we hypothesized that 6 weeks of daily morning BLT, compared to a placebo condition with an amber-light therapy (ALT) device, would improve sleep and, consequently, lead to changes in white matter water diffusion, improvements in cognitive abilities such as attention and memory, and daytime sleepiness. To this end, we investigated

whether individuals in the BLT and ALT groups showed significant changes in diffusion (i.e., GFA, NQA, and ISO), cognitive, and sleep measures. Furthermore, we examined the correlations between changes in diffusion measures from pre- to post-treatment and changes in neuropsychological performance and sleep onset latency.

MATERIALS AND METHODS

Participants

Twenty-eight individuals meeting criteria for mTBI (mean age = 21.48 ± 3.76 years, 15F) underwent neuroimaging using a Siemens Tim Trio 3T scanner (Erlangen, Germany) at the McLean Hospital Imaging Center. The majority of the individuals (19 out of 28) sustained an mTBI while engaged in a physical activity (e.g., soccer, rugby, hiking, and karate); whereas 9 individuals sustained an mTBI during either a vehicular or household accident. All of the mTBI individuals had a documented mTBI within the preceding 12 months, but not sooner than 4 weeks before their screening. An mTBI was defi ed based on the criteria established by the VA/DoD practice guidelines (36) as a traumatically induced event (e.g., head impact, blast wave) that was associated with an alteration in mental status (e.g., confusion, disorientation, retrograde, or anterograde amnesia), consciousness (i.e., loss of consciousness less than 30 min; alteration of consciousness up to 24 h), post-traumatic amnesia up to 24 h, and a Glascow Coma Scale from 13 to 15. All participants were right-handed and primary English speakers. All study participants were required to have some level of self-reported sleep problem, e.g., if they were sleepier during the day, having difficulty in sleeping at night and staying alert during the day, etc. Therefore, all participants were screened using a set of sleep questionnaires where they indicated self-reported sleep problems and endorsed that the sleep problems either emerged or worsened following the injury. Participants with any history of neurological, mood, or psychotic disorder with an onset before the mTBI, or who suffered a loss of consciousness exceeding 30 min following an injury were excluded. Participants were thoroughly briefed on the potential risks and benefits of the study and all completed written informed consent before enrollment. Participants were fi ancially compensated for their time. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Offi . All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Protocol

All the participants underwent DTI, neuropsychological testing, and MSLT sessions on two occasions; separated by 6 weeks of daily morning light therapy with either blue light or a sham placebo amber light. Participants were instructed to rest and relax during scanning. All data were collected within a period of 3 years. All eligible participants completed daily sleep diaries and questionnaires and were fitted with a wrist actigraph for sleep monitoring throughout the period of the study. Participants were asked to use a commercially available light therapy device (GoLite Blu®, Philips Electronics) for 6 weeks (i.e., 30 min everyday within 2 h of awakening, but before 11:00 a.m.). Half of the individuals (N = 14, mean age = 21.75 ± 4.43 years, 8F) were randomly assigned to BLT and half (N = 14, mean age = 21.21 ± 3.09 years, 7F) were assigned to ALT. ALT and BLT groups did not differ signifi antly in age [$F(1,26) = 0.14$, $p > 0.05$, one-way ANOVA], gender [$\chi^2(1) = 0.14$, $p > 0.05$, Pearson's Chi-square], and body-mass index [$F(1,25) = 2.77$, $p > 0.05$, one-way ANOVA]. However, two important covariates were included in our analyses: (1) "light compliance" was calculated as the percentage of the total number of days that the participant acknowledged actually using the light *via* self-report divided by the total number of days in the study (i.e., number of days between baseline and post-treatment assessments), and (2) "time since injury," which was calculated as the number of days between the index mTBI and the baseline assessment.

DTI Data Acquisition and Image Processing

Diffusion-weighted imaging (DWI) data were acquired along 72 directions with a b-value = 1,000 s/mm^2, voxel size = 1.75 mm × 1.75 mm × 3.5 mm, fl p angle = 90°, repetition time (TR) = 6,340 ms, echo time (TE) = 99, slices thickness = 3.5 mm, and number of slices = 40 encompassing the whole brain. A set of eight images with no diffusion weighting (b0 images) was also acquired. Using dcm2nii toolbox [part of MRIcron (37)], we converted DWI data from DICOM into NIFTI format. A b-value and b-vector file was generated during this step. Next, we performed standard eddy current correction using FMRIB Software Library v6.0 processing software package[1] on DWI data for head motion correction.

Neuropsychological Assessments and Sleep Measures

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (38), which included scales assessing delayed memory (DM), immediate memory (IM), attention (ATT), visuospatial/constructional (VC), and language (LAN) abilities was administered pre- and post-light exposure.

The RBANS IM is a measure of initial encoding and learning of simple and complex verbal information and RBANS DM is a measure of delayed recall of visual and verbal stimuli and recognition of verbal stimuli. The RBANS ATT is a measure of speed and accuracy of information processing. The RBANS VC is a measure of visuospatial perception, and RBANS LAN is a measure of ability to express language. Lower RBANS IM and DM scores represent difficulty in the recognition and recall of long-term memories and verbal learning, respectively. Lower RBANS ATT scores represent difficulty in the basic attention processes. Lower RBANS VC and LAN scores represent difficulty with using visuospatial information and language (expressive and receptive), respectively. The use of the RBANS has been shown to

[1] http://www.fmrib.ox.ac.uk/fsl.

be clinically valid and reliable screening tool to assess cognitive deficits following traumatic brain injury (39).

The MSLT has been shown to better reflect the degree of daytime sleepiness when compared to self-report, and with high test–retest reliability (40–42). During each assessment session, participants underwent a modified MSLT protocol, using a standard electrode montage for polysomnographic (PSG) recording (ALICE LE®, Phillips Respironics). Signals were recorded from EEG (C3A2, C4A2, O1A1, and O2A2), electrooculogram, submental electromylogram, and electrocardiogram. On three occasions throughout the testing session (11:50 a.m., 1:50 p.m., 3:50 p.m.), participants were given a 20-min opportunity to take a nap in a sound attenuated bedroom. Increased sleep propensity and/or abnormal daytime sleepiness is inferred from decreased sleep onset latency during these MSLT trials. PSG recordings were monitored for the duration and then scored by certified sleep technicians using 30-s epochs and Somnologica software. Sleep onset latency was classified as the first epoch in which >50% was identified as any stage of sleep. Sleep onset latency was quantified for each trial, as well as the average onset latency across the three MSLT administrations.

Data Analysis

For each participant, we estimated water diffusion parameters such as mean GFA, mean NQA, and mean ISO, using the Q-space diffeormophic reconstruction (QSDR) approach (43) implemented in DSI Studio.[2] QSDR is a model-free approach, which calculates the density distribution of water diffusion using a high-resolution standard brain atlas constructed from 90-diffusion spectrum imaging datasets in the ICBM-152 space. Tractography was performed using 25,000 sub-voxel seeds in each region of interest for each participant. A turning angle threshold of 60°, QA threshold of 0.10, and length constrained between 30 and 200 mm was used to estimate diffusion parameters. To ensure consistency across subjects, we normalized the QA measure by scaling the subject-wise maximum QA value to 1. Normalization of QA assumes that all the subjects have identical compactness of white matter. In order to avoid any bias among participants, an identical set of tracking parameters was used for each participant before and after the light therapy. For each participant, GFA, NQA, and ISO were estimated for all the possible tracts crossing 11 brain areas, namely the DLPFC, the genu, body and splenium of the CC, the left and the right uncinate fasciculus (lUF and rUF), the left and the right superior longitudinal fasciculus (lSLF and rSLF), the left and the right anterior corona radiata (lACR and rACR), and the thalamus. DLPFC is attributed anatomically to Brodmann areas (BAs) 9 and 46 (44). To define DLPFC in this study, we integrated BAs 9 and 46 whereas we used the ICBM-DTI-81 white matter labels atlas (45) and the JHU white matter tractography atlas (45) (implemented in DSI Studio) to define all other regions of interest. Diffusion parameters (GFA, NQA, and ISO) from tracts crossing the 11 specified seed regions were used in the analyses. In order to estimate the diffusion measures across all the possible tracts crossing each of the 11 brain areas, no waypoint regions of interest were included in the analysis.

Metrics of GFA, NQA, and ISO were compared using mixed analysis of covariance (ANCOVA), with light group (BLT/ALT) as a between groups variable and session (pre- versus post-treatment) as a within-subjects variable, while "time since injury" and "light compliance" were included as nuisance covariates. To test the association between the changes in white matter integrity with changes in neuropsychological performance and sleep latency measures, change metrics for each variable were evaluated with partial correlations, controlling for time since injury and light compliance. For this analysis, we used residualized change scores derived by regressing post-treatment scores on pre-treatment scores and determining the residual value for each participant. This provides a metric of post-treatment status controlling for pre-treatment status (i.e., residualized change). We report false discovery rate (FDR) corrected *p*-values for the partial correlations.

RESULTS

In order to estimate different diffusion parameters, we first performed whole-brain tractography, followed by limiting the white matter tracts to those passing through 11 predefined seed regions, namely—R01: the DLPFC, R02: genu, R03: body, R04: splenium of the CC, R05: the lUF, R06: the rUF, R07: the lSLF, R08: the rSLF, R09: the left anterior corona radiata (ACR), R10: right anterior corona radiata (ACR), and R11: the thalamus. Selection of these 11 regions was purely based on previous literature showing abnormalities water diffusion in these regions following mTBI (22–28). In **Figure 1**, we show fiber tracts crossing through each region for a representative participant. Here, fibers are colored coded to represent their direction, where "red" indicates fibers along the *X*-axis (i.e., left–right), "green" indicates fibers along the *Y*-axis (i.e., anterior–posterior), and "blue" indicates fibers along the *Z*-axis (i.e., inferior–superior).

Effect of Light Therapy on Diffusion Properties of the Brain following an mTBI

A detailed comparison of diffusion parameters, GFA, NQA, and ISO, was performed on fiber pathways crossing through the 11 specified seed regions (R01 to R11). All the results were corrected for multiple comparisons using Bonferroni's method. In Figure S1 in Supplementary Material, for each area, we showed subject and fiber averaged GFA, NQA, and ISO measures before and following 6 weeks of either ALT or BLT, where error bars represent the SEM. The presented data in Figure S1 in Supplementary Material are raw data, which are uncorrected for confounds.

GFA

There was a significant time (pre- and post-treatment) × group (ALT/BLT) interaction [$F(1,24) = 6.151$, $p = 0.021$] such that following BLT, but not ALT, individuals showed a significant decrease in GFA for only the fibers crossing the splenium of the CC. Furthermore, within-subject pairwise comparison showed a significant decrease in GFA following BLT [$F(1,24) = 5.619$,

[2] http://dsi-studio.labsolver.org.

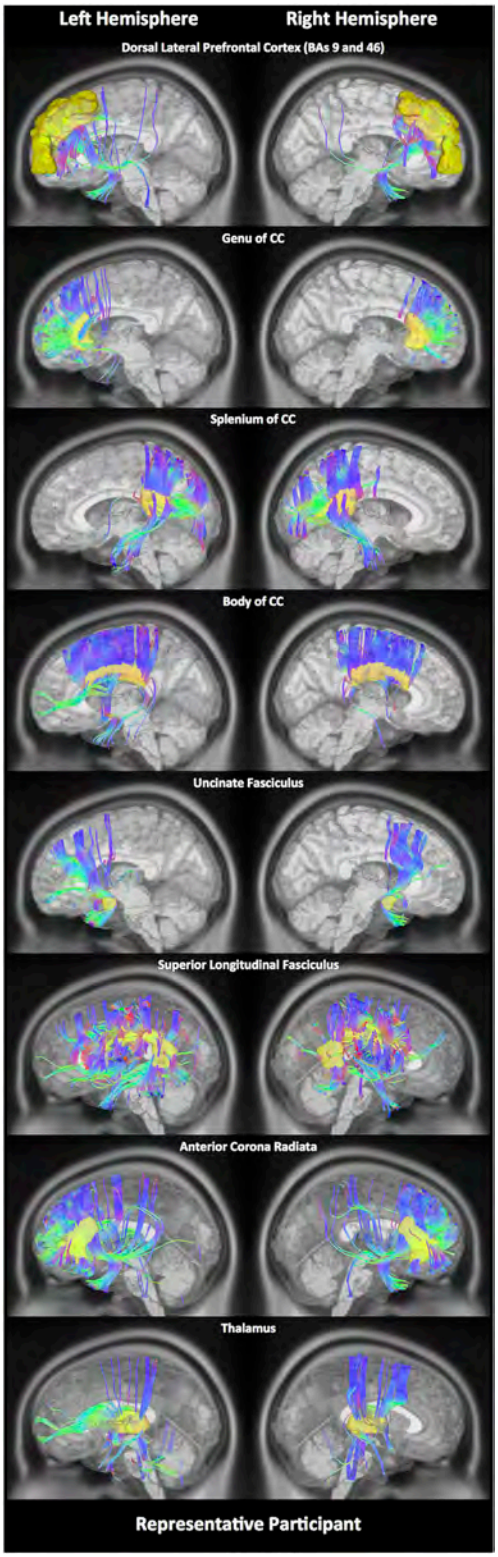


FIGURE 1 | White matter fiber tracking. Here, for a representative participant, we illustrate white matter fiber tracts for each of the 11 regions. Tracts shown in red indicate a fiber direction from left to right or *vice versa*. Blue indicates a fiber direction from anterior to posterior or *vice versa*. Green indicates a fiber direction from superior to inferior or *vice versa*.

$p = 0.026$], but not ALT [$F(1,24) = 1.511$, $p = 0.231$]. ANCOVA results for GFA of the fibers crossing the splenium of the CC are summarized in **Figure 2** and **Table 1**.

NQA

There was a signifi ant time (pre- and post-treatment) × group (ALT/BLT) interaction such that following BLT, but not ALT, individuals showed a signifi ant decrease in NQA for the fibers crossing three brain areas, i.e., body of CC [$F(1,24) = 4.932$, $p = 0.036$], the left ACR [$F(1,24) = 9.460$, $p = 0.005$], and thalamus [$F(1,24) = 5.688$, $p = 0.025$]. Furthermore, pairwise comparison showed that following BLT, there was signifi ant decrease in NQA for the fibers crossing these three areas, i.e., body of CC [$F(1,24) = 5.984$, $p = 0.022$], the left ACR [$F(1,24) = 12.347$, $p = 0.002$], and thalamus [$F(1,24) = 8.226$, $p = 0.008$], but not following ALT. ANCOVA results for NQA of the fibers crossing these three areas are summarized in **Figure 3** and **Table 2**.

ISO

There were no signifi ant changes in ISO for fibers crossing any of the 11 areas from pre- to post-treatment for either group.

Effect of Light Therapy on Neuropsychological Function and Sleep Onset Latency

Contrary to our expectations, we did not fi d signifi ant time (pre- versus post-treatment) × group (ALT/BLT) interaction for neuropsychological function and sleep onset latency. However, because we found signifi ant differences in GFA (for 1 out of 11 brain areas) as well as in NQA (for 3 out of 11 brain areas) following BLT, we then examined whether individual differences in white matter within these 4 brain regions were related to individual differences in our behavioral measures of neuropsychological function (attention and memory) and daytime sleep onset latency during the MSLT trials. Specifi ally, partial regression analyses were performed (corrected for "time since injury" and "light compliance") between diffusion measures (GFA and NQA) and neuropsychological function measures (i.e., RBANS scores) as well as sleep onset latency.

Neuropsychological Function

Following BLT or ALT, we did not fi d signifi ant association between residualized changes in any neuropsychological measures or MSLT scores and residualized changes in GFA for fibers crossing the splenium of the CC. But signifi ant negative partial correlations were observed between residualized changes in RBANS DM scores and residualized changes in NQA for fibers crossing two brain areas: the body of the CC ($r = -0.76$, $p = 0.00$; FDR corrected $p = 0.02$) (**Figure 4A**) and the thalamus ($r = -0.64$, $p = 0.02$; FDR corrected $p = 0.02$) (**Figure 4B**), i.e., greater changes in NQA were associated with better DM performance following BLT. After multiple comparisons correction, we did not fi d signifi ant association between residualized changes in any neuropsychological measure and residualized changes in NQA for fibers crossing any of the regions of interest following ALT (**Figures 4C,D**).

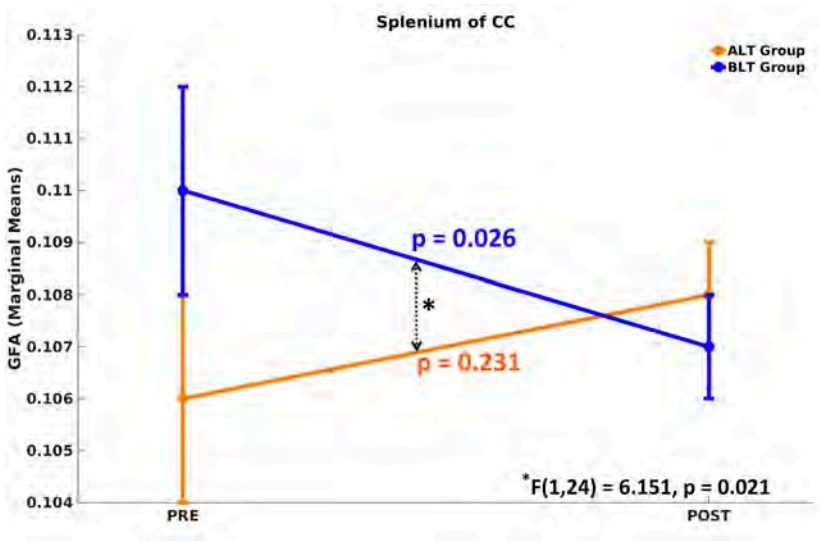


FIGURE 2 | Mixed analysis of covariance of generalized fractional anisotropy (GFA). Compared to baseline, only the fibers crossing the splenium of corpus callosum (CC) showed significant differences in GFA following blue-light therapy (BLT). No significant difference in GFA was found for fibers crossing any brain area, including the splenium of CC, following amber-light therapy (ALT).

TABLE 1 | Summary of analysis of variance (repeated measures ANOVA) for GFA.

Within-subjects effects					
Interaction					
Source	**Brain areas**	**Type III sum of squares**	**Mean square**	***F*(1, 24)**	**Significance (GFA)**
Time (pre and post) × group (ALT/BLT) (sphericity assumed)	Splenium of CC	0.000	0.000	6.151	0.021*
Pairwise comparisons (pre versus post)					
Effect of treatment	**Brain areas**	**Groups**	***F*(1, 24)**		**Significance (GFA)**
Pre versus post	Splenium of CC	ALT	1.511		0.231
		BLT	5.619		0.026**

GFA, generalized fractional anisotropy; BLT, blue-light therapy; ALT, amber-light therapy; CC, corpus callosum.
**Interaction is significant at $p < 0.05$.*
***Mean difference between post- and pre-treatment is significant at $p < 0.05$.*

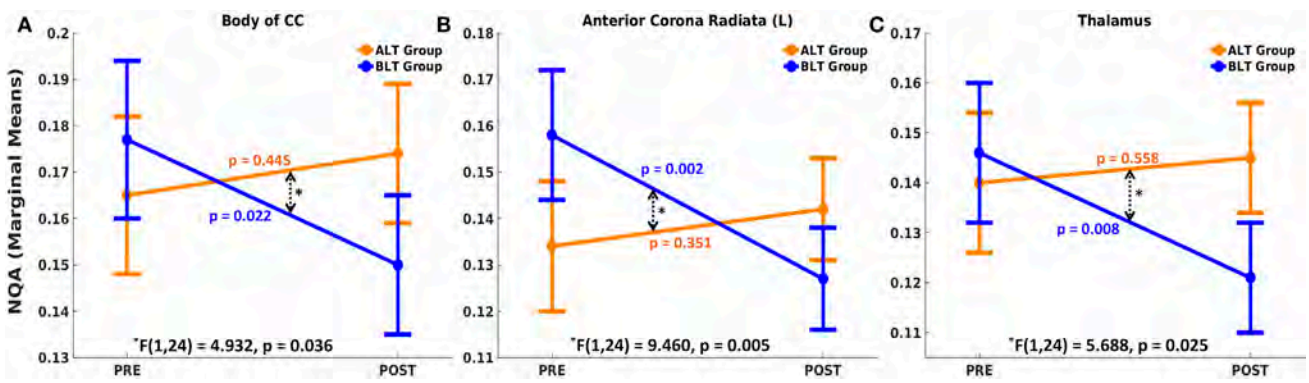


FIGURE 3 | Mixed analysis of covariance of normalized quantitative anisotropy (NQA). Fibers crossing three brain areas, the body of the corpus callosum (CC) **(A)**, left anterior corona radiata (ACR) **(B)**, and thalamus **(C)** showed significant time (pre and post) × group (ALT/BLT) interaction in normalized QA (NQA). Compared to baseline, pairwise comparison showed significant reduction in NQA for these three regions following BLT, but not following ALT. BLT, blue-light therapy; ALT, amber-light therapy.

TABLE 2 | Summary of analysis of variance (repeated measures ANOVA) for normalized quantitative anisotropy (NQA).

Within-subjects effects (ANCOVA)

Interaction					
Source	**Brain areas**	**Type III sum of squares**	**Mean square**	***F*(1, 24)**	**Significance[a] (NQA)**
Time (pre and post) × group (ALT/BLT) (sphericity assumed)	Body of CC	0.004	0.004	4.932	0.036*
	Left anterior corona radiata	0.005	0.005	9.460	0.005*
	Thalamus	0.003	0.003	5.688	0.025*
Pairwise comparisons (pre versus post)					
Effect of treatment	**Brain areas**	**Groups**	***F*(1, 24)**		**Significance[a] (NQA)**
Pre versus post	Body of CC	ALT	0.604		0.445
		BLT	5.984		0.022**
	Left anterior corona radiata	ALT	0.903		0.351
		BLT	12.347		0.002**
	Thalamus	ALT	0.352		0.558
		BLT	8.226		0.008**

NQA, normalized quantitative anisotropy; BLT, blue-light therapy; ALT, amber-light therapy; CC, corpus callosum; ANCOVA, analysis of covariance.

[a]*Adjustment for multiple comparisons using Bonferroni's method.*

**Interaction is significant at $p < 0.05$.*

***Mean difference between post- and pre-treatment is significant at $p < 0.05$.*

Daytime Sleep Onset Latency

Signifi ant negative partial correlations were observed between residualized changes in sleep onset latency during the fi st MSLT administration and residualized changes in NQA for fibers crossing ACR (L) ($r = -0.72$, $p = 0.01$; FDR corrected $p = 0.01$) (**Figure 4E**), i.e., greater changes in NQA were associated with delayed sleep onset latency during the day following BLT. However, after multiple comparisons correction, we did not fi d signifi ant association between residualized changes in sleep onset latency during any of the MSLT administrations and residualized changes in NQA for fibers crossing any of the regions of interest following ALT (**Figure 4F**). The fi dings above are summarized in **Table 3**.

DISCUSSION

In this study, we analyzed several white matter water diffusion properties including GFA, NQA, and ISO, for fibers crossing several brain areas in individuals with a recent mTBI. From a group of individuals with mTBI, half were randomly assigned to a placebo condition of ALT and the other half to an active condition of BLT. Consistent with our hypotheses, we observed signifi ant changes in some of these white matter properties (i.e., GFA and NQA) for multiple brain areas following BLT. Contrary to our hypotheses, we did not observe signifi ant changes in cognitive abilities such as attention and memory, or in the daytime sleep onset latency measures. However, an analysis of cognitive abilities and daytime sleep onset latency measures in relation to white matter properties revealed a signifi ant relationship between increased DM scores and decreased normalized quantitative anisotropy, as well as an association between increased daytime sleep onset latency and decreased normalized quantitative anisotropy after BLT. These fi dings suggest that BLT may provide an effective method for facilitating recovery from mTBI.

Previous DTI studies of mTBI have tended to focus on FA as a measure of the diffusion properties of white matter tracts. However, these studies have yielded somewhat inconsistent results, as some report abnormally high (30) and others report abnormally low FA (24) values following an mTBI (i.e., as compared to HCs). Such inconsistencies may be due to several factors, including type, severity and location of injury, time since injury, and variability across subject samples (30). In this study, we examined NQA and ISO, in addition to FA, in order to fully characterize potential treatment effects. In doing so, we found a signifi ant effect of BLT on white matter water diffusion properties (i.e., both GFA and NQA) for several brain areas, which were associated with signifi ant correlations between diffusion measures, behavioral measures of neuropsychological function, as well as daytime sleep onset latency. In contrast, none of the 11 brain areas showed signifi ant change in GFA, NQA, or ISO following the placebo ALT. More specifi ally, we found that, following BLT (but not ALT), there was signifi ant decrease in GFA for fibers passing through the splenium of the CC, and a signifi ant decrease in NQA for fibers passing through the body of CC, left ACR, and thalamus. These changes in NQA for fiber pathways going through the body of the CC and thalamus were also signifi antly negatively correlated with changes in RBANS DM scores, suggesting that decreases in NQA were associated with improvements in DM performance from pre- to post-treatment. In addition, changes in NQA for fiber pathways going through the left ACR were signifi antly negatively correlated with changes in MSLT scores, suggesting that decreases in NQA were associated with improvements in sleep onset latency during the day from pre- to post-treatment. The role of the CC during recovery following BLT might be due to the fact that CC

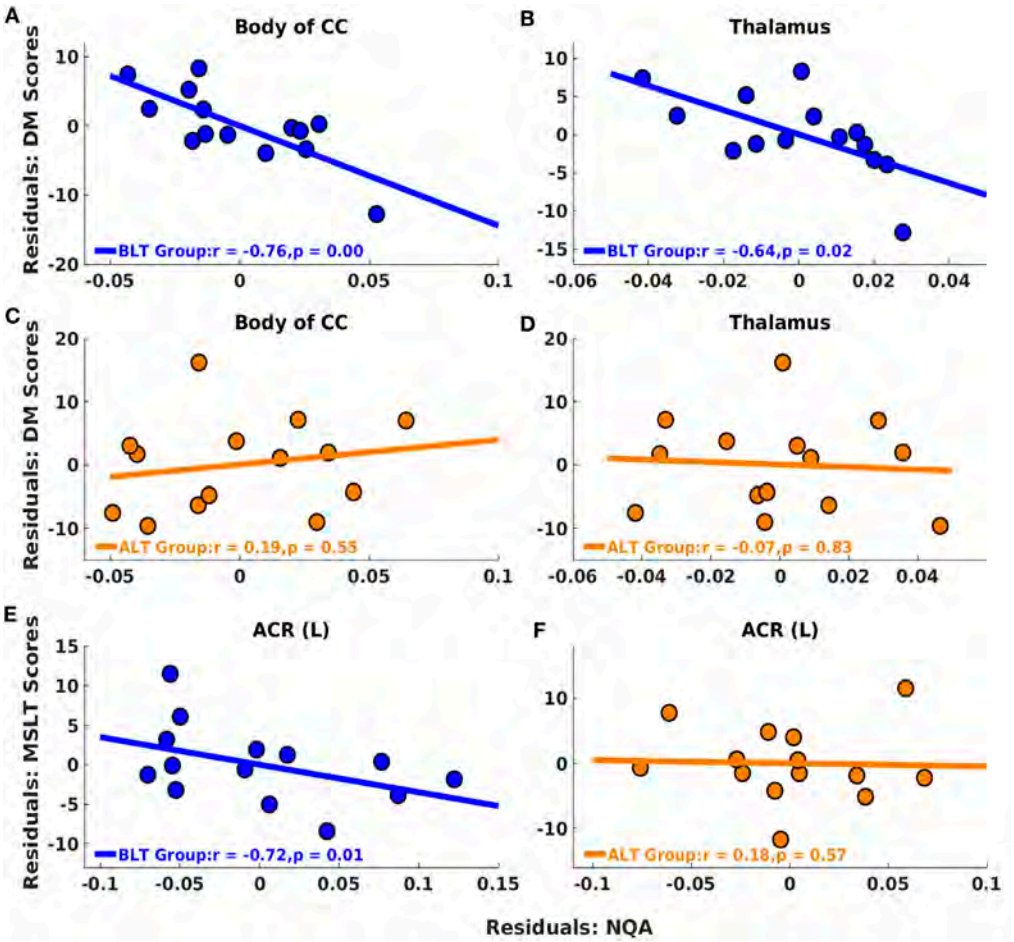


FIGURE 4 | Associations between residualized changes in white matter diffusion measures, neuropsychological measures, and multiple sleep latency test (MSLT) scores following BLT and ALT. For BLT and ALT groups, correlations found between residualized changes in NQA and neuropsychological function measures (DM) [BLT: **(A,B)**, ALT: **(C,D)**], and between residualized changes in NQA and MSLT scores [BLT: **(E)**, ALT: **(F)**] are reported. Significant negative correlations between residualized changes in Repeatable Battery for the Assessment of Neuropsychological Status DM scores and NQA measures were found for fibers crossing the body of the corpus callosum (CC) **(A)** and thalamus **(B)** for BLT group. No significant correlations were found for ALT group, including for fibers crossing the body of the CC **(C)** and thalamus **(D)**. Significant negative correlations between residualized changes in sleep onset latency during the first MSLT administration and NQA measures were also found for fibers crossing the left anterior corona radiata (ACR) **(E)** for BLT group but not for ALT group **(F)**. BLT, blue-light therapy; ALT, amber-light therapy, DM, delayed memory.

tracts facilitate communication of somatosensory information between parietal and occipital lobes (46) as well as communication between the two cortical hemispheres more generally (47). These tracts are known for their vital role in regulating several advanced brain skills such as memory, learning, and abstract thinking. Damage to these tracts could lead to loss of interhemispheric connections, causing multiple neuropsychological impairments (47). Moreover, the CC is also a common site affected following a brain injury. In the previous work, axons of the CC were reported to exhibit multiple stages of degeneration following a traumatic brain injury (48). In addition, generation of myelin sheaths within the CC could be responsible for its greater responsiveness to BLT. Furthermore, the connections between the anterior thalamus and hippocampal gyrus are believed to operate in parallel but with different organization and any damage to such network or any of the participating areas could contribute to impaired memory and discrimination skills (49, 50). The improvements in memory scores as a result of changes in NQA could be due to the effects of blue light exposure on sleep quality, which plausibly results in decreased daytime sleepiness and increases in alertness. Future work assessing PSG or actigraphic changes in sleep duration and quality will be necessary to test these hypotheses directly. In a diffusion kurtosis imaging study, several brain areas including the CC, thalamus, and IC showed correlations between changes in mean kurtosis or radial kurtosis between 1 and 6 months post mTBI and improvements in cognition between the 1- and 6-month visits (51). In that study, no signifi ant differences in other diffusion parameters (such as FA and mean diffusivity) were observed between mTBI patients and age-matched controls. The fi dings reported in our

TABLE 3 | Summary of correlations between residualized changes in neuropsychological function measures (DM) and GFA, and between residualized changes in MSLT scores and normalized quantitative anisotropy (NQA) measures.

#	ROIs	Partial correlations (*r*, *p*) between residualized changes in									
		GFA and					NQA and				
		DM	MSLT 1	MSLT 2	MSLT 3	Mean MSLT	DM	MSLT 1	MSLT 2	MSLT 3	Mean MSLT
BLT group											
1	Splenium of CC	0.35, 0.27	−0.33, 0.29	−0.17, 0.60	−0.48, 0.12	−0.37, 0.23			–		
2	Body of CC			–			−0.76, 0.00**	−0.18, 0.58	−0.43, 0.16	−0.17, 0.60	−0.37, 0.24
3	ACR (L)			–			−0.37, 0.23	−0.72, 0.01**	−0.45, 0.14	−0.45, 0.15	−0.58, 0.05
4	Thalamus			–			−0.64, 0.02**	−0.45, 0.14	−0.48, 0.11	−0.39, 0.21	−0.54, 0.07
ALT group											
1	Splenium of CC	−0.02, 0.96	−0.56, 0.06	−0.61, 0.04*	−0.38, 0.22	−0.61, 0.04*			–		
2	Body of CC			–			0.19, 0.55	−0.52, 0.08	−0.52, 0.08	−0.51, 0.09	0.60, 0.04*
3	ACR (L)			–			0.43, 0.16	0.18, 0.57	0.04, 0.91	−0.04, 0.92	0.07, 0.83
4	Thalamus			–			−0.07, 0.83	0.13, 0.70	−0.19, 0.56	0.42, 0.17	0.17, 0.60

ROIs, regions of interest; GFA, generalized fractional anisotropy; NQA, normalized quantitative anisotropy; DM, delayed memory; MSLT, multiple sleep latency test; BLT, blue-light therapy; CC, corpus callosum; ACR (L), anterior corona radiata (left); ALT, amber-light therapy; FDR, false discovery rate.

**p < 0.05 (uncorrected for multiple comparisons).*

***p < 0.05 (FDR corrected for multiple comparisons).*

study are also consistent with previous findings demonstrating microstructural white matter changes in the ACR for patients suffering from narcolepsy, a disorder characterized by rapid sleep onset latency during the daytime (52).

We observed a significant reduction in diffusion measures (GFA and NQA) following BLT. One of the potential explanations for changes in GFA and NQA measures could be attributed to the way axons are packed. Previously, changes in FA are reported to be dependent on axonal packing. It was reported that light axonal packing leaves more intercellular water as compared to dense packing causing less restriction to water molecules, which further results into lower FA values whereas higher degree of myelination results into higher FA values due to tight axonal packing (53). In addition, in a separate study, we recently demonstrated that acute exposure to 30 min of blue light subsequently led to increased functional brain responses within the prefrontal cortex and improved cognitive performance during a working memory task (54). Blue light exposure in the morning may therefore facilitate brain function later during the day, possibly when individuals are at work. If individuals are exposed to 30 min of morning blue light every day for 6 weeks and are able to sustain regular attentional focus, this may plausibly also be reflected in better white matter integrity and improved performance on neuropsychological tasks and decreased daytime sleepiness. Another possible reason for changes in diffusion measures (GFA and NQA) following BLT could be that before BLT, GFA, and NQA were higher and BLT helped to restore these diffusion levels back to normal. In fact, increased water diffusion after an mTBI has been associated with the stretching and deformations of axons following mTBI, which leads to an increase in intra- but decrease in extra-cellular water causing an increase in diffusion along the axons (55, 56). Modeling studies have shown that the inter-hemispheric fibers, especially of the CC, could be more sensitive to mechanical strain following brain deformation after a concussion (57). Diffusion of water molecules through strained axons could further be responsible for higher GFA or NQA. Abnormal disruption of water due to axonal swelling, compression of axons, and expansion of tissues may also lead to abnormal changes in water diffusion (30, 58). Myelin also plays a significant role in axon susceptibility following an mTBI. For instance, compared to myelinated axons, unmyelinated fibers within white matter are more adversely affected following traumatic axonal injury (59). BLT may improve myelination and help in regenerating new structural fibers, which could cause the observed improvements in neurobehavioral scores and possibly the observed changes in GFA and NQA values. However, the potential mechanism behind increased myelination or regeneration of structural fibers following light therapy is not completely understood. It may involve clearance of neurotoxins (34) and increases in oligodendrocyte precursor cells (35) due to shifts in circadian rhythms and improved sleep (18, 60, 61). Previously, it was reported that mean water diffusivity values were reduced within several brain regions including CC, corona radiata, and thalamic radiation in patients with obstructive sleep apnea compared to HCs (62). In a study of patients with bipolar disorder, reduced water diffusivity within the same regions identified here (CC, corona radiata, and thalamic radiation) indicated that sleep quantity could be associated with integrity of myelin sheaths (63). Therefore, BLT may enrich or stimulate the production of myelin-enriched brain debris, which may further stimulate microglial/macrophage activation in white matter tracts (64), especially within the CC, corona radiata, and thalamic radiation, which are associated with various sleep problems. Adaptive alterations in water diffusivity following BLT may also act to strengthen brain function. The association between sleep and variation in diffused water quantity could also be responsible for circadian changes in diffusion measures (65, 66), which may further lead to improvements in brain structure and function following BLT. Furthermore, it is known from other studies that acute exposure to blue light also has a positive impact on brain function and cognitive performance and it makes people faster at responding during working memory tasks without

loss of accuracy (54). Separate from the effects of blue light on melatonin suppression, it is possible that blue light may have more direct cognitive alerting effects *via* direct stimulation of the locus coeruleus, which in turn releases norepinephrine throughout the cerebral cortex (54, 67, 68). While speculative, it is conceivable that the effects could be even more robust during periods of insuffici t sleep that are extremely common following a traumatic brain injury (69). Th s is an important area for further research.

Finally, it is noteworthy that NQA appeared to yield a larger number of signifi ant fi dings than GFA or ISO. One possibility is that NQA is a more sensitive measure to detect microstructural changes of white matter integrity following an mTBI. By contrast, we predict that GFA could be a more sensitive measure to determine white matter differences between controls and mTBI patients. Th s is also consistent with the previous literature, which has suggested that density measures like NQA are more sensitive to individual physiological differences, whereas diffusivity measures like GFA are more sensitive to pathological conditions (70). NQA is also generally considered to be a more robust measure for deterministic tractography, due to its lower susceptibility to partial volume effects (31). It has also been found that NQA has the capability to filter out noisy fiber tracts, which further results in a higher spatial resolution in NQA-aided tractography. By contrast, voxel-based indices, such as GFA, are not capable of filtering out the noisy fibers since the same magnitude of anisotropy is shared by all the fiber orientations within a voxel (31). These considerations support the idea that NQA-aided tractography may be a better approach than GFA-based tractography for examining abnormal white matter content following an injury and injury-related therapies. It should be noted that the deterministic tractography methods implemented in DSI Studio has achieved the highest "valid connection" examined by an open competition among 96 methods submitted from 20 different research groups around the world.[3]

Th s study had several limitations. First, we acknowledge the fact that there is no way to assert the accuracy of tractography. Thus, further research will be needed to provide convergent validity to these fi dings. Second, our data sample was focused on participants with mTBI and did not include healthy controls. The goal was to compare the active versus a placebo condition on the recovery of a patient population, but future work would benefit from a sample of healthy individuals to determine the extent to which the outcomes represent full normalization of brain structure. Thi d, our mTBI sample also included individuals with different injury mechanisms. Mild injuries of this type are extremely heterogeneous and may vary signifi antly among samples. Finally, our data sample was relatively small. Low statistical power due to smaller sample size could account for the non-signifi ant fi dings observed in many neuropsychological function and sleep onset latency measures following BLT.

[3]http://www.tractometer.org/ismrm_2015_challenge/results.

In summary, these fi dings provide preliminary evidence that BLT can affect recovery of brain structure and function following mTBI. Following BLT, normalized values of water diffusion were associated with increases in memory and sleep latency scores. While more research is warranted, these preliminary fi dings raise the possibility that BLT might be useful as a means of facilitating brain and cognitive recovery among individuals with mTBI. Finally, our results also support the use of NQA as a sensitive measure to analyze the effect of treatment following a brain injury.

ETHICS STATEMENT

Participants were thoroughly briefed on the potential risks and benefits of the study and all completed written informed consent before enrollment. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Offic (HRPO). All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

SB conducted the neuroimaging analyses and wrote the initial draft of the manuscript and organized the revisions. JV, RS, and ND each contributed to the writing of revisions of the manuscript and helped with data analysis. WK designed the study, oversaw data collection and analysis, and contributed to writing revisions of the manuscript.

ACKNOWLEDGMENTS

Th s research was supported by a U.S. Army Medical Research and Materiel Command Grant (W81XWH-11-1-0056) to WK. Opinions, interpretations, conclusions, and recommendations in this study are those of the author and are not necessarily endorsed by the Department of Defense. We would also like to thank Dr. Fang-Cheng Yeh for answering our enquires on numerous occasions during data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fneur.2017.00616/full#supplementary-material.

FIGURE S1 | Subject-averaged generalized fractional anisotropy (GFA), NQA, and isotropic diffusion (ISO) measure. Here, we plot the subject-averaged magnitude of raw diffusion measures before and after either amber-light therapy (ALT) **(A–C)** or blue-light therapy (BLT) **(D–F)** for GFA **(A,D)**, NQA **(B,E)**, and ISO **(C,F)**. Error bars represent the SEM.

REFERENCES

1. Levin HS, Mattis S, Ruff RM, Eisenberg HM, Marshall LF, Tabaddor K, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg* (1987) 66(2):234–43. doi:10.3171/jns.1987.66.2.0234
2. Silver JM, McAllister TW, Arciniegas DB. Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry* (2009) 166(6): 653–61. doi:10.1176/appi.ajp.2009.08111676
3. Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. Self-reported changes to nighttime sleep after traumatic brain injury. *Arch Phys Med Rehabil* (2006) 87(2):278–85. doi:10.1016/j.apmr.2005.10.024
4. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* (2007) 130(Pt 7):1873–83. doi:10.1093/brain/awm109
5. Sullivan KA, Edmed SL, Allan AC, Karlsson LJ, Smith SS. Characterizing self-reported sleep disturbance after mild traumatic brain injury. *J Neurotrauma* (2015) 32(7):474–86. doi:10.1089/neu.2013.3284
6. Inglese M, Makani S, Johnson G, Cohen BA, Silver JA, Gonen O, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* (2005) 103(2):298–303. doi:10.3171/jns.2005.103.2.0298
7. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol* (2013) 246:35–43. doi:10.1016/j.expneurol.2012.01.013
8. Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Clark RS, Ruppel RA, et al. Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatrics* (2002) 109(2):E31. doi:10.1542/peds.109.2.e31
9. Ruff R. Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil* (2005) 20(1):5–18. doi:10.1097/00001199-200501000-00003
10. Cicerone KD, Smith LC, Ellmo W, Mangel HR, Nelson P, Chase RF, et al. Neuropsychological rehabilitation of mild traumatic brain injury. *Brain Inj* (1996) 10(4):277–86. doi:10.1080/026990596124458
11. Paniak C, Toller-Lobe G, Reynolds S, Melnyk A, Nagy J. A randomized trial of two treatments for mild traumatic brain injury: 1 year follow-up. *Brain Inj* (2000) 14(3):219–26. doi:10.1080/026990500120691
12. Petraglia AL, Maroon JC, Bailes JE. From the fi ld of play to the fi ld of combat: a review of the pharmacological management of concussion. *Neurosurgery* (2012) 70(6):1520–33; discussion 1533. doi:10.1227/NEU.0b013e31824cebe8
13. Kurowski BG, Wade SL, Dexheimer JW, Dyas J, Zhang N, Babcock L. Feasibility and potential benefits of a web-based intervention delivered acutely after mild traumatic brain injury in adolescents: a pilot study. *J Head Trauma Rehabil* (2016) 31(6):369–78. doi:10.1097/HTR.0000000000000180
14. Viola AU, James LM, Schlangen LJ, Dijk DJ. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health* (2008) 34(4):297–306. doi:10.5271/sjweh.1268
15. Phipps-Nelson J, Redman JR, Schlangen LJ, Rajaratnam SM. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiol Int* (2009) 26(5):891–912. doi:10.1080/07420520903044364
16. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* (2002) 295(5557):1070–3. doi:10.1126/science.1067262
17. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. *PLoS Biol* (2009) 7(6):e1000145. doi:10.1371/journal.pbio.1000145
18. Wright HR, Lack LC, Kennaway DJ. Differential effects of light wavelength in phase advancing the melatonin rhythm. *J Pineal Res* (2004) 36(2):140–4. doi:10.1046/j.1600-079X.2003.00108.x
19. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Gotz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS One* (2011) 6(1):e16429. doi:10.1371/journal.pone.0016429
20. Correa A, Barba A, Padilla F. Light effects on behavioural performance depend on the individual state of vigilance. *PLoS One* (2016) 11(11):e0164945. doi:10.1371/journal.pone.0164945
21. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair* (2014) 28(4):303–13. doi:10.1177/1545968313508472
22. Niogi SN, Mukherjee P, Ghajar J, Johnson CE, Kolster R, Lee H, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain* (2008) 131(Pt 12):3209–21. doi:10.1093/brain/awn247
23. Geary EK, Kraus MF, Pliskin NH, Little DM. Verbal learning differences in chronic mild traumatic brain injury. *J Int Neuropsychol Soc* (2010) 16(3): 506–16. doi:10.1017/S135561771000010X
24. Matsushita M, Hosoda K, Naitoh Y, Yamashita H, Kohmura E. Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. *J Neurosurg* (2011) 115(1):130–9. doi:10.3171/2011.2.JNS101547
25. Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, et al. Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology* (2010) 74(7):558–64. doi:10.1212/WNL.0b013e3181cff5d5
26. Xiong K, Zhu Y, Zhang Y, Yin Z, Zhang J, Qiu M, et al. White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident. *Brain Res* (2014) 1591:86–92. doi:10.1016/j.brainres.2014.10.030
27. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* (2007) 130(Pt 10):2508–19. doi:10.1093/brain/awm216
28. Lipton ML, Gulko E, Zimmerman ME, Friedman BW, Kim M, Gellella E, et al. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology* (2009) 252(3):816–24. doi:10.1148/radiol.2523081584
29. Mayer AR, Ling J, Mannell MV, Gasparovic C, Phillips JP, Doezema D, et al. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology* (2010) 74(8):643–50. doi:10.1212/WNL.0b013e3181d0ccdd
30. Ling JM, Pena A, Yeo RA, Merideth FL, Klimaj S, Gasparovic C, et al. Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: a longitudinal perspective. *Brain* (2012) 135(Pt 4):1281–92. doi:10.1093/brain/aws073
31. Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY. Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS One* (2013) 8(11):e80713. doi:10.1371/journal.pone.0080713
32. Tuch DS. Q-ball imaging. *Magn Reson Med* (2004) 52(6):1358–72. doi:10.1002/mrm.20279
33. Fritzsche KH, Laun FB, Meinzer HP, Stieltjes B. Opportunities and pitfalls in the quantifi ation of fiber integrity: what can we gain from Q-ball imaging? *Neuroimage* (2010) 51(1):242–51. doi:10.1016/j.neuroimage.2010.02.007
34. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Th yagarajan M, et al. Sleep drives metabolite clearance from the adult brain. *Science* (2013) 342(6156):373–7. doi:10.1126/science.1241224
35. Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C. Effects of sleep and wake on oligodendrocytes and their precursors. *J Neurosci* (2013) 33(36):14288–300. doi:10.1523/jneurosci.5102-12.2013
36. Management of Concussion/mTBI Working Group. VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury. *J Rehabil Res Dev* (2009) 46(6):C1–68. doi:10.1682/JRRD.2008.03.0038
37. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci* (2007) 19(7):1081–8. doi:10.1162/jocn.2007.19.7.1081
38. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* (1998) 20(3):310–9. doi:10.1076/jcen.20.3.310.823
39. McKay C, Casey JE, Wertheimer J, Fichtenberg NL. Reliability and validity of the RBANS in a traumatic brain injured sample. *Arch Clin Neuropsychol* (2007) 22(1):91–8. doi:10.1016/j.acn.2006.11.003
40. Carskadon MA. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* (1986) 9(4):519–24. doi:10.1093/sleep/9.4.519
41. Fong SY, Ho CK, Wing YK. Comparing MSLT and ESS in the measurement of excessive daytime sleepiness in obstructive sleep apnoea syndrome. *J Psychosom Res* (2005) 58(1):55–60. doi:10.1016/j.jpsychores.2004.05.004
42. Littner MR, Kushida C, Wise M, Davila G, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* (2005) 28(1):113–21. doi:10.1093/sleep/28.1.113

43. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage* (2011) 58(1):91–9. doi:10.1016/j.neuroimage.2011.06.021
44. Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, et al. Is there "One" DLPFC in cognitive action control? Evidence for heterogeneity from co-activation-based parcellation. *Cereb Cortex* (2013) 23(11):2677–89. doi:10.1093/cercor/bhs256
45. Mori S, Wakana S, van Zijl PCM, Nagae-Poetscher LM. *MRI Atlas of Human White Matter*. Amsterdam: Elsevier (2005).
46. Bekiesinska-Figatowska M, Duczkowska A, Szkudlinska-Pawlak S, Duczkowski M, Madzik J, Cabaj A, et al. Diffusion restriction in the corticospinal tracts and the corpus callosum in neonates after cerebral insult. *Brain Dev* (2016) 39(3):203–10. doi:10.1016/j.braindev.2016.10.003
47. Huang X, Du X, Song H, Zhang Q, Jia J, Xiao T, et al. Cognitive impairments associated with corpus callosum infarction: a ten cases study. *Int J Clin Exp Med* (2015) 8(11):21991–8.
48. Mierzwa AJ, Marion CM, Sullivan GM, McDaniel DP, Armstrong RC. Components of myelin damage and repair in the progression of white matter pathology after mild traumatic brain injury. *J Neuropathol Exp Neurol* (2015) 74(3):218–32. doi:10.1097/NEN.0000000000000165
49. Winocur G. The hippocampus and thalamus: their roles in short- and long-term memory and the effects of interference. *Behav Brain Res* (1985) 16(2–3):135–52. doi:10.1016/0166-4328(85)90088-9
50. Aggleton JP, O'Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur J Neurosci* (2010) 31(12):2292–307. doi:10.1111/j.1460-9568.2010.07251.x
51. Stokum JA, Sours C, Zhuo J, Kane R, Shanmuganathan K, Gullapalli RP. A longitudinal evaluation of diffusion kurtosis imaging in patients with mild traumatic brain injury. *Brain Inj* (2015) 29(1):47–57. doi:10.3109/02699052.2014.947628
52. Menzler K, Belke M, Unger MM, Ohletz T, Keil B, Heverhagen JT, et al. DTI reveals hypothalamic and brainstem white matter lesions in patients with idiopathic narcolepsy. *Sleep Med* (2012) 13(6):736–42. doi:10.1016/j.sleep.2012.02.013
53. Feldman HM, Yeatman JD, Lee ES, Barde LH, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. *J Dev Behav Pediatr* (2010) 31(4):346–56. doi:10.1097/DBP.0b013e3181dcaa8b
54. Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, et al. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* (2016) 39(9):1671–80. doi:10.5665/sleep.6090
55. Rosenblum WI. Cytotoxic edema: monitoring its magnitude and contribution to brain swelling. *J Neuropathol Exp Neurol* (2007) 66(9):771–8. doi:10.1097/nen.0b013e3181461965
56. Browne KD, Chen XH, Meaney DF, Smith DH. Mild traumatic brain injury and diffuse axonal injury in swine. *J Neurotrauma* (2011) 28(9):1747–55. doi:10.1089/neu.2011.1913
57. Viano DC, Casson IR, Pellman EJ, Zhang L, King AI, Yang KH. Concussion in professional football: brain responses by fin te element analysis: part 9. *Neurosurgery* (2005) 57(5):891–916; discussion 891–916. doi:10.1227/01.NEU.0000186950.54075.3B
58. Miller KE, Heidemann SR. What is slow axonal transport? *Exp Cell Res* (2008) 314(10):1981–90. doi:10.1016/j.yexcr.2008.03.004
59. Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: clues to axon and myelin repair capacity. *Exp Neurol* (2016) 275(Pt 3):328–33. doi:10.1016/j.expneurol.2015.02.011
60. Duffy JF, Czeisler CA. Effect of light on human circadian physiology. *Sleep Med Clin* (2009) 4(2):165–77. doi:10.1016/j.jsmc.2009.01.004
61. Carpenter JS, Abelmann AC, Hatton SN, Robillard R, Hermens DF, Bennett MR, et al. Pineal volume and evening melatonin in young people with affective disorders. *Brain Imaging Behav* (2016):1–10. doi:10.1007/s11682-016-9650-2
62. Kumar R, Chavez AS, Macey PM, Woo MA, Yan-Go FL, Harper RM. Altered global and regional brain mean diffusivity in patients with obstructive sleep apnea. *J Neurosci Res* (2012) 90(10):2043–52. doi:10.1002/jnr.23083
63. Benedetti F, Melloni EMT, Dallaspezia S, Bollettini I, Locatelli C, Poletti S, et al. Night sleep influences white matter microstructure in bipolar depression. *J Affect Disord* (2017) 218:380–7. doi:10.1016/j.jad.2017.05.008
64. Clarner T, Diederichs F, Berger K, Denecke B, Gan L, van der Valk P, et al. Myelin debris regulates inflammatory responses in an experimental demyelination animal model and multiple sclerosis lesions. *Glia* (2012) 60(10):1468–80. doi:10.1002/glia.22367
65. Jiang C, Zhang L, Zou C, Long X, Liu X, Zheng H, et al. Diurnal microstructural variations in healthy adult brain revealed by diffusion tensor imaging. *PLoS One* (2014) 9(1):e84822. doi:10.1371/journal.pone.0084822
66. Elvsashagen T, Norbom LB, Pedersen PO, Quraishi SH, Bjornerud A, Malt UF, et al. Widespread changes in white matter microstructure after a day of waking and sleep deprivation. *PLoS One* (2015) 10(5):e0127351. doi:10.1371/journal.pone.0127351
67. Foote SL, Berridge CW, Adams LM, Pineda JA. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. *Prog Brain Res* (1991) 88:521–32. doi:10.1016/S0079-6123(08)63831-5
68. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. *Brain Res* (1996) 742(1–2):89–97. doi:10.1016/S0006-8993(96)00967-5
69. Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. *J Head Trauma Rehabil* (2009) 24(3):155–65. doi:10.1097/HTR.0b013e3181a0b281
70. Yeh FC, Vettel JM, Singh A, Poczos B, Grafton ST, Erickson KI, et al. Quantifying differences and similarities in whole-brain white matter architecture using local connectome fi gerprints. *PLoS Comput Biol* (2016) 12(11):e1005203. doi:10.1371/journal.pcbi.1005203

Confl ct of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or fi ancial relationships that could be construed as a potential confli t of interest.

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Journal:	*Social Cognitive and Affective Neuroscience*
Manuscript ID	SCAN-19-314
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	04-Oct-2019
Complete List of Authors:	Bajaj, Sahil ; University of Arizona , Department of Psychiatry Raikes, Adam; University of Arizona , Department of Psychiatry Razi, Adeel; Monash University, Turner Institute for Brain and Mental Health; University College London, The Wellcome Centre for Human Neuroimaging; NED University of Engineering and Technology, Department of Electronic Engineering Miller, Michael; University of Arizona , Department of Psychiatry Killgore, William; University of Arizona , Department of Psychiatry
Keywords:	Diffusion tensor imaging, Resting-state fMRI, Effective brain connectivity, Light Therapy, Mood

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Blue-light therapy strengthens effective connectivity within default-mode network following mTBI

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Running title: Blue-light therapy and DMN following mTBI

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Abstract

Emerging evidence suggests that symptoms following mild traumatic brain injury (mTBI) may be improved through morning exposure to blue-wavelength light therapy (BLT). The mechanisms underlying these effects remain unknown. For healthy control (HC) participants at rest, we found an effective connectivity (EC) pattern within the default-mode network (DMN) that showed dominant out-going information flow from the left lateral parietal cortex (LPC). Following mTBI , the EC pattern within the DMN showed dominant out-going information flow from the right LPC. Compared to placebo (amber light), BLT improved EC from the left LPC to medial prefrontal cortex. Following BLT, the overall EC pattern within the DMN of mTBI individuals was strengthened and showed a similar EC pattern to HCs. This improvement in EC was accompanied by stronger structural connectivity between the two areas. Following BLT, the observed improvements in structure and function were also correlated with improvements in mood. Our findings indicate a potential compensatory connectivity pattern following mTBI within the hemisphere opposite to that observed for HCs. Our findings also provide evidence that short-wavelength light therapy could be used as a novel alternative rehabilitation technique for mTBI, and indicate the EC patterns as crucial biomarkers following mTBI and light therapy.

Keywords

Diffusion tensor imaging, Resting-state fMRI, Effective brain connectivity, Light Therapy, Mood

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Introduction

A mild traumatic brain injury (mTBI) occurs when an individual experiences a blow to the head or body (McCrory P et al. 2013) that leads to a temporary alteration in consciousness or cognition (Blyth BJ and JJ Bazarian 2010; McInnes K et al. 2017). Within the brain, this physical force leads to sheared axons and microscopic changes in brain tissue (Su E and M Bell 2016). These injuries are common in contact sports such as soccer, hockey, football, and boxing, and are also among the most prevalent injuries sustained by military service members both in theater and garrison. Within the military alone, recent statistics suggest that more than 380,000 military personnel have sustained a traumatic brain injury since the year 2000, with 82.3% of these being in the mild range (DVBIC; 2018 Q1: https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi). Individuals with mild traumatic brain injuries may exhibit independent or simultaneous alterations in brain function and structure (Eierud C et al. 2014; Narayana PA 2017), and may lead to several post-concussive symptoms, including mood disturbances (Jorge RE and DB Arciniegas 2014; Emery CA et al. 2016) and impaired cognitive abilities (Malojcic B et al. 2008; McInnes K et al. 2017), including concentration/attention (Barman A et al. 2016) and memory problems (Vakil E 2005), and most commonly fatigue and sleep problems (Parcell DL et al. 2006; Ponsford JL et al. 2012; Grima N et al. 2016; Wickwire EM et al. 2016; Raikes AC et al. 2018). Because approximately half of all individuals who sustain a concussion will go on to complain sleep-related problems following their injury (Viola-Saltzman M and NF Watson 2012), recent treatment approaches have begun to focus on potential interventions to improve sleep within this population (Zeitzer JM et al. 2009; Gilbert KS et al. 2015), with the hope that better sleep will facilitate recovery from other post-concussion symptoms. Presently, there are few broadly accepted non-pharmacological treatments to facilitate sleep improvements from an mTBI (Diaz-Arrastia R et al. 2014). One particularly promising approach to regulating sleep and reducing fatigue in patients with mTBI is the use of daily morning blue-wavelength light therapy (i.e., light within the short wavelengths at ~480 nm) (BLT). Exposure to blue light is known to have a powerful influence on the circadian rhythm of sleep and wake (Chellappa SL et al. 2011). Blue light stimulates intrinsically photosensitive retinal ganglion cells (ipRGCs) that project to the suprachiasmatic nucleus (SCN) of the hypothalamus, which serves as the "master clock" of the body and the primary regulator of the circadian rhythm. Consequently, precisely timed BLT has been proposed as one possible, safe, and non-pharmacological way of regulating

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the circadian rhythm of sleep and, thereby, improving post-concussive symptoms among individuals with a TBI (Sinclair KL et al. 2014). Preliminary findings suggest that for individuals recovering from concussion morning BLT may be effective at reducing fatigue and daytime sleepiness (Sinclair KL *et al.* 2014), and at changing white-matter compactness within specific areas in association with improvements in sleep latency and delayed memory (Bajaj S et al. 2017).

A close link between sleep measures such as daytime sleepiness and sleep deprivation, and connectivity within the default-model network (DMN) - which is usually 'active' when an individual is at rest, cognitively disengaged, or during mind wandering - has been established in the past (De Havas JA et al. 2012; Ward AM et al. 2013). The impact of mTBI on functional brain connectivity (representing temporal correlations) within the DMN has also been extensively studied (Zhou Y et al. 2012; Iraji A et al. 2015; Alhourani A et al. 2016; Santhanam P et al. 2019). The frontal lobe, particularly the medial prefrontal cortex - an integral part of the DMN, is particularly vulnerable to disruption by mTBI (Eierud C *et al*. 2014), and this particular region plays a critical role in the generation and regulation of emotions (Dixon ML et al. 2017). Notably, mood disruption is also a common symptom following mTBI. BLT has also been shown to be helpful at improving mood (Strong RE et al. 2009; Holzman DC 2010; Lieverse R et al. 2011) in various other populations, and it is likely that it would have similar mood enhancing effects in patients with mTBI. Mood can be influenced by a number of factors, but it is well known that mood and DMN activation are closely related (Harrison BJ et al. 2008; Luo Y et al. 2016; Soares JM et al. 2017; Taruffi L et al. 2017). Despite this strong association between mood states and activation of the DMN, the effect of BLT on functional connectivity, particularly directed connectivity and structural connectivity measures within the DMN along with their association with mood states following an mTBI has not been explored.

Various neuroimaging methodologies allow the assessment of brain function and structure *in vivo*. Numerous studies have repeatedly demonstrated the inextricable association between measures of brain function and structure as well as highlighted the importance of unique information provided by each methodology (Greicius MD et al. 2009; Huang HQ and MZ Ding 2016; Zimmermann J et al. 2018). Recently, more advanced neuroimaging approaches and analysis techniques, such as effective connectivity (Friston KJ 2011) and diffusion-weighted structural imaging (Yeh FC et al. 2013), have been developed to better quantify the information flow within small and large-scale neural networks (Razi A et al. 2017). For

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instance, dynamic causal modeling (DCM) (Friston KJ et al. 2003; Friston KJ et al. 2014; Friston KJ et al. 2016) - an effective connectivity approach - is usually implemented to estimate directed connectivity within the brain (Friston KJ 2011). Effective connectivity here represents an explicit functional influence of one neural system over the other. DCM is based on theoretical assumptions specifying a set of hypotheses in terms of different models. Using the Bayesian model selection approach (Friston KJ *et al.* 2016), an optimal model is found in DCM by calculating model exceedance probability, which represents a degree of belief about a model having higher posterior probability than other remaining models. Diffusion weighted approaches can identify white-matter pathways using metrics such as fractional anisotropy (FA), which refers to *diffusivity* or *speed* of water diffusion along white matter fiber bundles. Similarly, quantitative anisotropy (QA), is another diffusion weighted metric that refers to *density* or *quantity* of water diffusion along white matter fiber bundles, and is sensitive to density characteristics of these bundles, such as fiber compactness (Yeh FC *et al.* 2013; Yeh FC, JM Vettel, et al. 2016). Compared to diffusivity measures, density measures are less susceptible to partial volume effects and are better able to filter out noisy values (Yeh FC *et al.* 2013).

In this study, we propose that measures of effective and structural connectivity (FA/QA) could be used in conjunction to better understand the dynamics of neural networks following an mTBI. Furthermore, we used this novel multi-modal approach to quantify the impact of BLT on the functional/structural architecture of the DMN and its association with mood. Therefore, the present study focused on identifying changes in effective connectivity in terms of directional influence within the DMN for healthy controls (HCs) and post-mTBI before and after a course of light therapy. Our first aim was to determine the post-mTBI damaged connectivity pattern (if any) within the DMN. Second, we then sought to identify the effect of six-weeks of daily morning exposure to BLT or a placebo amber-light therapy (ALT) on the altered effective connectivity of the DMN and calculate the extent to which the post-treatment connectivity pattern resembled that of the HCs. From diffusion-weighted data, we further investigated if there was any associated treatment effect (BLT versus ALT) on FA and QA measures within the DMN. Lastly, due to the close association between the DMN and mood, *especially* self-reported happiness (Luo Y *et al.* 2016; Taruffi L *et al.* 2017), we investigated whether changes in effective connectivity or characteristics of white-matter (FA or QA) following treatment with BLT were associated with changes in happiness. Overall, due to the known impact of BLT on mood and the close association between mood and DMN functioning, we

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hypothesized that BLT would strengthen the effective as well as structural characteristics of the DMN. Secondly, given the prior evidence of mood improvement with light treatment, we hypothesized that changes in the effective connectivity and both FA and QA following BLT would be associated with changes in self-reported happiness. Lastly, we predicted that the changes in effective connectivity (for both ALT and BLT groups) would be associated with changes in the characteristics of white matter in terms of FA and QA.

Methods

Participants

Forty-one healthy controls (HCs; mean age = 26.07±5.01 years, 25 F) and 28 individuals with an mTBI (mean age = 21.50±3.76 years, 15 F) (Table 1) underwent neuroimaging scans using a Siemens Tim Trio 3T scanner (Erlangen, Germany) at the McLean Hospital Imaging Center. Participants with an mTBI had to have experienced at least one traumatic injury or blow to the head leading to altered consciousness that may have resulted in complete loss of consciousness (less than 30 minutes) or post-traumatic amnesia (no longer than 24 hours) (Marshall S et al. 2012). All of the post-mTBI individuals were injured between 2 months and 18 months (mean = 6.84±4.0 months) prior to their screening and provided written documentation from a doctor, medical provider, physician, or other qualified individual. Individuals with any history of neurological or psychiatric disorder with an onset prior to the mTBI were excluded. All of the HCs were recruited as part of a separate study but completed an identical resting-state fMRI scan in the same scanner. All of the HCs were screened via a comprehensive telephone interview and excluded if they had any history of significant medical problems, current use of psychotropic medications, or current use of illicit substances. All participants provided written informed consent prior to enrollment and were financially compensated for their time. The Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Office (HRPO) approved the experimental protocol.

Procedure

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Individuals in the HC group underwent one neuroimaging session that included a T1-weighted structural MRI scan and a resting-state functional MRI scan. The mTBI group underwent a T1-weighted structural MRI scan, a resting-state functional MRI scan, and a diffusion-weighted MRI scan on two different occasions, separated by 6-weeks. After the first scanning session (baseline data collection), individuals in the mTBI group were randomly assigned to either the blue-light treatment (BLT; N = 14, mean age = 21.78±4.42 years, 8 F) or placebo amber-light treatment (ALT; N = 14, mean age = 21.21±3.09 years, 7 F) (Table 1) and provided with a commercially available light therapy device (GoLite Blu®, or matched amber device, Philips Electronics). All participants were instructed to use the device daily for six weeks (i.e., 30 minutes each morning, within 2 hours of awakening, but starting before 11:00 A.M). These devices provided controlled exposure to a narrow band of either blue wavelength light (λ = 469 nm) or amber wavelength light (λ = 578 nm), and consisted of a table-mounted, 13.5 x 14 cm plastic encased device with a 10-by-6 LED array.

Data acquisition

Automated Neuropsychological Assessment Metrics (ANAM4)

Participants in the mTBI group completed the ANAM4 Concussion Battery at baseline and post-treatment. The ANAM (v4) battery is an automated computer-based battery to test the cognitive performance of the participants (Cognitive Science Research Center (CSRC) 2014). It mainly includes detailed TBI questionnaire, seven subtests: Code Substitution Delayed, Code Substitution, Matching-to-Sample, Mathematical Processing, Procedural Reaction Time, Simple Reaction Time (SRT) and Simple Reaction Time Repeated (SR2), sleepiness scale and mood scale. Construct validity and test-retest reliability of ANAM measures have been shown in previous studies (Short P et al. 2007; Johnson DR et al. 2008). In particular, the ANAM Mood Scale includes measures of anger, depression, fatigue, happiness, vigorousness, restlessness, and anxiety. For each mood category, participants were asked to select their predominant mood state, representing 'how' they felt at that time using a 7-point (0 for *not at all*, midpoint 3 for *somewhat*, and 6 for *very much*) Likert scale. Because of previously published studies describing a close association between functional connectivity within the DMN and happiness (Luo Y *et al.* 2016;

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Taruffi L *et al.* 2017), and for the purpose of this manuscript, only the happiness scores (HAP) reported in the Mood scale of ANAM battery were used for the analysis.

Questionnaire for morningness and eveningness

Trained research assistants administered the Horne-Ostberg Morningness-Eveningness Questionnaire (Horne JA and O Ostberg 1976) to each participant. In the present sample, scores on the questionnaire ranged from 42 to 65, with a mean of 51.88±5.52. Here, lower scores represent greater preference for evening activities, and higher scores represent the tendency to prefer morning activities (i.e., fewer preferences for evening activities).

T1-weighted and resting-state functional magnetic resonance imaging (rsfMRI) data

Structural and functional MRI data from all of the participants were recorded using a 3T Siemens TIM Trio whole-brain MR scanner located at the McLean Hospital Imaging Center. During both scans, participants were instructed to relax and remain still during scanning. T1-weighted data from HCs were acquired using a 3D magnetization-prepared rapid acquisition gradient echo sequence which consisted of 128 sagittal slices (voxel resolution = 1.33×1×1 mm^3, field of view (FOV) = 256 mm) with TR/TE/FA/inversion time of 2100 ms/2.25 ms/12°/1100 ms. T1-weighted data from mTBI individuals were also acquired using a 3D magnetization-prepared rapid acquisition gradient echo sequence which consisted of 176 sagittal slices (voxel resolution = 1×1×1 mm^3, field of view (FOV) = 256 mm) with TR/TE/FA/inversion time of 2100 ms/2.30 ms/12°/1100 ms. The resting-state scan lasted for 6 minutes, and data were acquired using a T2*-weighted echo-planner imaging (EPI) sequence, which consisted of 180 frames (voxel resolution = 3.5×3.5×3.5 mm^3, field of view (FOV) = 384 mm) with TR/TE/FA of 2000 ms/30 ms/90°. During resting state scanning, participants were asked to keep their eyes open and to let their mind wander.

Diffusion-weighted imaging (DWI) data

The DWI data were acquired along 72 directions with maximum *b*-value = 1,000 s/mm^2, eight images with no diffusion weighting (b0 images), voxel size = 1.75 mm × 1.75 mm × 3.5 mm, FA/TR/TE/slice thickness

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of 90°/6,340 ms/99 ms/3.5 mm, and number of slices = 40 encompassing the whole brain. We converted DWI data from DICOM into NIFTI format using the dcm2nii function available in the MRIcron package (Rorden C et al. 2007), which also generated a *b*-value and *b*-vector file for each participant.

Data analysis

Outlier detection

Two participants from the mTBI sample, one from the ALT group and the second from the BLT group, showed excessive head-motion during functional and diffusion-weighted scans, and were excluded from further analysis. Next, ANAM Happy mood data were screened for outliers. None of the data points on the mood scale were identified as outliers (i.e., a value of more than 1.5 inter-quartile range below/above the top or bottom quartiles).

Functional image preprocessing and directed brain connectivity analysis

Standard preprocessing steps, including slice-timing correction, motion-correction, co-registration, spatial normalization, and smoothing at 6 mm full width at half maximum were completed in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were resliced for isotropic voxel dimensions of 2x2x2 mm^3. Four spherical regions within the DMN, namely the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and left and right lateral parietal cortex (LLPC/RLPC) with a radius of 8 mm and peak MNI co-ordinates at (0, -52, 27), (-1, 54, 27), (-46, -66, 30) and (49, -63, 33) respectively (Raichle ME 2011), were used as regions of interest (ROIs). For estimating the effective brain connectivity within the DMN, the spectral dynamical causal modeling approach (Friston KJ *et al.* 2014) was used. Individual connectivity parameters for all participants were modeled at the group-level using a Bayesian GLM with a regressor for each group's mean value per connection. Here, mean centered 'age' and 'sex' were included as covariates for comparison between (i) HCs and individuals with mTBI, (ii) pre- and post-treatment conditions for ALT and BLT groups, and (iii) HCs and post-treatment (APost and BPost) conditions for individuals with mTBI. However, two additional covariates - 'time since injury' and 'number of days light was used' were included for comparisons between pre- and post-treatment conditions

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for ALT and BLT groups. We then used an automatic search using Bayesian model reduction (Friston KJ *et al.* 2016) to compare reduced models nested within the fully connected model and 'pruned' connection parameters; parameters of the best 256 pruned models (in the last Occam's window) were averaged and weighted by their evidence (i.e. Bayesian Model Averaging) to generate final estimates of connection parameters. Only the parameters that exceeded 95% posterior probability (Pp) were interpreted. Also, for convenience we did not interpret the self-connections. For brain-behavior correlations, subject-wise connectivity values for the connections, which showed an improvement in connectivity strength, were extracted.

Diffusion-weighted image (DWI) processing: Fractional and quantitative anisotropy (FA/QA) analysis

For head-motion correction, standard eddy current correction was performed on diffusion-weighted data using the FMRIB Software Library v6.0 processing software package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). The motion-corrected data were imported into DSI Studio (http://dsi-studio.labsolver.org) and converted into SRC format, which stores the DWI volumes, image dimensions, voxel size and b-table. Each SRC file underwent thorough examination using quality control (QC) procedures to ensure the quality and integrity of data in terms of consistency of image dimensions, resolution, DWI count, and neighboring DWI correlation (NDC). NDC represents the correlation coefficient of low-b diffusion volumes, which have similar gradient directions. In other words, DSI Studio computes a voxel-wise correlation coefficient between every two DWIs of closest b-vector (multiplied by b-value), and NDC represents the average of those coefficients. Here, higher NDC values represent good data quality, and vice-versa. NDC values for the current data set were greater than 0.95. None of the NDC values was identified as outlier (i.e., with a value greater than 3 times the mean).

For estimating the structural connectivity in terms of FA and QA for the white-matter fiber tracts connecting the regions that showed an improvement in directed connectivity from pre-treatment to post-treatment, the diffusion MRI connectometry technique was implemented (Yeh FC, D Badre, et al. 2016). This technique, implemented in DSI Studio, was used to extract FA and QA values from each subject for each group. Here a FA and QA component database was created in normalized standard space (HCP842 template for young adults) using the Q-space diffeormophic reconstruction (QSDR) (Yeh FC and WY

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Tseng 2011) approach. QSDR is a model free approach, which calculates the distribution of water diffusion using a high-resolution standard brain atlas constructed from 90-diffusion spectrum imaging datasets in the ICBM-152 space. Automated registration to standard template space was used for each subject. All of the ROIs were defined in MNI space in order to perform diffusion MRI connectometry in QSDR space. A seed count of 50,000 sub voxels (randomized) for each region was used for connectometry analysis. All the ROIs were dilated by 5 mm to extend to white matter. The default direction interpolation (trilinear) method and default-tracking algorithm (streamline) were used to perform tractography. To limit the tracts between specific regions, a length threshold between 50 mm and 200 mm, an angle threshold of 70 degrees, differential tracking threshold of 0.30, and a default Otsu threshold of 0.60 were applied. Tract pruning was conducted using a single iteration.

Associations between estimated effective connectivity, HAP, FA and QA

Initially, ANAM HAP, FA and QA parameters were compared using paired sample t-tests. The associations between effective connectivity and HAP, FA and HAP, and between QA and HAP were calculated by using residualized change scores which were derived by regressing subject-wise post-treatment measures of connectivity, HAP, FA and QA on pre-treatment measures of connectivity, HAP, FA and QA respectively. Several important covariates including 'age', sex' and 'body-weight' were included in the correlation analysis. Because of the close association between mTBI and sleep, as well as between sleep and blue-light therapy, the 'score on the morningness and eveningness questionnaire at baseline (chronotype)' was also included as an additional covariate.

Results

For simplification, we will use the following abbreviations in this section:

- APre/APost: for pre/post-treatment condition of individuals with mTBI in ALT group
- BPre/BPost: for pre/post-treatment condition of individuals with mTBI in BLT group

Demographics

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HC and mTBI groups differed significantly in age, but not gender. The ALT and BLT groups did not differ significantly in age, sex, time-since injury (TSI), number of days light used within 2 hours of waking-up, or baseline levels of happiness. These findings are summarized in Table 1.

Effective brain connectivity within the DMN

HCs and mTBI (pre-treatment): In Figure 1 (A-B), we show the subject average connectivity strength (in Hz) of all the connections within the DMN for HCs (A) and mTBI (B). In Figure 1C, we show the differences of connectivity strengths between HCs and mTBI. Positive and negative values in Figures 1A and 1B represent the excitatory and inhibitory connections respectively. The positive values for Figure 1C represent the connections that are more positive in HCs than the mTBI group, whereas the negative values here represent the connections that are more negative in HCs than the mTBI group. Connections exceeding the posterior probability of 95% are indicated by '*' in Figure 1 (A-C), and are shown in Figure 1D (HCs), 1E (mTBI) and 1F (HCs > mTBI). Here, we noticed that for HCs the network pattern was more dominant within the left hemisphere, particularly involving the LLPC, and interestingly, for mTBI the network pattern was more dominant within the right hemisphere particularly involving the RLPC. Both these regions (LLPC for HCs and RLPC for mTBI) were acting as 'sources' indicating out-going information flow.

APost vs. APre, BPost vs. BPre, and HCs vs. APost and BPost: In Figure 2 (A-D), we showed the comparisons of connectivity strengths between APost and APre (A), BPost and BPre (B), HCs and APost (C), and HCs and BPost (D). The positive values in Figure 2A and 2B represent the connections that are more positive in APost and BPost than APre and BPre respectively, whereas the negative values here represent the connections that are more negative in APost and BPost than APre and BPre respectively. Similarly, the positive values for Figures 2C and 2D represent the connections that are more positive in HCs than APost and BPost respectively, whereas the negative values here represent the connections that are more negative in HCs than APost and BPost respectively. Connections exceeding the posterior probability of 95% are indicated by '*' in Figure 2 (A-D), and are shown in Figures 2E (APost > APre), 2F (BPost > BPre), 2G (HCs > APost), and 2H (HCs > BPost). Here, as expected, for individuals who underwent amber-light placebo therapy, the network pattern did not show any difference between post-treatment condition compared to pre-treatment at a posterior probability of 95%. Interestingly, for individuals who

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underwent blue-light therapy, the connectivity strength from LLPC to MPFC was greater for the post-treatment condition compared to pre-treatment at a posterior probability of 95%, i.e., LLPC was acting as a 'source' to deliver information to MPFC. In addition, the information flow from LLPC to other regions, including PCC and RLPC was still greater for HCs than mTBI individuals who underwent amber-light placebo therapy. However, it was only one connection i.e., from LLPC to PCC, which showed greater information flow in HCs than mTBI individuals who underwent blue-light therapy.

APost and BPost: In Figure 3 (A-B), we showed the subject average connectivity strength of all the connections within the DMN for APost (A) and BPost (B). Positive and negative values in Figure 3 represent the excitatory and inhibitory connections respectively. Connections exceeding the posterior probability of 95% are indicated by '*' in Figure 3 (A-B), and are shown in Figures 3C (APost) and 3D (BPost). Here, we noticed that at posterior probability of 95%, the individuals who underwent amber-light placebo therapy had a different connectivity pattern compared to HCs with a dominant role of the RLPC, whereas the individuals who underwent blue-light therapy show very similar connectivity pattern to HCs with a dominant role of the LLPC.

FA, QA and Happiness

FA and QA: From effective connectivity analysis at posterior probability of 95%, we observed that following amber-light placebo therapy, none of the connections showed an improvement in connectivity strength, whereas following blue-light therapy, one connection from LLPC to MPFC was improved and the overall connectivity pattern was almost normalized back to that observed in the HCs for BLT group. Therefore, the structural connectivity analysis was limited to the tracts connecting LLPC (seed region) and MPFC (region of interest). Subject averaged maps of structural connectivity (in terms of QA) between LLPC and MPFC are shown in Figure 4 (A: ALT Group and B: BLT Group). We found that there was no significant difference in FA for tracts connecting LLPC and MPFC for either ALT group (APre vs. APost) (paired t-test, $t(12) = -0.31$, $p = 0.760$) (Figure 5A) or BLT group (BPre vs. BPost) (paired t-test, $t(12) = -0.45$, $p = 0.662$) (Figure 5B). Also, there was no significant difference in QA for tracts connecting LLPC and MPFC for ALT group (APre vs. APost) (paired t-test, $t(12) = -0.75$, $p = 0.468$) (Figure 5C), but there

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was a clear trend of greater QA for BPost compared to BPre (paired t-test, t (12) = 2.1, p = 0.057) (Figure 5D).

Happiness: We found no significant change in levels of happiness (from 3.89±1.06 (pre) to 3.40±1.56 (post) on raw scale, or 64.74±17.73 (pre) to 56.62±26.07 (post) on relative percent scale) for individuals who used amber-light placebo therapy compared to their pre-treatment condition (paired t-test, t (12) = -1.46, p = 0.170) (Figure 5E). Similarly, levels of happiness did not change significantly (from 4.26±1.07 (pre) to 4.28±1.06 (post) on raw scale, or 70.94±17.81 (pre) to 71.37±17.73 (post) on relative percent scale) for individuals who used blue-light therapy compared to their pre-treatment condition (paired t-test: t (12) = 0.1, p = 0.924) (Figure 5F). Error bars in Figure 5 represent 'standard error of the mean'. Here, relative percent of happiness scale as shown in Figure 5 (E-F) represents the average of the responses across the adjectives of each category relative to the maximum possible rating (Vincent AS et al. 2012).

Associations among changes in directed connectivity (Conn), FA, QA, and HAP

Conn vs. Happiness: We found that for ALT group, there was no significant association between residualized changes in effective connectivity (Res Conn) from LLPC to LMPC and residualized changes in happiness (Res Happiness) (r = -0.36, *p* = 0.27) (Figure 6A). Interestingly, we found that for BLT group, there was significant positive association between residualized changes in directed connectivity (Res Conn) from LLPC to LMPC and residualized changes in happiness (Res Happiness) (r = 0.63, *p* = 0.03) (Figure 6B). Correlation coefficients between 'Res Conn' and 'Res Happiness' were also significantly different between ALT and BLT groups (z = -2.5, p = 0.01).

FA vs. Happiness: We found that for the ALT group, there was no significant association between residualized changes in FA (Res FA) for tracts connecting LLPC and LMPC and residualized changes in happiness (Res Happiness) (r = -0.02, *p* = 0.96) (Figure 6C). Consistent with the effective connectivity findings above, we found that for BLT group, there was significant positive association between residualized changes in FA (Res FA) for tracts connecting LLPC and LMPC and residualized changes in

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happiness (Res Happiness) ($r = 0.90$, $p < 0.01$) (Figure 6D). Correlation coefficients between 'Res FA' and 'Res Happiness' were also significantly higher for the BLT than the ALT group ($z = -3.34$, $p < 0.01$).

QA vs. Happiness: We found that for the ALT group, there was no significant association between residualized changes in QA (Res QA) for tracts connecting LLPC and LMPC and residualized changes in happiness (Res Happiness) ($r = -0.46$, $p = 0.13$) (Figure 6E). However, we found that for the BLT group, there was a clear trend showing a positive association between residualized changes in QA (Res QA) for tracts connecting LLPC and LMPC and residualized changes in happiness (Res Happiness) ($r = 0.59$, $p = 0.06$) (Figure 6D). Correlation coefficients between 'Res QA' and 'Res Happiness' were also significantly different between ALT and BLT groups ($z = -2.63$, $p < 0.01$).

Conn vs. FA and QA: Three important covariates – 'age', 'sex', and 'body weight' were used for the partial correlation analysis between residualized changes in effective brain connectivity (Res Conn) from LLPC to MPFC and residualized changes in structural brain connectivity (Res FA for FA and Res QA for QA) for the tracts connecting LLPC and MPFC. We found that there was no significant association between 'Res Conn' and either 'Res FA' or 'Res QA' for either the ALT group (Res Conn vs. Res FA: $r = -0.22$, $p = 0.51$ (Figure 7A); Res Conn vs. Res QA: $r = -0.30$, $p = 0.37$ (Figure 7B)), or BLT group (Res Conn vs. Res FA: $r = 0.03$, $p = 0.92$ (Figure 7C); Res Conn vs. Res QA: $r = -0.48$, $p = 0.13$ (Figure 7D)). The overall sample (combined ALT and BLT groups) also did not show any association between 'Res Conn' and either 'Res FA' or 'Res QA' (Res Conn vs. Res FA: $r = -0.12$, $p = 0.58$ (Figure 7E); Res Conn vs. Res QA: $r = -0.22$, $p = 0.30$ (Figure 7F)).

Discussion

Our findings suggest that relative to healthy-controls, there are identifiable group-level differences in directed (effective) connectivity within the DMN among individuals recovering from a recent mTBI, suggesting a compensatory connectivity pattern for individuals with an mTBI. We also found an improvement over the course of treatment for effective connectivity within the DMN, particularly from LLPC to MPFC, for those receiving blue-light therapy, and normalizing the overall connectivity pattern

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back to that seen in healthy controls. This pattern was not observed for the placebo group. We observed that following blue-light therapy; individuals with mTBI also had greater white-matter compactness. Finally, we found that changes in the strength of effective connectivity from LLPC to MPFC and both FA and QA from pre to post treatment were associated with greater levels of happiness for the BLT group, but not ALT group. We discuss each of these findings in greater detail below.

Effective connectivity within the DMN for HCs and post-mTBI

We found that in comparison to HCs, post-mTBI participants had weaker connectivity between several regions within the DMN. Our findings extend previous reports published on functional brain connectivity following mTBI. For instance, weaker functional connectivity within the DMN involving the posterior cingulate cortex and parietal areas was reported following mTBI (Zhou Y *et al.* 2012). Decreased cortical volume (Levine B et al. 2008) as well as grey matter atrophy (Yount R et al. 2002) within the posterior regions of the brain have often been reported among individuals with mTBI. We observed that for HCs, the PCC and the parietal cortex within the left hemisphere were significantly involved. The connectivity strength within the left hemisphere involving the PCC and the parietal cortex was weaker following mTBI, whereas the connectivity strength within the right hemisphere among these same regions was stronger following mTBI. These findings suggest that following a concussion, the DMN may reorganize some connectivity patterns. The independent components involving distinct connectivity patterns within each hemisphere may play important roles in compensating for potential deficits following an mTBI. Previous brain connectivity studies, although not specific to mTBI, support our notion and suggest that the damaged brain connectivity within the affected hemisphere could be compensated for by the expression of stronger brain connectivity within the less affected hemisphere (Bajaj S et al. 2016; Celeghin A et al. 2017). Therefore, in our study, stronger effective connectivity for the mTBI group (prior to treatment), particularly in the hemisphere opposite to the one where stronger connectivity was observed for HCs, may indicate compensatory reorganization of the DMN following injury.

Effect of light-therapy on happiness, effective connectivity and white-matter characteristics

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Happiness. First, it should be noted in our study that the ANAM battery data were not available within the HCs sample so a direct comparison between HCs and individuals with mTBI regarding scores on happiness scale was not possible. However, established normative data collected from more than 100,000 active duty service members ranging from 17 to 65 years of age suggests that the average relative percent score on happiness scale for the mTBI group at baseline reported in this study (67.84 ±17.69) was within the normal range of average scores between 64.4±21.6 and 68.2±21.2 collected from de-identified service members aged between 17-35 (Vincent AS *et al.* 2012). Therefore, non-significant changes in happiness levels following either therapy could be either due to the normal levels of happiness in mTBI individuals at the baseline, and/or due to the fact that the two light groups were not well matched at baseline in terms of mood.

Effective connectivity and QA. BLT showed an improvement in both effective and structural connectivity patterns within the DMN. Emerging evidence suggests that blue light exposure can have a wide range of effects on cognition (Yamadera H et al. 2000) as well as on functional and structural neural characteristics (Alkozei A et al. 2016; Bajaj S *et al.* 2017). It remains a question of interest as to why blue-light exposure would have a positive effect on effective and associated structural connectivity within the DMN. The following proposed theories might indirectly explain the underlying mechanisms responsible for the observed changes in functional and structural neural characteristics following blue-light therapy for post-mTBI. The strongest evidence for the role of blue light involves its effects on circadian and sleep systems. Notably, dysfunctions in sleep patterns are among the most common problems observed in individuals with traumatic brain injury (Castriotta RJ et al. 2007; Orff HJ et al. 2009; Castriotta RJ and JN Murthy 2011; Viola-Saltzman M and NF Watson 2012; Sullivan KA et al. 2016), and it has been reported that morning exposure to blue-light can lead to improved circadian timing and greater daytime alertness resulting in overall improvements in sleep quality (Yamadera H *et al.* 2000; Vandewalle G et al. 2009; Wang H-B et al. 2017). In addition, better sleep quality may modulate the mechanisms underlying the proliferation of oligodendrocyte precursor cells (Bellesi M et al. 2013), as well as the removal of neurotoxins that accumulate during waking hours (Xie L et al. 2013). Although direct improvements in sleep quality were not reported in this study, it is still possible that the observed improvements from BLT within the DMN may be one of the consequences of improved sleep. Blue-light may also cause a phase shift in the circadian

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timing of sleep onset by suppressing melatonin production from the pineal gland (Brainard GC and JP Hanifin 2005). Light in the morning, as occurred in this study, leads to a phase advance of the rhythm, which tends to lead to an earlier bedtime and wake time. This phenomenon may also play an important role in modulating neural repair processes following an mTBI. While we propose that the positive influences that emerge from blue-wavelength light could be due to its impact on circadian mechanisms, further work is required to confirm the neural basis of these underlying improvements. To our knowledge, this is the first study demonstrating the effects of BLT on effective connectivity in conjunction with white-matter characteristics within the DMN, and its associated effects on mood.

Association between happiness and DMN connectivity. While we did not see a direct difference between the light groups in mood scores, we did observe strong positive associations between residualized change in scores on the happiness scale and both residualized change in effective connectivity strength from the left lateral parietal cortex to the medial prefrontal cortex as well as measures of white-matter integrity (FA) and compactness (QA) for white-matter fiber tracts between the same two regions following BLT, but not following ALT. However, prior studies reported a negative association between DMN functional connectivity and happiness in healthy-controls. In particular, Luo and colleagues reported that compared to happy individuals, individuals with lower levels of happiness had stronger functional connectivity within the DMN (Luo Y *et al.* 2016). Taruffi and colleagues found higher scores on a mind-wandering scale during sad music as compared to happy music, as well as to happy but slow music compared to happy fast music (Taruffi L *et al.* 2017). In a web-app based study of 2250 participants, it was found that the mind-wandering phenomenon tends to be most associated with feelings of unhappiness (Killingsworth MA and DT Gilbert 2010). It should be noted that all of these studies established the association between DMN and levels of happiness only in healthy-controls or in general, whereas our findings show the association between the two following a treatment for individuals recovering from mTBI. Therefore, our findings do not contradict the previous literature; rather our results indicate that for individuals recovering from an mTBI, the improvements in effective connectivity within the DMN following blue-light therapy are associated with improvement in self-rated feelings of happiness.

Association between changes in directed connectivity, and changes in FA and QA

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Contrary to our hypothesis, we did not observe an association between residualized changes in effective connectivity and residualized changes in FA or QA. Absence of association between the two may indicate the distinct independent neural mechanisms underlying significant changes in effective connectivity and white-matter characteristics (FA or QA) following blue-light therapy, but still each of these (i.e., effective connectivity, FA and QA) holding a significant association with changes in scores on the happiness scale. Previously, Greicius and colleagues reported that resting state functional connectivity within the DMN reflects the underlying anatomical connectivity to a large degree (Greicius MD *et al.* 2009). In that study, the authors made it clear that functional connectivity can still exist even in the absence of direct structural connections, although the existence of anatomical connectivity in absence of functional connectivity is relatively less plausible, suggesting that overall both functional connectivity and anatomical connectivity can exist independently. Our findings are further supported by the fact that anatomical connectivity constrains, rather than determines, directed connectivity, because changes in directed connectivity depend on recent functional changes or transmission of neuronal signals within a synapse (Zucker RS and WG Regehr 2002), even in the absence of associated structural change (Stephan KE et al. 2009). Stephan and colleagues suggested that due to the dependence of neuronal signal transmission on temporal components resulting from several mechanisms including membrane potential and opening/closing of ion gated channels, anatomical connectivity may not be engaged during a specific directed connection or signal flow (Stephan KE *et al.* 2009).

Limitations

Findings from this study should be interpreted in light of several limitations. First, the changes in effective connectivity following an mTBI reported in this study might not be generalizable across heterogeneous mTBI profiles, because every mTBI may represent a unique injury and it is highly unlikely that specific connectivity values would reflect changes common to most mTBIs. Replication will be required to determine the stability of the patterns we observed here. Second, our mTBI sample was fairly heterogeneous with regard to time since injury, and it is conceivable that connectivity patterns may differ across the recovery period. While we constrained this time to no more than 18 months post injury, there

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was considerable variability in time since injury within this time frame. Nevertheless, we do not believe this was a significant contributor to the outcomes, as we statistically controlled for this variable in the analyses. Third, the sample sizes of both treatment groups were relatively small. Future studies are needed to replicate our findings with larger sample size. However, despite the small sample sizes for the treatment conditions, we found that BLT, not ALT, appears to strengthen the connectivity within the DMN. Lastly, our study focused on only the default-mode network. Future studies should make use of large-scale DCM (Razi A *et al.* 2017) technique to explore the impact of light –therapy on other functional networks of the brain.

Conclusions

Our results demonstrate that the DMN is susceptible to mild head injury. Moreover, our empirical findings also suggest that six-weeks of morning blue-light therapy produces stronger effective connectivity as well as greater white-matter compactness within the DMN, *especially* between the lateral parietal and medial prefrontal regions, and sustained levels of happiness. However, the neural mechanisms causing the underlying associations between changes in functional/structural connectivity patterns and the changes in mood could be independent, as evidenced by non-significant associations between changes in effective connectivity and structural influences. In sum, the present findings suggest that short-wavelength light therapy could be used as a novel alternative rehabilitation technique that can potentially strengthen the functional and structural pathways within the DMN.

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Acknowledgements

This research was supported by grants from the U.S. Army Medical Research and Materiel Command to WDSK (W81XWH-11-1-0056 and W81XWH-09-1-0730). Opinions, interpretations, conclusions and recommendations in this study are those of the author and are not necessarily endorsed by the Department of Defense. A.R. is funded by the Australian Research Council Discovery Early Career Research Award Fellowship (DE170100128) and the Wellcome Trust.

Author contributions

SB analyzed the data and wrote the initial draft. ACR contributed to the statistical analysis and writing of the initial draft. AR contributed to spectral DCM analysis and contributed to the writing of the manuscript. MAM contributed to writing of the manuscript. WDSK designed the study, obtained the funding, supervised all aspects of the study, and contributed to writing of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Table

Table 1. Demographics

Figure Legends

Figure 1. Effective connectivity for HCs and individuals with mTBI. Here we showed the subject average connectivity strength (in Hz) of all the connections within the DMN for HCs (A) and post mTBI (B). Positive and negative values here represent the exhibitory and inhibitory connections respectively. In Figure 1C, we showed the comparisons of connectivity strengths between HCs and post mTBI. The positive values here represent the connections that are more positive in HCs than post mTBI, whereas the negative values here represent the connections that are more negative in HCs than post mTBI. Connections exceeding the posterior probability of 95% are indicated by '*' in Figure 1 (A-C), and are shown in Figure 1D (HCs), 1E (mTBI) and 1F (HCs vs. mTBI).

Figure 2. Comparisons of directed connectivity for APost vs. APre, BPost vs. BPre, and HCs vs. APost and BPost: Here we showed the comparisons of connectivity strengths between APost and APre (A), BPost and BPre (B), HCs and APost (C), and HCs and BPost (D). The positive values (A-B) represent the connections that are more positive in APost and BPost than APre and BPre respectively, whereas the negative values here represent the connections that are more negative in APost and BPost than APre and BPre respectively. Similarly, the positive values for Figure 2C and 2D represent the connections that are more positive in HCs than APost and BPost respectively, whereas the negative values here represent the

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connections that are more negative in HCs than APost and BPost respectively. Connections exceeding the posterior probability of 95% are indicated by '*' (A-D), and are shown in Figures 2E (APost > APre), 2F (BPost > BPre), 2G (HCs > APost), and 2H (HCs > BPost).

Figure 3. Effective connectivity for APost and BPost. Here we showed the subject average connectivity strength of all the connections within the DMN for APost (A) and BPost (B). Positive and negative values (A-B) represent the exhibitory and inhibitory connections respectively. Connections exceeding the posterior probability of 95% are indicated by '*' (A-B), and are shown in Figures 3C (APost) and 3D (BPost).

Figure 4. White-matter tractography for ALT and BLT groups. Here we showed subject averaged maps of structural connectivity (in terms of QA) between LLPC and MPFC (A: ALT Group and B: BLT Group).

Figure 5. Comparisons of FA, QA, and levels of happiness (HAP). We found that there was no significant difference in FA for tracts connecting LLPC and MPFC for either ALT group (APre vs. APost) (paired t-test, $p = 0.760$) (Figure 5A) or BLT group (BPre vs. BPost) (paired t-test, $p = 0.662$) (Figure 5B). Also, there was no significant difference in QA for tracts connecting LLPC and MPFC for ALT group (APre vs. APost) (paired t-test, $p = 0.468$) (Figure 5C), but there was a clear trend of greater QA for BPost compared to BPre (paired t-test, $p = 0.057$) (Figure 5D). Lastly, we found non-significant reduction in levels of happiness for individuals who used amber-light therapy compared to their pre-treatment condition (paired t-test, $p = 0.170$) (Figure 5E). However, levels of happiness sustained for individuals who used blue-light therapy compared to their pre-treatment condition (paired t-test: $p = 0.924$) (Figure 5F). Error bars here represent 'standard error of the mean'.

Figure 6. Associations between residualized changes (pre- to post-treatment) in happiness (Res Happiness) vs. residualized changes (pre- to post-treatment) in directed connectivity (Conn), FA, and QA. We did not find significant association between residualized changes in happiness scores (Res Happiness) and residualized changes in directed connectivity (Res Conn) from LLPC to MPFC for ALT

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group (A), but there was significant positive association between Res Happiness and Res Conn from LLPC to MPFC for BLT group (B). There was no significant association between Res Happiness and Res FA for tracts connecting LLPC and MPFC for ALT group (C), but there was significant positive association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for BLT group (D). Lastly, there was no significant association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for ALT group (E), but there was clear trend showing a positive association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for BLT group (F).

Figure 7. Associations between residualized changes (post- to pre-treatment) in directed connectivity (Conn) vs. residualized changes (post- to pre-treatment) in FA and QA. Neither of the groups ALT (A-B) or BLT (C-D) showed significant association between residualized changes in Conn (Res Conn) from LLPC to MPFC and residualized changes in either FA (Res FA) (A, C) or QA (Res QA) (B, D) for tracts connecting LLPC and MPFC. Overall sample also did not show significant association between Res Conn from LLPC to MPFC and either Res FA (E) or Res QA (F) for tracts connecting LLPC and MPFC.

References

Alhourani A, Wozny TA, Krishnaswamy D, Pathak S, Walls SA, Ghuman AS, Krieger DN, Okonkwo DO, Richardson RM, Niranjan A. 2016. Magnetoencephalography-based identification of functional connectivity network disruption following mild traumatic brain injury. J Neurophysiol. 116:1840-1847.

Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, Shane BR, Knight SA, Killgore WD. 2016. Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. Sleep. 39:1671-1680.

Bajaj S, Housley SN, Wu D, Dhamala M, James GA, Butler AJ. 2016. Dominance of the Unaffected Hemisphere Motor Network and Its Role in the Behavior of Chronic Stroke Survivors. Front Hum Neurosci. 10:650.

Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore WDS. 2017. Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. Front Neurol. 8:616.

Barman A, Chatterjee A, Bhide R. 2016. Cognitive Impairment and Rehabilitation Strategies After Traumatic Brain Injury. Indian J Psychol Med. 38:172-181.

For Peer Review

Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C. 2013. Effects of sleep and wake on oligodendrocytes and their precursors. J Neurosci. 33:14288-14300.

Blyth BJ, Bazarian JJ. 2010. Traumatic alterations in consciousness: traumatic brain injury. Emerg Med Clin North Am. 28:571-594.

Brainard GC, Hanifin JP. 2005. Photons, clocks, and consciousness. J Biol Rhythms. 20:314-325.

Castriotta RJ, Murthy JN. 2011. Sleep disorders in patients with traumatic brain injury: a review. CNS Drugs. 25:175-185.

Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. 2007. Prevalence and consequences of sleep disorders in traumatic brain injury. J Clin Sleep Med. 3:349-356.

Celeghin A, Diano M, de Gelder B, Weiskrantz L, Marzi CA, Tamietto M. 2017. Intact hemisphere and corpus callosum compensate for visuomotor functions after early visual cortex damage. Proc Natl Acad Sci U S A. 114:E10475-E10483.

Chellappa SL, Steiner R, Blattner P, Oelhafen P, Gotz T, Cajochen C. 2011. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? Plos One. 6:e16429.

Cognitive Science Research Center (CSRC). 2014. ANAM Military Battery, Administration Manual. In. Norman, OK.

De Havas JA, Parimal S, Soon CS, Chee MWL. 2012. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. Neuroimage. 59:1745-1751.

Diaz-Arrastia R, Kochanek PM, Bergold P, Kenney K, Marx CE, Grimes CJ, Loh LT, Adam LT, Oskvig D, Curley KC, Salzer W. 2014. Pharmacotherapy of traumatic brain injury: state of the science and the road forward: report of the Department of Defense Neurotrauma Pharmacology Workgroup. J Neurotrauma. 31:135-158.

Dixon ML, Thiruchselvam R, Todd R, Christoff K. 2017. Emotion and the prefrontal cortex: An integrative review. Psychol Bull. 143:1033-1081.

Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, LaConte SM. 2014. Neuroimaging after mild traumatic brain injury: review and meta-analysis. Neuroimage Clin. 4:283-294.

Emery CA, Barlow KM, Brooks BL, Max JE, Villavicencio-Requis A, Gnanakumar V, Robertson HL, Schneider K, Yeates KO. 2016. A Systematic Review of Psychiatric, Psychological, and Behavioural

For Peer Review

Outcomes following Mild Traumatic Brain Injury in Children and Adolescents. Can J Psychiat. 61:259-269.

Friston KJ. 2011. Functional and effective connectivity: a review. Brain Connect. 1:13-36.

Friston KJ, Harrison L, Penny W. 2003. Dynamic causal modelling. Neuroimage. 19:1273-1302.

Friston KJ, Kahan J, Biswal B, Razi A. 2014. A DCM for resting state fMRI. Neuroimage. 94:396-407.

Friston KJ, Litvak V, Oswal A, Razi A, Stephan KE, van Wijk BCM, Ziegler G, Zeidman P. 2016. Bayesian model reduction and empirical Bayes for group (DCM) studies. Neuroimage. 128:413-431.

Gilbert KS, Kark SM, Gehrman P, Bogdanova Y. 2015. Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. Clin Psychol Rev. 40:195-212.

Greicius MD, Supekar K, Menon V, Dougherty RF. 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex. 19:72-78.

Grima N, Ponsford J, Rajaratnam SM, Mansfield D, Pase MP. 2016. Sleep Disturbances in Traumatic Brain Injury: A Meta-Analysis. J Clin Sleep Med. 12:419-428.

Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yucel M. 2008. Modulation of Brain Resting-State Networks by Sad Mood Induction. Plos One. 3.

Holzman DC. 2010. What's in a color? The unique human health effect of blue light. Environ Health Perspect. 118:A22-27.

Horne JA, Ostberg O. 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 4:97-110.

Huang HQ, Ding MZ. 2016. Linking Functional Connectivity and Structural Connectivity Quantitatively: A Comparison of Methods. Brain Connect. 6:99-108.

Iraji A, Benson RR, Welch RD, O'Neil BJ, Woodard JL, Ayaz SI, Kulek A, Mika V, Medado P, Soltanian-Zadeh H, Liu TM, Haacke EM, Kou ZF. 2015. Resting State Functional Connectivity in Mild Traumatic Brain Injury at the Acute Stage: Independent Component and Seed-Based Analyses. Journal of Neurotrauma. 32:1031-1045.

Johnson DR, Vincent AS, Johnson AE, Gilliland K, Schlegel RE. 2008. Reliability and construct validity of the Automated Neuropsychological Assessment Metrics (ANAM) mood scale. Arch Clin Neuropsychol. 23:73-85.

Jorge RE, Arciniegas DB. 2014. Mood disorders after TBI. Psychiatr Clin North Am. 37:13-29.

For Peer Review

Killingsworth MA, Gilbert DT. 2010. A wandering mind is an unhappy mind. Science. 330:932.

Levine B, Kovacevic N, Nica EI, Cheung G, Gao F, Schwartz ML, Black SE. 2008. The Toronto traumatic brain injury study: injury severity and quantified MRI. Neurology. 70:771-778.

Lieverse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. 2011. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry. 68:61-70.

Luo Y, Kong F, Qi S, You X, Huang X. 2016. Resting-state functional connectivity of the default mode network associated with happiness. Soc Cogn Affect Neurosci. 11:516-524.

Malojcic B, Mubrin Z, Coric B, Susnic M, Spilich GJ. 2008. Consequences of mild traumatic brain injury on information processing assessed with attention and short-term memory tasks. J Neurotrauma. 25:30-37.

Marshall S, Bayley M, McCullagh S, Velikonja D, Berrigan L. 2012. Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Can Fam Physician. 58:257-267, e128-240.

McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvořák J, Echemendia RJ, Engebretsen L, Johnston K, Kutcher JS, Raftery M, Sills A, Benson BW, Davis GA, Ellenbogen RG, Guskiewicz K, Herring SA, Iverson GL, Jordan BD, Kissick J, McCrea M, McIntosh AS, Maddocks D, Makdissi M, Purcell L, Putukian M, Schneider K, Tator CH, Turner M. 2013. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. British Journal of Sports Medicine. 47:250-258.

McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. 2017. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. Plos One. 12.

McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. 2017. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. Plos One. 12:e0174847.

Narayana PA. 2017. White matter changes in patients with mild traumatic brain injury: MRI perspective. Concussion. 2:CNC35.

Orff HJ, Ayalon L, Drummond SP. 2009. Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil. 24:155-165.

Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. 2006. Self-reported changes to nighttime sleep after traumatic brain injury. Arch Phys Med Rehabil. 87:278-285.

For Peer Review

Ponsford JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Phipps-Nelson J, Rajaratnam SM. 2012. Fatigue and sleep disturbance following traumatic brain injury--their nature, causes, and potential treatments. J Head Trauma Rehabil. 27:224-233.

Raichle ME. 2011. The restless brain. Brain Connect. 1:3-12.

Raikes AC, Bajaj S, Dailey NS, Smith RS, Alkozei A, Satterfield BC, Killgore WDS. 2018. Diffusion Tensor Imaging (DTI) Correlates of Self-Reported Sleep Quality and Depression Following Mild Traumatic Brain Injury. Front Neurol. 9:468.

Razi A, Seghier ML, Zhou Y, McColgan P, Zeidman P, Park HJ, Sporns O, Rees G, Friston KJ. 2017. Large-scale DCMs for resting-state fMRI. Netw Neurosci. 1:222-241.

Rorden C, Karnath HO, Bonilha L. 2007. Improving lesion-symptom mapping. J Cogn Neurosci. 19:1081-1088.

Santhanam P, Wilson SH, Oakes TR, Weaver LK. 2019. Effects of mild traumatic brain injury and post-traumatic stress disorder on resting-state default mode network connectivity. Brain Res.

Short P, Cernich A, Wilken JA, Kane RL. 2007. Initial construct validation of frequently employed ANAM measures through structural equation modeling. Arch Clin Neuropsychol. 22 Suppl 1:S63-77.

Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. 2014. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. Neurorehabil Neural Repair. 28:303-313.

Soares JM, Marques P, Magalhaes R, Santos NC, Sousa N. 2017. The association between stress and mood across the adult lifespan on default mode network. Brain Structure & Function. 222:101-112.

Stephan KE, Tittgemeyer M, Knosche TR, Moran RJ, Friston KJ. 2009. Tractography-based priors for dynamic causal models. Neuroimage. 47:1628-1638.

Strong RE, Marchant BK, Reimherr FW, Williams E, Soni P, Mestas R. 2009. Narrow-band blue-light treatment of seasonal affective disorder in adults and the influence of additional nonseasonal symptoms. Depress Anxiety. 26:273-278.

Su E, Bell M. 2016. Diffuse Axonal Injury. In: Laskowitz D, Grant G, editors. Translational Research in Traumatic Brain Injury Boca Raton (FL).

Sullivan KA, Berndt SL, Edmed SL, Smith SS, Allan AC. 2016. Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. Appl Neuropsychol Adult. 23:426-435.

For Peer Review

Taruffi L, Pehrs C, Skouras S, Koelsch S. 2017. Effects of Sad and Happy Music on Mind-Wandering and the Default Mode Network. Sci Rep. 7:14396.

Vakil E. 2005. The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: a selective review. J Clin Exp Neuropsychol. 27:977-1021.

Vandewalle G, Maquet P, Dijk DJ. 2009. Light as a modulator of cognitive brain function. Trends in cognitive sciences. 13:429-438.

Vincent AS, Roebuck-Spencer T, Gilliland K, Schlegel R. 2012. Automated Neuropsychological Assessment Metrics (v4) Traumatic Brain Injury Battery: military normative data. Mil Med. 177:256-269.

Viola-Saltzman M, Watson NF. 2012. Traumatic Brain Injury and Sleep Disorders. Neurologic Clinics. 30:1299-1312.

Wang H-B, Whittaker DS, Truong D, Mulji AK, Ghiani CA, Loh DH, Colwell CS. 2017. Blue light therapy improves circadian dysfunction as well as motor symptoms in two mouse models of Huntington's disease. Neurobiology of Sleep and Circadian Rhythms. 2:39-52.

Ward AM, McLaren DG, Schultz AP, Chhatwal J, Boot BP, Hedden T, Sperling RA. 2013. Daytime Sleepiness Is Associated with Decreased Default Mode Network Connectivity in Both Young and Cognitively Intact Elderly Subjects. Sleep. 36:1609-1615.

Wickwire EM, Williams SG, Roth T, Capaldi VF, Jaffe M, Moline M, Motamedi GK, Morgan GW, Mysliwiec V, Germain A, Pazdan RM, Ferziger R, Balkin TJ, MacDonald ME, Macek TA, Yochelson MR, Scharf SM, Lettieri CJ. 2016. Sleep, Sleep Disorders, and Mild Traumatic Brain Injury. What We Know and What We Need to Know: Findings from a National Working Group. Neurotherapeutics. 13:403-417.

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. 2013. Sleep drives metabolite clearance from the adult brain. Science. 342:373-377.

Yamadera H, Ito T, Suzuki H, Asayama K, Ito R, Endo S. 2000. Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in Alzheimer-type dementia. Psychiatry Clin Neurosci. 54:352-353.

Yeh FC, Badre D, Verstynen T. 2016. Connectometry: A statistical approach harnessing the analytical potential of the local connectome. Neuroimage. 125:162-171.

For Peer Review

Yeh FC, Tseng WY. 2011. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage. 58:91-99.

Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY. 2013. Deterministic diffusion fiber tracking improved by quantitative anisotropy. Plos One. 8:e80713.

Yeh FC, Vettel JM, Singh A, Poczos B, Grafton ST, Erickson KI, Tseng WI, Verstynen TD. 2016. Quantifying Differences and Similarities in Whole-Brain White Matter Architecture Using Local Connectome Fingerprints. PLoS computational biology. 12:e1005203.

Yount R, Raschke KA, Biru M, Tate DF, Miller MJ, Abildskov T, Gandhi P, Ryser D, Hopkins RO, Bigler ED. 2002. Traumatic brain injury and atrophy of the cingulate gyrus. J Neuropsychiatry Clin Neurosci. 14:416-423.

Zeitzer JM, Friedman L, O'Hara R. 2009. Insomnia in the context of traumatic brain injury. Journal of rehabilitation research and development. 46:827-836.

Zhou Y, Milham MP, Lui YW, Miles L, Reaume J, Sodickson DK, Grossman RI, Ge Y. 2012. Default-mode network disruption in mild traumatic brain injury. Radiology. 265:882-892.

Zimmermann J, Griffiths JD, McIntosh AR. 2018. Unique Mapping of Structural and Functional Connectivity on Cognition. Journal of Neuroscience. 38:9658-9667.

Zucker RS, Regehr WG. 2002. Short-term synaptic plasticity. Annu Rev Physiol. 64:355-405.

For Peer Review

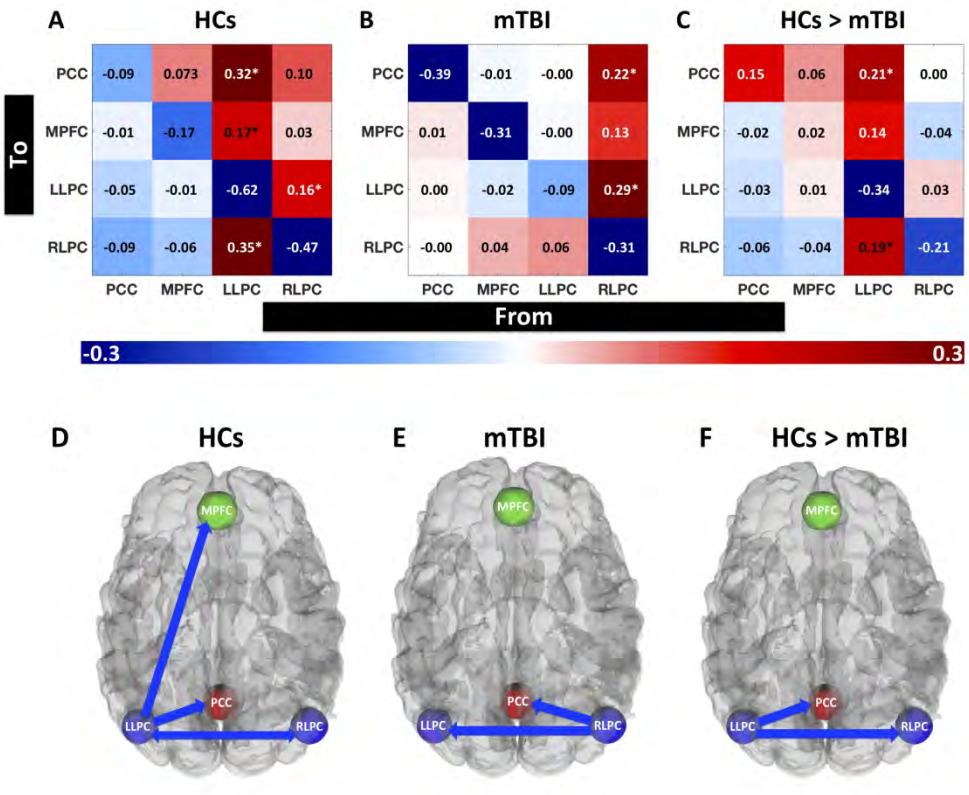


Figure 1. Effective connectivity for HCs and individuals with mTBI. Here we showed the subject average connectivity strength (in Hz) of all the connections within the DMN for HCs (A) and post mTBI (B). Positive and negative values here represent the exhibitory and inhibitory connections respectively. In Figure 1C, we showed the comparisons of connectivity strengths between HCs and post mTBI. The positive values here represent the connections that are more positive in HCs than post mTBI, whereas the negative values here represent the connections that are more negative in HCs than post mTBI. Connections exceeding the posterior probability of 95% are indicated by '*' in Figure 1 (A-C), and are shown in Figure 1D (HCs), 1E (mTBI) and 1F (HCs vs. mTBI).

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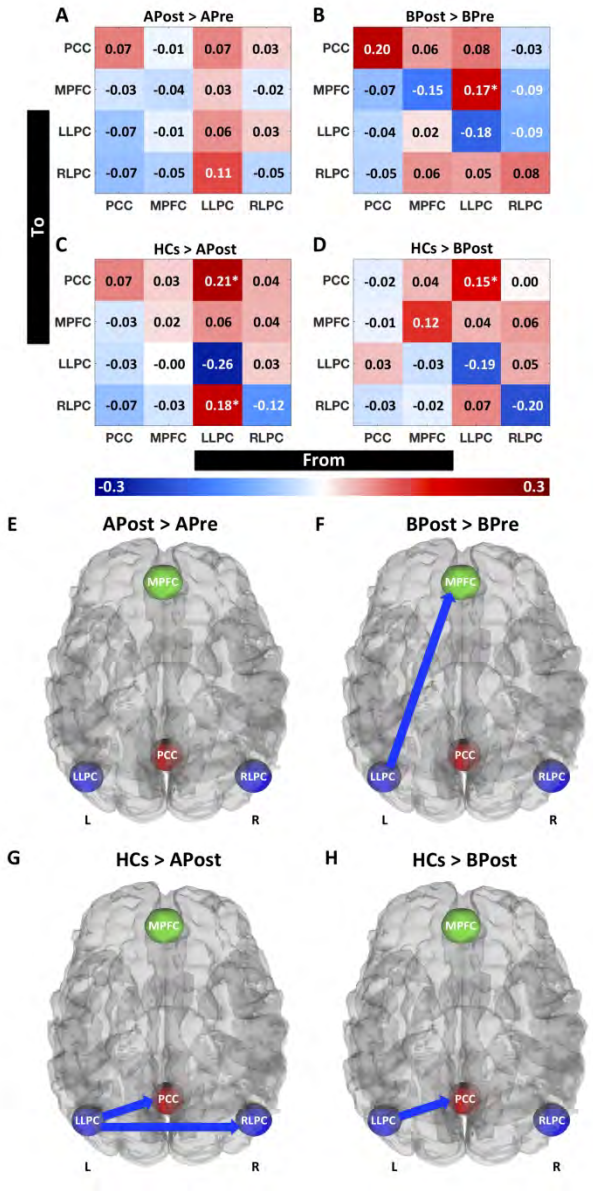


Figure 2. Comparisons of directed connectivity for APost vs. APre, BPost vs. BPre, and HCs vs. APost and BPost: Here we showed the comparisons of connectivity strengths between APost and APre (A), BPost and BPre (B), HCs and APost (C), and HCs and BPost (D). The positive values (A-B) represent the connections that are more positive in APost and BPost than APre and BPre respectively, whereas the negative values here represent the connections that are more negative in APost and BPost than APre and BPre respectively. Similarly, the positive values for Figure 2C and 2D represent the connections that are more positive in HCs than APost and BPost respectively, whereas the negative values here represent the connections that are more negative in HCs than APost and BPost respectively. Connections exceeding the posterior probability of 95% are indicated by '*' (A-D), and are shown in Figures 2E (APost > APre), 2F (BPost > BPre), 2G (HCs > APost), and 2H (HCs > BPost).

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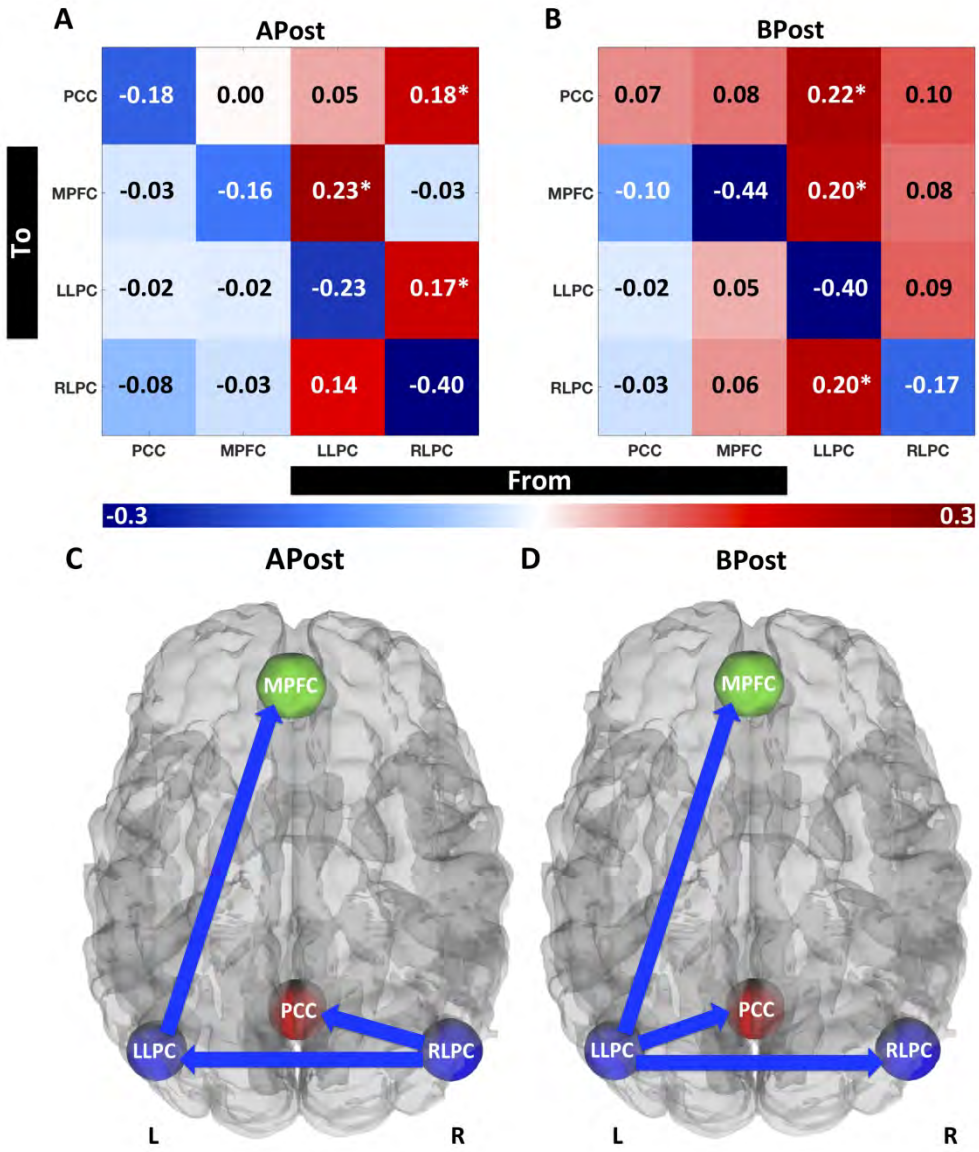


Figure 3. Effective connectivity for APost and BPost. Here we showed the subject average connectivity strength of all the connections within the DMN for APost (A) and BPost (B). Positive and negative values (A-B) represent the exhibitory and inhibitory connections respectively. Connections exceeding the posterior probability of 95% are indicated by '*' (A-B), and are shown in Figures 3C (APost) and 3D (BPost).

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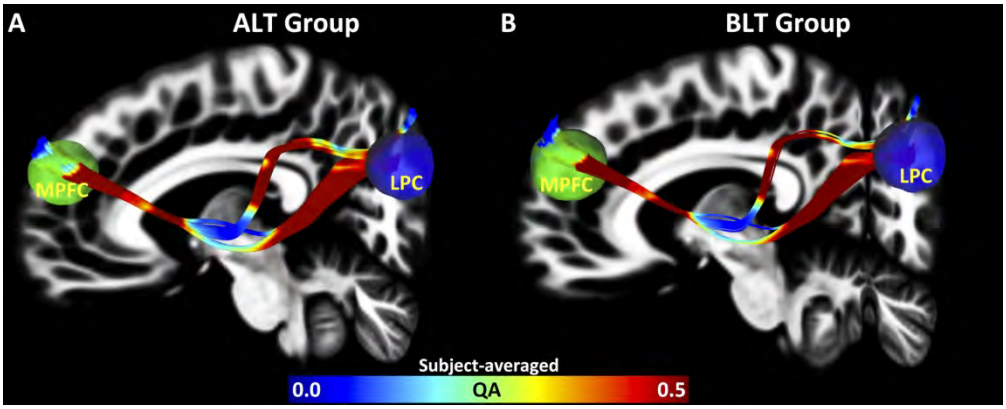


Figure 4. White-matter tractography for ALT and BLT groups. Here we showed subject averaged maps of structural connectivity (in terms of QA) between LLPC and MPFC (A: ALT Group and B: BLT Group).

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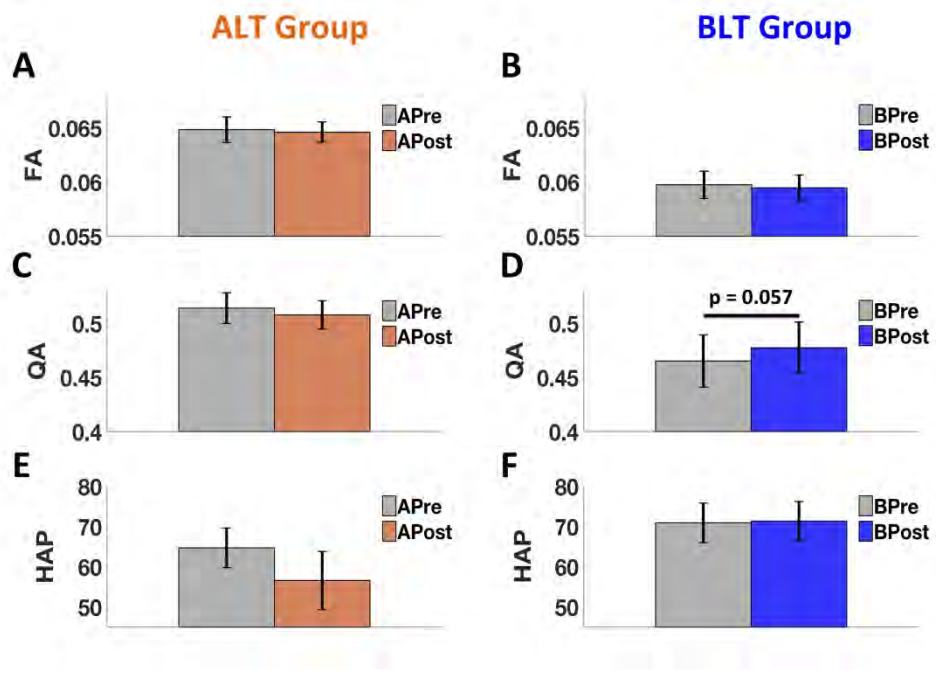


Figure 5. Comparisons of FA, QA, and levels of happiness (HAP). We found that there was no significant difference in FA for tracts connecting LLPC and MPFC for either ALT group (APre vs. APost) (paired t-test, p = 0.760) (Figure 5A) or BLT group (BPre vs. BPost) (paired t-test, p = 0.662) (Figure 5B). Also, there was no significant difference in QA for tracts connecting LLPC and MPFC for ALT group (APre vs. APost) (paired t-test, p = 0.468) (Figure 5C), but there was a clear trend of greater QA for BPost compared to BPre (paired t-test, p = 0.057) (Figure 5D). Lastly, we found non-significant reduction in levels of happiness for individuals who used amber-light therapy compared to their pre-treatment condition (paired t-test, p = 0.170) (Figure 5E). However, levels of happiness sustained for individuals who used blue-light therapy compared to their pre-treatment condition (paired t-test: p = 0.924) (Figure 5F). Error bars here represent 'standard error of the mean'.

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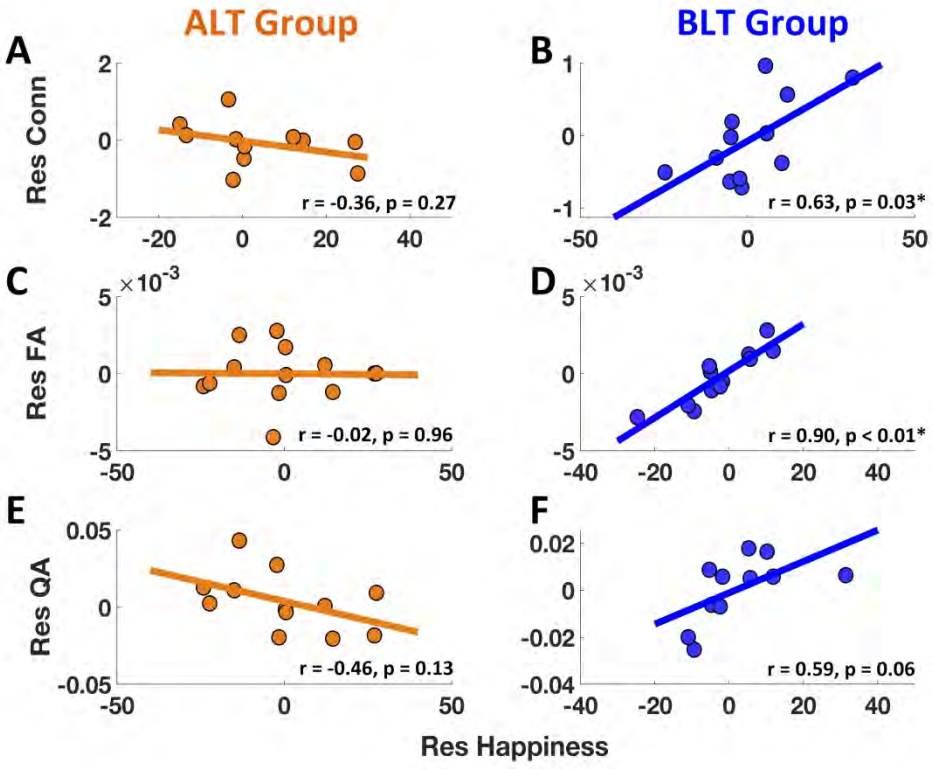


Figure 6. Associations between residualized changes (pre- to post-treatment) in happiness (Res Happiness) vs. residualized changes (pre- to post-treatment) in directed connectivity (Conn), FA, and QA. We did not find significant association between residualized changes in happiness scores (Res Happiness) and residualized changes in directed connectivity (Res Conn) from LLPC to MPFC for ALT group (A), but there was significant positive association between Res Happiness and Res Conn from LLPC to MPFC for BLT group (B). There was no significant association between Res Happiness and Res FA for tracts connecting LLPC and MPFC for ALT group (C), but there was significant positive association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for BLT group (D). Lastly, there was no significant association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for ALT group (E), but there was clear trend showing a positive association between Res Happiness and Res QA for tracts connecting LLPC and MPFC for BLT group (F).

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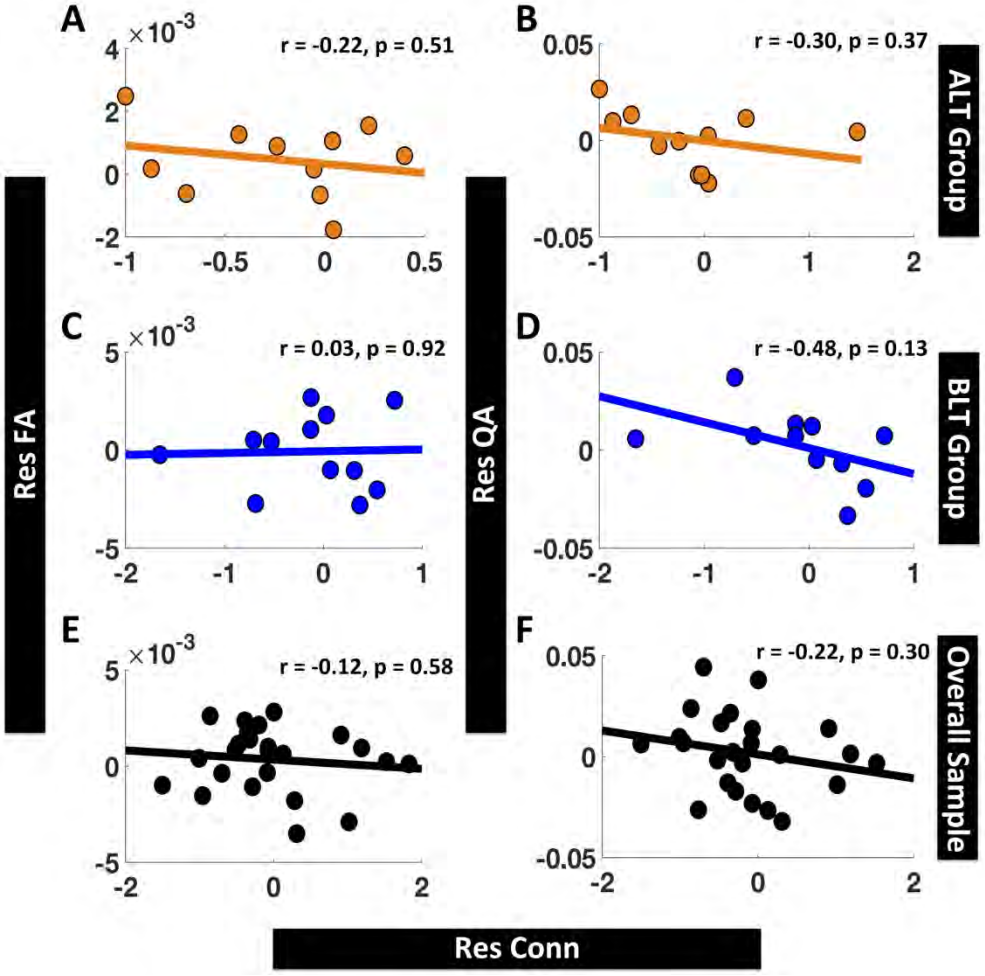


Figure 7. Associations between residualized changes (post- to pre-treatment) in directed connectivity (Conn) vs. residualized changes (post- to pre-treatment) in FA and QA. Neither of the groups ALT (A-B) or BLT (C-D) showed significant association between residualized changes in Conn (Res Conn) from LLPC to MPFC and residualized changes in either FA (Res FA) (A, C) or QA (Res QA) (B, D) for tracts connecting LLPC and MPFC. Overall sample also did not show significant association between Res Conn from LLPC to MPFC and either Res FA (E) or Res QA (F) for tracts connecting LLPC and MPFC.

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Table 1 Demographics

Demographics	Healthy Controls (N = 41)	MTBI (Overall) (N = 28)	MTBI (ALT Group) (N = 14)	MTBI (BLT Group) (N = 14)	Significance (Independent sample t-test/ Chi-square)
Mean age (S.D.) (in years)	26.07 (5.01)	21.50 (3.76)	-	-	T (67) = 4.10, p < 0.001, Cohen's d = 1.03
Sex (% female)	61	54	-	-	$\chi^2(1) = 0.34$, p = 0.56
Mean age (S.D.) (in years)	-	-	21.21 (3.09)	21.78 (4.42)	T (26) = -0.40, p = 0.69, Cohen's d = 0.15
Sex (% female)	-	-	50	57	$\chi^2(1) = 0.16$, p = 0.69
Mean TSI (S.D.) (in months)	-	-	7.11 (3.53)	6.57 (4.57)	T (26) = 0.35, p = 0.73
Days light used (S.D.)	-	-	34.78 (9.17)	37.85 (4.36)	T (26) = -1.13, p = 0.27
Levels of happiness at baseline (S.D.)	-	-	64.74 (17.73)	70.94 (17.81)	T (24) = -0.89, p = 0.78, Cohen's d = 0.35

MTBI: Mild Traumatic Brain Injury; S.D.: Standard Deviation; TSI: Time Since Injury.

For Peer Review

Effect of blue light therapy on brain structure and simple reaction time following mild traumatic brain injury

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Abstract

There are very few broadly accepted and viably safe non-pharmacologic treatments to facilitate recovery from mild traumatic brain injury (mTBI). Here we aim to determine the effect of blue-light therapy (BLT) on reaction time (RT) and normalized cortical volume (NCV) of individuals with mTBI. The regions of interest (ROIs) were identified by comparing NCV between healthy controls and mTBI individuals to further test the impact of light therapy. A total of seven ROIs: four within the frontal lobe, one within the parietal lobe and two within the temporal lobe were identified that showed lower NCV in individuals with mTBI compared to healthy-controls at medium effect sizes (Cohen's $d \geq 0.5$). None of the regions showed greater NCV for mTBI individuals compared to healthy-controls at medium or large effect sizes (Cohen's $d < 0.2$). Our findings show that there was significant improvement in RT following BLT, but not following placebo amber-light therapy (ALT). There was a significant group (ALT/BLT) x time (pre/post) interaction for NCV within the right orbital part of inferior frontal gyrus (R.ParsOrb), suggesting that the ALT and BLT had opposite effects on NCV i.e., BLT protects and also shows some improvements in NCV within R.ParsOrb and ALT shows time-dependent decay (i.e., reduction) in NCV within R.ParsOrb. Moreover, following BLT, changes in NCV of the R.ParsOrb was significantly correlated with improved RT. Our findings suggest that targeted blue-light exposure may improve attention abilities and may sustain the decay and even improve the inferior frontal volume of mTBI individuals.

Keywords

Concussion, Cortical Volume, Light Therapy, Attention, Structural MRI

Highlights

- Regions specifically within the frontal lobe are susceptible to brain injuries.
- BLT helps to improve RT and protects the volumetric decay of the right orbital part of inferior frontal gyrus.
- BLT can be a novel intervention to improve brain structure and function after mTBI.

- Future work should study the factors that contribute to the effectiveness of BLT.

Introduction

Mild traumatic brain injury (mTBI) accounts for approximately 75% of all traumatic brain injury cases each year in the United States (National Center for Injury Prevention and Control, 2003). These injuries occur when an individual experiences a blow to the head or body (McCrory et al., 2013) that leads to a temporary alteration in consciousness or cognition (Blyth & Bazarian, 2010; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017). Such injuries may cause alterations in brain structure (Bajaj, Dailey, Rosso, Rauch, & Killgore, 2018; Govindarajan et al., 2016; Wang et al., 2015) and impaired cognitive abilities (Cicerone, 1996; Pontifex et al., 2012; Silver, McAllister, & Arciniegas, 2009). Previous studies have shown that compared to other lobes, the frontal lobe, especially the prefrontal cortex, is more vulnerable to mTBI (Clark et al., 2018; Eierud et al., 2014; Epstein et al., 2016). In addition, the role of the prefrontal cortex has been linked to attention(Knight, Grabowecky, & Scabini, 1995) and the ability to respond quickly to a stimulus (Stuss et al., 2005; Trivino, Correa, Arnedo, & Lupianez, 2010). Furthermore, brain injuries are often associated with several other post-concussive symptoms, including sleep disruption, poor performance during working memory tasks, and difficulties in information processing (Dean & Sterr, 2013; Laskowski, Creed, & Raghupathi, 2015; Parcell, Ponsford, Rajaratnam, & Redman, 2006; Theadom et al., 2015). In particular, over half of the TBI individuals experience severe daytime sleepiness and nearly 22% experience delays in sleep onset (Verma, Anand, & Verma, 2007). While most of the above mentioned symptoms abate rapidly (e.g., within a matter of hours to days) following a mTBI, many individuals will experience prolonged post-concussive symptoms such as associated with sleep that become chronic in nature (Dean & Sterr, 2013; McInnes et al., 2017).

Presently, there are very limited broadly accepted non-pharmacologic treatments to facilitate recovery from mTBI (Diaz-Arrastia et al., 2014). Because approximately half of all individuals who sustain a brain injury will go on to complain of sleep-related problems following their injury (Viola-Saltzman & Watson, 2012), recent treatment approaches have begun to focus on potential interventions to improve sleep within this population (Gilbert, Kark, Gehrman, & Bogdanova, 2015; Zeitzer, Friedman, & O'Hara, 2009). Daily morning blue-wavelength light therapy (i.e., light within the short wavelengths at ~480 nm) (BLT) has been proposed as a viable, safe, non-pharmacologic way of reducing fatigue and improving daytime sleepiness among individuals with a TBI (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014). BLT has important positive effects on cognitive performance on tasks requiring sustained attention and in the regulation of circadian rhythms (Chellappa et al., 2011). Notably, intrinsically photosensitive ganglion cells within the retina are particularly sensitive to light with short wavelengths and transmit signals to hypothalamic nuclei that are responsible for regulating the release of melatonin from the pineal gland and entraining the circadian rhythm (Cajochen et al., 2005; Lockley et al., 2006). Timing of exposure for light therapy is crucial. Blue-wavelength light exposure in the morning hours suppresses the production of melatonin, leading to a phase advance of the circadian rhythm, greater daytime alertness, and earlier sleep onset times in the evening (Wright, Lack, & Kennaway, 2004).

While it appears that BLT can improve cognitive and affective functioning, the structural aspects of the brain underlying these effects remain to be fully identified. To our knowledge, none of the previous studies have investigated the impact of light therapy on cortical structure of individuals with mTBI. Some of the previous studies

from our laboratory investigated whether blue-light plays a significant role in improving function and white-matter structure of the brain. In a study on healthy-controls, Alkozei and colleagues reported that an acute exposure to blue wavelength light had an positive impact on verbal memory performance after approximately 1.5 hours of memory consolidation (Alkozei, Smith, Dailey, Bajaj, & Killgore, 2017), as well as it improves working memory performance and increases activation within the prefrontal cortex(Alkozei et al., 2016). In a study on individuals with mTBI, an improvement in executive function was observed following blue-light therapy (Killgore, Alkozei, & Weber, 2018). In another study on individuals with mTBI, Bajaj and colleagues reported significant impact of blue-wavelength light on quantitative anisotropy – a measure of compactness of white-matter fibers, and associated improvements in sleep latency and cognitive performance (Bajaj, Vanuk, Smith, Dailey, & Killgore, 2017). Above cited studies and lack of literature exploring the interaction between blue-wavelength light and cortical structure indicate a crucial need to advance our understanding of structural neural substrates influenced by blue-wavelength exposure in clinical human population, particularly in individuals with mTBI.

The present study focused on determining the effect of daily morning exposure of BLT on simple reaction time (RT) as a measure of attention and structural changes in the brain following an mTBI. The aims of this study were threefold: 1) to identify brain regions where individuals with an mTBI may have different normalized cortical volume (NCV) than healthy controls (HCs) and determine whether these regions, once identified, exhibit volumetric changes following six-weeks of short-wavelength morning BLT compared to a placebo amber light treatment (ALT); 2) to determine whether there is an improvement in RT during a simple stimulus task; and 3) to investigate whether structural changes in targeted brain areas were associated with changes in RT, in each treatment condition. Based on previous limited literature on blue-light exposure, we hypothesized that BLT may also help to improve NCV and RT in individuals with mTBI compared to the placebo condition.

Methods

Participants

A total of 62 young participants (28 individuals with mTBI: 27 out of 28 (i.e., 96.4 %) participants had age range between 18 to 30 years and one participant was 35 years old, mean age = 21.50±3.76 years, 15 F and 34 healthy-controls — HCs with age range between 18 to 30 years of age, mean age = 25.19±3.38 years, 20 F) were included in this study who underwent neuroimaging using Siemens Tim Trio 3T scanner (Erlangen, Germany) at the McLean Hospital Imaging Center. Participants with mTBI had to have experienced at least one traumatic injury or blow to the head leading to altered consciousness or complete loss of consciousness (less than 30 minutes) or post-traumatic amnesia (no longer than 24 hours) (Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012). All of the mTBI individuals had injury within the preceding 18 months but not sooner than 4 weeks prior to their screening and provided documentation from either a doctor, medical provider or other qualified professional (e.g., physician or trainer). All mTBI participants were screened using a set of sleep questionnaires. Participants who indicated some level of self-reported sleep problem or who endorsed that the sleep problems either emerged or worsened following the brain injury, were included in the study. In addition, participants with any history of neurological or psychiatric disorder with an onset before the mTBI were excluded. The HCs were included as a comparison group for anatomical

morphometry. All HCs were recruited as part of a separate study of 45 participants but completed an identical structural scanning sequence in the same scanner. All HCs were screened via a comprehensive telephone interview indicating no self-reported history of head injury/concussion, psychiatric, neurological, or significant medical problems. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV Axis I Disorders) (SCID) (First, Spitzer, Gibbon, & Williams, 2002) was used to determine the psychiatric inclusion/exclusion eligibility of all HCs. None of the participants from HC group met the diagnostic criteria for any current or lifetime Axis I disorder. More details about the selection criteria can be found in a previous report (Rosso et al., 2017). All participants provided written informed consent prior to enrollment and were financially compensated for their time. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Office (HRPO).

Procedure

Individuals in the HC group were used as a healthy normative sample. They underwent only one session of anatomical brain scanning, and did not participate in the light therapy portion of this study. In contrast, the mTBI group underwent anatomical brain scanning on two different occasions, separated by 6-weeks of daily morning bright light therapy with either blue light or a placebo amber light. Participants were pseudo-randomly assigned to the light conditions using a block randomization procedure and all research staff were blind to subject group assignment during data collection. During the treatment portion of the study, participants were asked to use a commercially available light therapy device (GoLite Blu®, Philips Electronics) for six weeks (i.e., 30 minutes every day, within 2 hours of awakening, but before 11:00 A.M). The device provided controlled exposure to narrow band of either amber wavelength light with peak at 578 nm or blue wavelength light with peak at 469 nm and consists of a table-mounted, 13.5 x 14 cm plastic encased device with a 10-by-6 LED array. Fourteen individuals with mTBI (mean age = 21.21±3.09 years, 7 F) were randomly assigned to ALT and the rest (N = 14, mean age = 20.78±4.42 years, 8 F) were assigned to BLT.

Data acquisition

Automated Neuropsychological Assessment Metrics (ANAM4)

The ANAM (v4) battery, developed by the department of defense, is an automated computer-based battery to test the cognitive performance of the participants (Cognitive Science Research Center (CSRC), 2014). It includes details about demographic information, TBI questionnaire, sleepiness scale, mood scale and seven other subtests: Code Substitution Delayed, Code Substitution, Matching-to-Sample, Mathematical Processing, Procedural Reaction Time, Simple Reaction Time (SRT), and Simple Reaction Time Repeated (SR2). Here, SR2 is just a repeat of SRT test. In previous studies, ANAM has been extensively used to measure impaired cognitive abilities across broad range of neurological disorders (Bleiberg et al., 2004; Cole, Gregory, Arrieux, & Haran, 2018; Friedl et al., 2007; Kane, Roebuck-Spencer, Short, Kabat, & Wilken, 2007). For the purpose of this manuscript, only the raw SRT and SR2 values were used for analysis. SRT test measures reaction time, which is automatically recorded when the

participants press a button when they are shown a series of "*" symbol and asked to respond as quickly as possible when the symbol appears. This stimulus "*" is repeated 40 times at different intervals and average reaction time over 40 trials is calculated for each participants for each task – SRT and SR2.

Neuroanatomical data

For all the participants (HCs and participants with mTBI), high resolution neuroanatomical images were acquired using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence which consisted of 176 sagittal slices (voxel resolution = 1×1×1 mm^3, field of view (FOV) = 256 mm) with TR/TE/FA/inversion time of 2100 ms/2.30 ms/12°/1100 ms. All participants were instructed to relax and remain still during scanning.

Data analysis

Preprocessing

Simple reaction time data, collected on both occasions, i.e. SRT and SR2, were screened for outliers. Two data points due to extremely slow responses – one during pre-treatment condition for SRT and second during post-treatment condition for SR2 were identified as extreme outliers (i.e., with a value more than 3.0 inter-quartile range above the upper quartile) and were excluded from data analysis. To determine any possible imaging artifacts, raw anatomical T1-weighted data were visually inspected for each participant before passing to the "recon-all" pipeline in FreeSurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/fswiki). None of the participants showed any such artifact. Initially, for comparisons between HCs and mTBI patients, the standard cross-sectional "recon-all" pipeline was used to process anatomical images for all participants. However, to determine the changes from pre-treatment to post-treatment condition, the longitudinal "recon-all" pipeline (Reuter, Schmansky, Rosas, & Fischl, 2012) was used to preprocess images for all mTBI participants, which involved the creation of an unbiased within-subject template using robust inverse consistent registration (Reuter, Rosas, & Fischl, 2010). The processing pipeline also involved intensity normalization, followed by brain extraction (i.e., removal of skull, skin, neck and eyeballs), automated transformation to the Talairach coordinate system and volumetric segmentation (Fischl et al., 2002). The Desikan atlas, which was previously reported to yield a highly accurate set of automatic regions of interest with average intraclass correlation coefficient of 0.835, was used to perform cortical segmentation of the cerebral cortex into 34 regions for each hemisphere (Desikan et al., 2006). Using a high-resolution surface based averaging technique, all images were aligned to a standard surface template. In order to increase the reliability and statistical power, the above steps were initialized with common information extracted from the within-subject template for longitudinal comparisons (Reuter et al., 2012). Accuracy of skull-stripped brain masks and brain surfaces was visually inspected for all individuals. None of the participants showed badly or inaccurately extracted brain masks or brain surfaces. Due to smaller clinical sample size and in order to improve the signal to noise ratio and detect larger effects rather than focal, data were smoothed using larger Gaussian kernels of size 15 mm full-width at half maximum (FWHM) prior to parcellation.

Identification of regions of interest (ROIs)

Initially, the measures of raw cortical volume (CV) were evaluated for 34 regions per hemisphere for each participant, followed by an estimation of total intracranial volume (ICV: grey matter volume + white-matter volume + cerebrospinal fluid volume). Regional CV and ICV data were scanned for outliers. One healthy control subject showed an extreme outlier in ICV values (i.e., with a value more than 3.0 inter-quartile range above the upper quartile), indicating larger head size for a participant compared to others, and was excluded from further analysis. Further, to account for subjectwise variability in head size, regional CV was divided by ICV to calculate the proportion of ICV for each region i.e., normalized CV (NCV). The measure of NCV for each region was further adjusted to regress out the effect of 'age' when performing group analysis between the mTBI group and HCs to identify the ROIs. ROIs for treatment effects were identified as those exhibiting medium to large effect size (Cohen's $d \geq 0.5$) differences between mTBI and HC participants. These effect sizes were unadjusted for any multiple comparisons, and therefore should be treated as exploratory.

Estimating the impact of treatment

Average reaction time (RT), calculated from SRT and SR2, and NCV parameters were compared using analysis of covariance (ANCOVA) and pairwise comparisons, with light group (ALT/BLT) as between group variable and session (pre- versus post-treatment) as a within subject variable. Three important parameters - 'age', 'days light used' and 'time since injury' were included as covariates. Subjectwise variability (e.g., differences in head sizes due to sex differences) was accounted for by using normalized values of CV – raw CV divided by intracranial volume (ICV). To be consistent across number of covariates for CV and RT, we compared RT data between 'males' and 'females' at baseline. We found that the mean RT did not differ between 'males' (mean 279.27 ±24.51) and 'females' (286.95±20.08) at baseline (two sample t-test, $F(24) = 0.07$, $p = 0.40$, Cohen's $d = 0.34$). Therefore, 'sex' was also not used as a covariate for comparison of RT. To determine the association between adjusted residualized differences in NCV and RT, these scores were derived by regressing post-treatment measures of NCV and RT on pre-treatment measures of NCV and RT respectively, with the same three covariates – 'age', 'days light used' and 'time since injury'.

Results

Demographics

HCs and mTBI groups differed significantly in age, but not sex. Moreover, in general, head size, which was estimated from intracranial volume (ICV), also differed (marginally significant) between two groups . The ALT and BLT groups did not differ significantly in age, sex, head-size, time-since injury (TSI), or number of days light used. Statistics related to above findings are reported in Table 1.

Differences in NCV between HCs and individuals with mTBI

NCV for 34 areas for each hemisphere (Desikan atlas (Desikan et al., 2006)) was estimated and compared between the HCs and mTBI groups to identify regions showing differences in cortical structure/normalized cortical volume prior to light therapy. Three regions within the left hemisphere, including the left caudal middle frontal gyrus (L.CMFG) (Figure 1, shown in dark red color), left inferior parietal cortex (L.IPC) (Figure 1, shown in light violet color) and left middle temporal cortex (L.MTC) (Figure 1, shown in orange color), showed lower NCV in mTBI individuals compared to HCs (medium effect size, $0.5 \leq$ Cohen's $d \leq 0.6$). Further, four regions within the right hemisphere, including the right lateral orbitofrontal cortex (R.LOFC) (Figure 2A, shown in dark green color), right pars orbitalis (R.ParsOrb) (Figure 2A, shown in light green color), right middle temporal cortex (R.MTC) (Figure 2B, shown in orange color) and right rostral middle frontal gyrus (R.RMFG) (Figure 2B, shown in dark violet color), showed lower NCV in mTBI individuals compared to HCs (medium effect size, $0.5 \leq$ Cohen's $d \leq 0.6$). None of the regions were larger for the mTBI individuals compared to the healthy controls (Cohen's $d < 0.2$, all regions). Anatomical locations of the regions shown in Figures 1 and 2 were extracted from Desikan's atlas (Desikan et al., 2006). Horizontal 'green' colored lines in Figures 1 and 2 represent mean of the adjusted NCV values of corresponding regions.

Effect of BLT versus placebo ALT on RT and NCV

RT

For ALT group, mean raw RT scores were 284.28±15.65 ms and 275.96±4±21.05 ms before and after amber-light therapy respectively. For BLT group, mean raw RT scores were 284.30±26.88 and 267.86±24.32 before and after blue-light therapy respectively. There was no significant time (pre- and post-treatment) x group (ALT/BLT) interaction for RT. However, within-subject pairwise comparison showed a significant decrease in RT following BLT, but not following ALT. Moreover, there were no significant differences between ALT and BLT groups at the baseline ($F(1,21) = 0.003$, $p = 0.95$, partial $\eta^2 = 0.00$) or post-treatment condition ($F(1,21) = 0.79$, $p = 0.38$, partial $\eta^2 = 0.04$). The statistics related to these findings are summarized in Table 2. Violin plots for residualized differences between pre-treatment and post-treatment RT values (after adjusting for covariates) for ALT and BLT groups are shown in Figure 3A.

NCV

There was significant time (pre- and post-treatment) x group (ALT/BLT) interaction for R.ParsOrb, such that changes in NCV for this region following ALT and BLT, were in opposite direction. Within-subject pairwise comparison showed a significant decrease in NCV within the R. ParsOrb following ALT, but not following BLT. Moreover, there were no significant differences between ALT and BLT groups at the baseline ($F(1,23) = 0.86$, $p = 0.36$, partial $\eta^2 = 0.04$) or at the post-treatment condition ($F(1,23) = 0.07$, $p = 0.79$, partial $\eta^2 = 0.003$). The statistics related to these findings are summarized in Table 2. Violin plots for residualized differences between pre-treatment and post-treatment NCV values for R. ParsOrb (after adjusting for covariates) for ALT and BLT groups are shown in Figure 3B. None of the other ROIs either within the left hemisphere (Figure 4, Table 3) or within the right hemisphere

(Figure 5, Table 4) showed significant time (pre- and post-treatment) x group (ALT/BLT) interaction or significant pairwise differences for either ALT or BLT group.

Association between residualized differences in NCV and RT for ALT and BLT groups

We found that following BLT there was a significant negative association between residualized changes in NCV within the R.ParsOrb and residualized changes in RT (Spearman's correlation, r = -0.65, $p = 0.02$), however, following ALT, there was no such association between the two (Spearman's correlation, r = -0.24, $p = 0.47$) (Figure 3C). The scales of adjusted residualized differences in NCV and RT shown in Figure 3A and 3B are slightly different than the scales shown in Figure 3C because –

(i) adjusted residualized difference RT data plotted in Figures 3A is after excluding two extreme outliers in RT (one for ALT group i.e., n = 13 and the second for BLT group i.e., n = 13).

(ii) there was no extreme outlier observed in NCV values for R. ParsOrb, therefore adjusted residualized difference NCV data plotted in Figures 3B was from 14 subjects for each condition (i.e., n = 14 for ALT and n = 14 for BLT).

(iii) for correlation analysis, the NCV data from same two participants were excluded which had extreme outliers in RT. In other words, adjusted residualized differences for RT and NCV were again calculated for ALT (n = 13) and BLT (n = 13) conditions after excluding those two participants. Moreover, any data points in the scatter plot with Cook's distance greater than four times the mean were also considered as outliers and were not included. Two such data points for ALT group and one such data point for BLT group were identified, and were therefore excluded from the correlation analysis.

Discussion

In this study, our findings suggest that there are identifiable group-level differences in NCV within the frontal, parietal and temporal lobes that can be observed following an mTBI. We also found a significant improvement over time for reaction time among those receiving BLT, but not those receiving ALT. Furthermore, we found a significant light group (blue/amber) x time (pre/post) interaction for the NCV of the R.ParsOrb, suggesting a time-dependent decay in NCV of R.ParsOrb for ALT, but sustaining that decay and some improvement in NCV of this region for BLT. Finally, we found that increases in NCV within the R.ParsOrb from pre- to post-treatment were associated with decreases in reaction time for the BLT group.

In addition, we noticed that the density of data points was within a short range for BLT group (i.e., low variability) and was within a large range for ALT group (i.e., greater variability) (Figures 3B and 3C), which might indicate that the blue-light exposure could have a specific impact on NCV and RT, rather than a random and highly distributed impact following amber-light exposure or simply due to time-dependent decay. Our results demonstrate that 6-weeks of morning BLT is associated with protecting or even improving the NCV within the inferior frontal region of the brain and a corresponding improvement in reaction time. We discuss each of these findings in greater detail below.

Structural abnormalities following mTBI

We found that in comparison to HCs, mTBI participants had lower NCV in several regions within the frontal, parietal and temporal lobes. Our findings are in line with previous reports published on traumatic brain injury that have shown alterations of cortical structure, especially within the frontal brain areas (Epstein et al., 2016; Fogleman et al., 2017; Urban et al., 2017) as the frontal brain areas have been shown to be particularly sensitive to the brain injury (Bigler & Maxwell, 2012). For instance, studies have also found significantly smaller volume within the rostral-middle frontal cortex, superior fontal cortex and orbitofrontal cortex in individuals within mild to severe as well as moderate to severe brain injury (Spitz et al., 2013; Wilde et al., 2005). Furthermore, thinner cortex within the frontal cortex and orbitofrontal cortex is also reported following mTBI (Epstein et al., 2016; Tate et al., 2014). Warner and colleagues reported that in a combined sample of individuals with mild and severe traumatic axonal injury with majority of individuals having severe TBI, in addition to frontal lobe, the parietal cortex is also one of the most prominent sites, which shows volume loss (Warner et al., 2010). Consistent with our findings, the middle temporal cortex was also reported to be affected following mTBI in young individuals. For instance, List and colleagues reported that individuals with mTBI had thinner R. MTC as compared to the control group, and this thinning was further associated with number of mTBIs (List, Ott, Bukowski, Lindenberg, & Floel, 2015). Significant reduction in cortical thickness within the left middle temporal cortex was also found in individuals with mTBI compared to controls (Govindarajan et al., 2016). Several theories have been proposed explaining the underlying mechanisms responsible for the structural changes following traumatic brain injury. It has been suggested that such injuries result in a quick, abnormal release of specific enzymes and proteins such as neuron-specific enolase (NSE) and S100B, which lead to neuronal death causing further pathological alterations in structural integrity and neuropsychological functioning of the brain (Berger et al., 2002). Recently demonstrated relationships between cell density and cortical thickness (Carlo & Stevens, 2013; Rockel, Hiorns, & Powell, 1980) indicate that cortical atrophy following injury may be due to either immediate loss of neuronal cells, neuritis, or changes in neuronal and vascular densities. However, confirming the role of these mechanisms in observed cortical difference between healthy-controls and mTBI in our study is beyond the scope of current study.

Effect of BLT on reaction time and brain structure

First, it should be noted that the ANAM battery data were not available for the HCs sample so a direct comparison between HCs and mTBI individuals was not possible. However, established normative data collected from 54 military bases suggests that the average simple reaction time for the mTBI group reported in this study was higher than the simple reaction time collected from de-identified service members, which ranged between 257 and 264 ms for individuals aged between 17-35 (Vincent, Roebuck-Spencer, Gilliland, & Schlegel, 2012). In this study, we found that following ALT, the average reaction time reduced from 284 ms to 275 ms. However, following BLT, the average reaction time reduced from 284 ms to 267 ms, which falls more closely to the range reported in normative data. Our findings are in line with previous reports, showing that short-wavelength light exposure can improve alertness and cognitive performance (Beaven & Ekstrom, 2013; Chellappa et al., 2011; Newman et al., 2016; Rahman et al., 2014). To our knowledge, this is the first study demonstrating the effects of BLT on NCV and its associated

effects on reaction time. For instance, we also found that BLT was associated with protecting or even improving NCV within the ParsOrb relative to ALT in our sample of participants with mTBI, and there was a significant association between decreased RT and changes in NCV within the ParsOrb for BLT group. Anatomically, the ParsOrb is the orbital part of inferior frontal cortex (OFC), which is known to play critical role in a variety of executive functions, including cognitive and behavioral performance (Depue, Burgess, Bidwell, Willcutt, & Banich, 2010) and decision making (Bechara, Damasio, & Damasio, 2000; Bechara & Van Der Linden, 2005). The possible neural mechanisms underlying the observations related to BLT are outlined below:

Existing treatments, light therapy and their underlying potential mechanisms

In the past, effects of other interventions such as physical exercise and cognitive behavior therapy have been reported to alter gray matter brain structure (Killgore, Olson, & Weber, 2013; Levy-Gigi, Szabo, Kelemen, & Keri, 2013). It has been suggested that physical exercise reduces the degree of blood oxygenation, which in turn, leads to angiogenesis in the brain (Bloor, 2005). Additionally, growth factors such as brain derived neurotropic factor (BDNF) and vascular endothelial growth factor (VEGF), which occur during exercise, are considered to be responsible for expansion of neural structures (McAllister, Katz, & Lo, 1999) and the production of new blood vessels (Bloor, 2005) respectively. Cognitive-behavioral therapy has also been shown to modify dysfunctional neuronal activity and lead to the enhancement of neurogenesis in the hippocampal regions, as well as increased neuronal size, dendritic arborization, or proliferation of glial cells, which could be among several other possible mechanisms underlying structural modifications (Bremner, Elzinga, Schmahl, & Vermetten, 2008; Levy-Gigi et al., 2013). Although we have shown that BLT appears to significantly reduce reaction time and protect as well as improve NCV within the inferior frontal region, it remains to be determined whether such changes are due to one or more of the previously described mechanisms, and why such changes are more sensitive within the frontal lobe.

While considerable evidence suggests that light exposure can have a wide range of effects on cognition (Yamadera et al., 2000), the underlying mechanisms responsible for these changes are not fully understood. As mentioned above, some proposed potential mechanisms include the enhancement of neurogenesis, neuronal size, dendritic arborization, and glial cell proliferation (Bremner et al., 2008; Levy-Gigi et al., 2013), but these possibilities have not yet been adequately investigated. It remains an open question as to why BLT would have a positive effect on NCV. It is possible that the observed structural changes resulting from BLT may actually be a secondary consequence of improved sleep, perhaps as a function of improved circadian timing and regularity induced by morning blue light exposure (Wang et al., 2017; Yamadera et al., 2000). This is because blue light can stimulate many aspects of the visual system. The primary effect of blue light on sleep and circadian rhythms is believed to occur through its non-visual effects on intrinsically photosensitive retinal ganglion cells (ipRGCs) which are specifically attuned to the blue wavelengths of light. These ipRGCs project predominantly to the suprachiasmatic nucleus (SCN) of the hypothalamus, the primary circadian pacemaker of the brain (Provencio et al., 2000). When ipRGCs are stimulated with blue light in the morning, this results in signals to the SCN to suppress melatonin production from the pineal gland and a slight phase advance in the circadian timing of sleep onset (Brainard & Hanifin, 2005). Consequently, regular morning exposure to BLT can lead to greater daytime alertness and better overall sleep quality (Vandewalle, Maquet, & Dijk, 2009). Moreover, poor sleep quality is among the most common

symptoms observed in individuals with a recent history of mTBI (Orff, Ayalon, & Drummond, 2009). Therefore, an improvement in sleep following morning blue-light exposure may play an important role in facilitating neural repair processes, and without sufficient high-quality sleep, an individual is less likely to make a full recovery from an mTBI (Sullivan, Berndt, Edmed, Smith, & Allan, 2016). Previous research has shown that during sleep, the space between neurons is increased to allow for the removal of toxic molecules that build up during waking hours (Xie et al., 2013). In addition, sleep also appears to increase the proliferation of oligodendrocyte precursor cells (Bellesi et al., 2013). Above factors could be significantly involved in aiding brain repair processes and may further contribute to reduce response time and protecting or even improving NCV by increasing the number of glial cells near the affected tissue.

Statistical considerations

Our findings – first the identification of regions of interest by comparing cortical structure between HCs and mTBI individuals at baseline, and second testing the impact of light therapy on normalized volume of identified regions of interest should be interpreted after accounting for a few statistical considerations.

First, it is important to justify the statistical approach of using the effect size to identify the regions of interest for main analysis of comparing cortical structure between HCs and mTBI individuals at baseline. Most importantly, the primary goal of our study was not to identify and report regions showing differences in cortical structure between controls and mTBI individuals. Instead, our aim was to analyze the impact of six-weeks of short-wavelength morning light therapy on specific regions of interest, which may have different cortical volume in individuals with mTBI relative to HCs. Second, our data contained only young participants, aged between 18-35 years. Previously, it has been found that changes in cortical structure are generally minimal and spatially less specific during adolescence and early adulthood (Ashburner et al., 2003). Therefore, we preferred to use a less conservative statistical approach i.e., identification of regions of interest from whole-brain region-specific analysis in order to capture the subtle differences and minimize the chances of loss of information due to small differences in cortical structure.

Because of our strong a priori interest in simple effects of blue-light exposure (pre- versus post-treatment for reaction time and cortical volume), we performed pairwise comparisons regardless of whether the group x time interaction was significant or not.

Lastly, as explained below, to observe any possible subtle or even widely distributed impact of blue-light exposure on cortical volume, our findings did not include correction for multiple comparisons. The Desikan atlas used in our study parcellates the whole brain into 68 areas – including the parcellation of only the frontal lobe into 12 areas per hemisphere. Following this parcellation, we found that out of seven regions of interest, the blue-light exposure had a non-significant protective impact or a non-significant improvement within four areas and significant group-time interaction for one area within the frontal lobe – but without correcting for multiple comparisons correction. These non-significant protective impacts or improvements for most of the areas, and significant protective impact and improvement within the frontal lobe i.e., for R.ParsOrb may indicate that the positive impact of blue-light exposure could have been distributed over several regions tested within the frontal, temporal and parietal lobes rather than targeting a specific area of Desikan atlas. This could be one of the potential reasons of not observing a strong impact of blue-light exposure on cortical volume of individuals with mTBI.

Limitations and Strengths

The findings of this study should be considered in light of several limitations. First, the normalized cortical volume reductions reported in this study may not be generalizable across heterogeneous mTBI profiles. By definition, mTBI is a heterogeneous injury and can be caused by a variety of mechanisms and forces impacting the brain in different ways. Thus, every mTBI represents a unique injury and it is unlikely that any one-brain region would reflect changes common to most mTBIs. On the other hand, it is likely that many mTBIs share common mechanisms and effects as well as some anatomical locations may be more susceptible to rotational forces, shearing, or other forms of damage. Second, although we controlled the effects of age, it should be noted that the HC group was approximately 3.7 years older than the mTBI group on average. Though statistically significant, all participants were young adults (range: 18-35 years) and therefore it is unlikely that the observed brain differences are due to developmental inequalities between the groups, particularly after statistical covariation for age in the analyses. Third, the light therapy conditions had relatively few participants and were likely to be underpowered for some effects, which might account for the lack of significant findings in some analyses (e.g. non-significant group x time interaction for RT).

This was the first study to examine the effects of light therapy on brain volume, so the present findings should be considered preliminary and in need of replication with larger samples. Nonetheless, despite the small sample sizes in addition to above mentioned limitations, we found that BLT helped to protect or even improve NCV and reduce RT, and showed significant associations between increased NCV and reduced RT for individuals with mTBI. Additionally, future studies focusing on other cortical measures such as cortical surface area and cortical folding are necessary to further elaborate the impact of BLT on recovery following mTBI.

Conclusions

The present data suggest that the specific regions especially within the frontal lobe may be particularly susceptible to mild traumatic brain injuries. Our preliminary findings suggest that 6-weeks of daily morning exposure to blue light can play an important role in facilitating some aspects of recovery from mTBI by protecting and improving NCV of a region within the inferior frontal cortex, which may also lead to a reduction in reaction time during simple stimulus task. As there are no widely accepted non-pharmacologic treatments to facilitate recovery from mTBI, the present findings suggest a novel alternative intervention that may have positive impacts on brain structure and function. While we speculate that many of the positive benefits that emerge from exposure to blue light result from its effects on sleep and circadian processes, further work will be necessary to identify the underlying mechanisms and the inter-individual difference factors that may contribute to the effectiveness of this approach. Further research will also be necessary to determine the effects of blue light exposure on neurocognitive performance during more challenging tasks and symptoms of post-concussion syndrome.

Acknowledgements

This research was supported by a grant from the U.S. Army Medical Research and Development Command to WDSK (W81XWH-11-1-0056) and SLR (W81XWH-12-1-0109). Opinions, interpretations, conclusions and recommendations in this study are those of the author and are not necessarily endorsed by the Department of Defense.

Authors contributions

SB analyzed the data and wrote the initial draft. NSD, AR and JRV helped with data analysis and contributed to the writing of the initial draft. MW conducted data collection, data processing, and edited versions of the manuscript. IMR and SLR contributed to study design and edited versions of the manuscript. WDSK designed and supervised all aspects of the study and contributed to writing of the manuscript.

Declaration of Interests

The authors have no conflicts of interest to declare with regard to this work.

References

Alkozei, A., Smith, R., Dailey, N. S., Bajaj, S., & Killgore, W. D. S. (2017). Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *Plos One, 12*(9), e0184884. doi:10.1371/journal.pone.0184884

Alkozei, A., Smith, R., Pisner, D. A., Vanuk, J. R., Berryhill, S. M., Fridman, A., . . . Killgore, W. D. (2016). Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. *Sleep, 39*(9), 1671-1680. doi:10.5665/sleep.6090

Ashburner, J., Csernansky, J. G., Davatzikos, C., Fox, N. C., Frisoni, G. B., & Thompson, P. M. (2003). Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol, 2*(2), 79-88.

Bajaj, S., Dailey, N. S., Rosso, I. M., Rauch, S. L., & Killgore, W. D. S. (2018). Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury. *Hum Brain Mapp, 39*(5), 1886-1897. doi:10.1002/hbm.23951

Bajaj, S., Vanuk, J. R., Smith, R., Dailey, N. S., & Killgore, W. D. S. (2017). Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. *Front Neurol, 8*, 616. doi:10.3389/fneur.2017.00616

Beaven, C. M., & Ekstrom, J. (2013). A comparison of blue light and caffeine effects on cognitive function and alertness in humans. *Plos One, 8*(10), e76707. doi:10.1371/journal.pone.0076707

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex, 10*(3), 295-307.

Bechara, A., & Van Der Linden, M. (2005). Decision-making and impulse control after frontal lobe injuries. *Curr Opin Neurol, 18*(6), 734-739.

Bellesi, M., Pfister-Genskow, M., Maret, S., Keles, S., Tononi, G., & Cirelli, C. (2013). Effects of sleep and wake on oligodendrocytes and their precursors. *J Neurosci, 33*(36), 14288-14300. doi:10.1523/jneurosci.5102-12.2013

Berger, R. P., Pierce, M. C., Wisniewski, S. R., Adelson, P. D., Clark, R. S., Ruppel, R. A., & Kochanek, P. M. (2002). Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatrics, 109*(2), E31.

Bigler, E. D., & Maxwell, W. L. (2012). Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging and Behavior, 6*(2), 108-136. doi:10.1007/s11682-011-9145-0

Bleiberg, J., Cernich, A. N., Cameron, K., Sun, W., Peck, K., Ecklund, P. J., . . . Warden, D. L. (2004). Duration of cognitive impairment after sports concussion. *Neurosurgery, 54*(5), 1073-1078; discussion 1078-1080.

Bloor, C. M. (2005). Angiogenesis during exercise and training. *Angiogenesis, 8*(3), 263-271. doi:10.1007/s10456-005-9013-x

Blyth, B. J., & Bazarian, J. J. (2010). Traumatic alterations in consciousness: traumatic brain injury. *Emerg Med Clin North Am, 28*(3), 571-594. doi:10.1016/j.emc.2010.03.003

Brainard, G. C., & Hanifin, J. P. (2005). Photons, clocks, and consciousness. *J Biol Rhythms, 20*(4), 314-325. doi:10.1177/0748730405278951

Bremner, J. D., Elzinga, B., Schmahl, C., & Vermetten, E. (2008). Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res, 167*, 171-186. doi:10.1016/S0079-6123(07)67012-5

Cajochen, C., Munch, M., Kobialka, S., Krauchi, K., Steiner, R., Oelhafen, P., . . . Wirz-Justice, A. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *J Clin Endocrinol Metab, 90*(3), 1311-1316. doi:10.1210/jc.2004-0957

Carlo, C. N., & Stevens, C. F. (2013). Structural uniformity of neocortex, revisited. *Proceedings of the National Academy of Sciences of the United States of America, 110*(4), 1488-1493. doi:10.1073/pnas.1221398110

Chellappa, S. L., Steiner, R., Blattner, P., Oelhafen, P., Gotz, T., & Cajochen, C. (2011). Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *Plos One, 6*(1), e16429. doi:10.1371/journal.pone.0016429

Cicerone, K. D. (1996). Attention deficits and dual task demands after mild traumatic brain injury. *Brain Injury, 10*(2), 79-90. doi:10.1080/026990596124566

Clark, A. L., Merritt, V. C., Bigler, E. D., Bangen, K. J., Werhane, M., Sorg, S. F., . . . Delano-Wood, L. (2018). Blast-Exposed Veterans With Mild Traumatic Brain Injury Show Greater Frontal Cortical Thinning and Poorer Executive Functioning. *Frontiers in Neurology, 9*(873). doi:10.3389/fneur.2018.00873

Cognitive Science Research Center (CSRC). (2014). ANAM Military Battery, Administration Manual. In. Norman, OK.

Cole, W. R., Gregory, E., Arrieux, J. P., & Haran, F. J. (2018). Intraindividual Cognitive Variability: An Examination of ANAM4 TBI-MIL Simple Reaction Time Data from Service Members with and without Mild Traumatic Brain Injury. *J Int Neuropsychol Soc, 24*(2), 156-162. doi:10.1017/S1355617717001187

Dean, P. J., & Sterr, A. (2013). Long-term effects of mild traumatic brain injury on cognitive performance. *Front Hum Neurosci, 7*, 30. doi:10.3389/fnhum.2013.00030

Depue, B. E., Burgess, G. C., Bidwell, L. C., Willcutt, E. G., & Banich, M. T. (2010). Behavioral performance predicts grey matter reductions in the right inferior frontal gyrus in young adults with combined type ADHD. *Psychiatry Res, 182*(3), 231-237. doi:10.1016/j.pscychresns.2010.01.012

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Hyman, B. T. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*. doi:10.1016/j.neuroimage.2006.01.021

Diaz-Arrastia, R., Kochanek, P. M., Bergold, P., Kenney, K., Marx, C. E., Grimes, C. J., . . . Salzer, W. (2014). Pharmacotherapy of traumatic brain injury: state of the science and the road forward: report of the Department of Defense Neurotrauma Pharmacology Workgroup. *J Neurotrauma, 31*(2), 135-158. doi:10.1089/neu.2013.3019

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: review and meta-analysis. *Neuroimage Clin, 4*, 283-294. doi:10.1016/j.nicl.2013.12.009

Epstein, D. J., Legarreta, M., Bueler, E., King, J., McGlade, E., & Yurgelun-Todd, D. (2016). Orbitofrontal cortical thinning and aggression in mild traumatic brain injury patients. *Brain Behav, 6*(12), e00581. doi:10.1002/brb3.581

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders (SCID-I/P)*. New York: New York: New York State Psychiatric Institute.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., . . . Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*(3), 341-355.

Fogleman, N. D., Naaz, F., Knight, L. K., Stoica, T., Patton, S. C., Olson-Madden, J. H., . . . Depue, B. E. (2017). Reduced lateral prefrontal cortical volume is associated with performance on the modified Iowa Gambling Task: A surface based morphometric analysis of previously deployed veterans. *Psychiatry Res Neuroimaging, 267*, 1-8. doi:10.1016/j.pscychresns.2017.06.014

Friedl, K. E., Grate, S. J., Proctor, S. P., Ness, J. W., Lukey, B. J., & Kane, R. L. (2007). Army research needs for automated neuropsychological tests: monitoring soldier health and performance status. *Arch Clin Neuropsychol, 22 Suppl 1*, S7-14. doi:10.1016/j.acn.2006.10.002

Gilbert, K. S., Kark, S. M., Gehrman, P., & Bogdanova, Y. (2015). Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clin Psychol Rev, 40*, 195-212. doi:10.1016/j.cpr.2015.05.008

Govindarajan, K. A., Narayana, P. A., Hasan, K. M., Wilde, E. A., Levin, H. S., Hunter, J. V., . . . McCarthy, J. J. (2016). Cortical Thickness in Mild Traumatic Brain Injury. *J Neurotrauma, 33*(20), 1809-1817. doi:10.1089/neu.2015.4253

Kane, R. L., Roebuck-Spencer, T., Short, P., Kabat, M., & Wilken, J. (2007). Identifying and monitoring cognitive deficits in clinical populations using Automated Neuropsychological Assessment Metrics (ANAM) tests. *Arch Clin Neuropsychol, 22 Suppl 1*, S115-126. doi:10.1016/j.acn.2006.10.006

Killgore, W., Alkozei, A., & Weber, M. (2018). Blue Light Therapy Improves Executive Function Following Mild Traumatic Brain Injury. *Biological Psychiatry, 83*(9), S416-S416. doi:DOI 10.1016/j.biopsych.2018.02.1070

Killgore, W. D. S., Olson, E. A., & Weber, M. (2013). Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans. *Sci Rep, 3*, 3457. doi:10.1038/srep03457

Knight, R. T., Grabowecky, M. F., & Scabini, D. (1995). Role of human prefrontal cortex in attention control. *Adv Neurol, 66*, 21-34; discussion 34-26.

Laskowski, R. A., Creed, J. A., & Raghupathi, R. (2015). Pathophysiology of Mild TBI: Implications for Altered Signaling Pathways. In F. H. Kobeissy (Ed.), *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. Boca Raton (FL).

Levy-Gigi, E., Szabo, C., Kelemen, O., & Keri, S. (2013). Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. *Biol Psychiatry, 74*(11), 793-800. doi:10.1016/j.biopsych.2013.05.017

List, J., Ott, S., Bukowski, M., Lindenberg, R., & Floel, A. (2015). Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults. *Front Hum Neurosci, 9*, 228. doi:10.3389/fnhum.2015.00228

Lockley, S. W., Evans, E. E., Scheer, F. A., Brainard, G. C., Czeisler, C. A., & Aeschbach, D. (2006). Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep, 29*(2), 161-168.

Marshall, S., Bayley, M., McCullagh, S., Velikonja, D., & Berrigan, L. (2012). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Can Fam Physician, 58*(3), 257-267, e128-240.

McAllister, A. K., Katz, L. C., & Lo, D. C. (1999). Neurotrophins and synaptic plasticity. *Annu Rev Neurosci, 22*, 295-318. doi:10.1146/annurev.neuro.22.1.295

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvořák, J., Echemendia, R. J., . . . Turner, M. (2013). Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *British Journal of Sports Medicine, 47*(5), 250-258. doi:10.1136/bjsports-2013-092313

McInnes, K., Friesen, C. L., MacKenzie, D. E., Westwood, D. A., & Boe, S. G. (2017). Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. *Plos One, 12*(4), e0174847. doi:10.1371/journal.pone.0174847

National Center for Injury Prevention and Control. (2003). *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem*. Atlanta, GA.

Newman, D. P., Lockley, S. W., Loughnane, G. M., Martins, A. C., Abe, R., Zoratti, M. T., . . . Bellgrove, M. A. (2016). Ocular exposure to blue-enriched light has an asymmetric influence on neural activity and spatial attention. *Sci Rep, 6*, 27754. doi:10.1038/srep27754

Orff, H. J., Ayalon, L., & Drummond, S. P. (2009). Traumatic brain injury and sleep disturbance: a review of current research. *The Journal of Head Trauma Rehabilitation, 24*(3), 155-165. doi:10.1097/HTR.0b013e3181a0b281

Parcell, D. L., Ponsford, J. L., Rajaratnam, S. M., & Redman, J. R. (2006). Self-reported changes to nighttime sleep after traumatic brain injury. *Arch Phys Med Rehabil, 87*(2), 278-285. doi:10.1016/j.apmr.2005.10.024

Pontifex, M. B., Broglio, S. P., Drollette, E. S., Scudder, M. R., Johnson, C. R., O'Connor, P. M., & Hillman, C. H. (2012). The relation of mild traumatic brain injury to chronic lapses of attention. *Res Q Exerc Sport, 83*(4), 553-559. doi:10.1080/02701367.2012.10599252

Provencio, I., Rodriguez, I. R., Jiang, G., Hayes, W. P., Moreira, E. F., & Rollag, M. D. (2000). A novel human opsin in the inner retina. *J Neurosci, 20*(2), 600-605.

Rahman, S. A., Flynn-Evans, E. E., Aeschbach, D., Brainard, G. C., Czeisler, C. A., & Lockley, S. W. (2014). Diurnal spectral sensitivity of the acute alerting effects of light. *Sleep, 37*(2), 271-281. doi:10.5665/sleep.3396

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: a robust approach. *Neuroimage, 53*(4), 1181-1196. doi:10.1016/j.neuroimage.2010.07.020

Reuter, M., Schmansky, N. J., Rosas, H. D., & Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage, 61*(4), 1402-1418. doi:10.1016/j.neuroimage.2012.02.084

Rockel, A. J., Hiorns, R. W., & Powell, T. P. (1980). The basic uniformity in structure of the neocortex. *Brain, 103*(2), 221-244. doi:10.1093/brain/103.2.221

Rosso, I. M., Killgore, W. D. S., Olson, E. A., Webb, C. A., Fukunaga, R., Auerbach, R. P., . . . Rauch, S. L. (2017). Internet-based cognitive behavior therapy for major depressive disorder: A randomized controlled trial. *Depress Anxiety, 34*(3), 236-245. doi:10.1002/da.22590

Silver, J. M., McAllister, T. W., & Arciniegas, D. B. (2009). Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry, 166*(6), 653-661. doi:10.1176/appi.ajp.2009.08111676

Sinclair, K. L., Ponsford, J. L., Taffe, J., Lockley, S. W., & Rajaratnam, S. M. (2014). Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair, 28*(4), 303-313. doi:10.1177/1545968313508472

Spitz, G., Bigler, E. D., Abildskov, T., Maller, J. J., O'Sullivan, R., & Ponsford, J. L. (2013). Regional cortical volume and cognitive functioning following traumatic brain injury. *Brain Cogn, 83*(1), 34-44. doi:10.1016/j.bandc.2013.06.007

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., . . . Katz, D. I. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43*(3), 396-417. doi:10.1016/j.neuropsychologia.2004.06.010

Sullivan, K. A., Berndt, S. L., Edmed, S. L., Smith, S. S., & Allan, A. C. (2016). Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. *Appl Neuropsychol Adult, 23*(6), 426-435. doi:10.1080/23279095.2016.1172229

Tate, D. F., York, G. E., Reid, M. W., Cooper, D. B., Jones, L., Robin, D. A., . . . Lewis, J. (2014). Preliminary findings of cortical thickness abnormalities in blast injured service members and their relationship to clinical findings. *Brain Imaging and Behavior, 8*(1), 102-109. doi:10.1007/s11682-013-9257-9

Theadom, A., Cropley, M., Parmar, P., Barker-Collo, S., Starkey, N., Jones, K., . . . Group, B. R. (2015). Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med, 16*(8), 926-932. doi:10.1016/j.sleep.2015.04.013

Trivino, M., Correa, A., Arnedo, M., & Lupianez, J. (2010). Temporal orienting deficit after prefrontal damage. *Brain, 133*(Pt 4), 1173-1185. doi:10.1093/brain/awp346

Urban, K. J., Riggs, L., Wells, G. D., Keightley, M., Chen, J. K., Ptito, A., . . . Sinopoli, K. J. (2017). Cortical Thickness Changes and Their Relationship to Dual-Task Performance following Mild Traumatic Brain Injury in Youth. *J Neurotrauma, 34*(4), 816-823. doi:10.1089/neu.2016.4502

Vandewalle, G., Maquet, P., & Dijk, D. J. (2009). Light as a modulator of cognitive brain function. *Trends Cogn Sci, 13*(10), 429-438. doi:10.1016/j.tics.2009.07.004

Verma, A., Anand, V., & Verma, N. P. (2007). Sleep disorders in chronic traumatic brain injury. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 3*(4), 357.

Vincent, A. S., Roebuck-Spencer, T., Gilliland, K., & Schlegel, R. (2012). Automated Neuropsychological Assessment Metrics (v4) Traumatic Brain Injury Battery: military normative data. *Mil Med, 177*(3), 256-269.

Viola-Saltzman, M., & Watson, N. F. (2012). Traumatic Brain Injury and Sleep Disorders. *Neurologic Clinics, 30*(4), 1299-1312. doi:http://dx.doi.org/10.1016/j.ncl.2012.08.008

Wang, H.-B., Whittaker, D. S., Truong, D., Mulji, A. K., Ghiani, C. A., Loh, D. H., & Colwell, C. S. (2017). Blue light therapy improves circadian dysfunction as well as motor symptoms in two mouse models of Huntington's disease. *Neurobiology of Sleep and Circadian Rhythms, 2*(Supplement C), 39-52. doi:https://doi.org/10.1016/j.nbscr.2016.12.002

Wang, X., Xie, H., Cotton, A. S., Tamburrino, M. B., Brickman, K. R., Lewis, T. J., . . . Liberzon, I. (2015). Early cortical thickness change after mild traumatic brain injury following motor vehicle collision. *J Neurotrauma, 32*(7), 455-463. doi:10.1089/neu.2014.3492

Warner, M. A., Youn, T. S., Davis, T., Chandra, A., Marquez de la Plata, C., Moore, C., . . . Diaz-Arrastia, R. (2010). Regionally selective atrophy after traumatic axonal injury. *Arch Neurol, 67*(11), 1336-1344. doi:10.1001/archneurol.2010.149

Wilde, E. A., Hunter, J. V., Newsome, M. R., Scheibel, R. S., Bigler, E. D., Johnson, J. L., . . . Levin, H. S. (2005). Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. *J Neurotrauma, 22*(3), 333-344. doi:10.1089/neu.2005.22.333

Wright, H. R., Lack, L. C., & Kennaway, D. J. (2004). Differential effects of light wavelength in phase advancing the melatonin rhythm. *J Pineal Res, 36*(2), 140-144.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377. doi:10.1126/science.1241224

Yamadera, H., Ito, T., Suzuki, H., Asayama, K., Ito, R., & Endo, S. (2000). Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in Alzheimer-type dementia. *Psychiatry Clin Neurosci, 54*(3), 352-353. doi:10.1046/j.1440-1819.2000.00711.x

Zeitzer, J. M., Friedman, L., & O'Hara, R. (2009). Insomnia in the context of traumatic brain injury. *J Rehabil Res Dev, 46*(6), 827-836.

Figures and Tables

Figure Legends

Figure 1. Left hemisphere: Identification of regions of interest (ROIs). Three regions within the left hemisphere, including the left caudal middle frontal gyrus (L.CMFG) (shown in dark red color), left inferior parietal cortex (L.IPC) (shown in light violet color) and left middle temporal cortex (L.MTC) (shown in orange color), which showed lower NCV in mTBI patients compared to HCs (medium effect size, $0.5 \leq$ Cohen's d ≤ 0.6) were considered

as ROIs for the main analysis. Here, the horizontal 'green' colored lines represent mean of the adjusted NCV values of corresponding regions.

Figure 2. Right hemisphere: Identification of regions of interest (ROIs). Four regions in the right hemisphere, including the right lateral orbitofrontal cortex (R.LOFC) (2A, shown in dark green color), right pars orbitalis (R.ParsOrb) (2A, shown in light green color), right middle temporal cortex (R.MTC) (2B, shown in orange color), and right rostral middle frontal gyrus (R.RMFG) (2B, shown in dark violet color), which showed lower NCV in mTBI patients compared to HCs (medium effect size, $0.5 \leq$ Cohen's $d \leq 0.6$) were considered as ROIs for the main analysis. Here, the horizontal 'green' colored lines represent mean of the adjusted NCV values of corresponding regions.

Figure 3. Effect of BLT versus placebo ALT on reaction time (RT) and normalized cortical volume (NCV). We found that there was no significant time (pre- and post-treatment) x group (ALT/BLT) interaction for adjusted RT, however, within-subject pairwise comparison showed a significant decrease in adjusted RT following BLT, but not following ALT (A). There was significant time (pre- and post-treatment) x group (ALT/BLT) interaction for adjusted NCV within the R. ParsOrb (B). The horizontal 'green' colored lines represent mean of the adjusted residualized differences in RT (A) and NCV (B) for R. ParsOrb. We also found a significant negative association between adjusted residualized differences in RT and adjusted residualized differences in NCV for BLT group, but not for ALT group (C).

Figure 4. Left hemisphere: Effect of BLT versus placebo ALT on normalized cortical volume (NCV). None of these areas - (A) left caudal middle frontal gyrus (L. CMFG), (B) left inferior parietal cortex (L. IPC), or (C) left middle temporal cortex (L. MTC) showed significant time (pre- and post-treatment) x group (ALT/BLT) interaction or significant pairwise differences for either ALT or BLT group.

Figure 5. Right hemisphere: Effect of BLT versus placebo ALT on normalized cortical volume (NCV). None of these areas - (A) right lateral orbitofrontal cortex (R. LOFC), (B) right middle temporal cortex (R. MTC), or (C) right rostral middle frontal gyrus (R. RMFG) showed significant time (pre- and post-treatment) x group (ALT/BLT) interaction or significant pairwise differences for either ALT or BLT group.

Table Legends

Table 1. Demographic characteristics of healthy-controls (HCs) and mTBI participants.
Table 2. Summary of analysis of covariance (ANCOVA) analysis for adjusted RT and adjusted NCV within the right ParsOrbitalis (R. ParsOrb).
Table 3. Summary of analysis of covariance (ANCOVA) analysis for adjusted NCV within the left hemisphere.
Table 4. Summary of analysis of covariance (ANCOVA) analysis for adjusted NCV within the right hemisphere.

Figure 1.

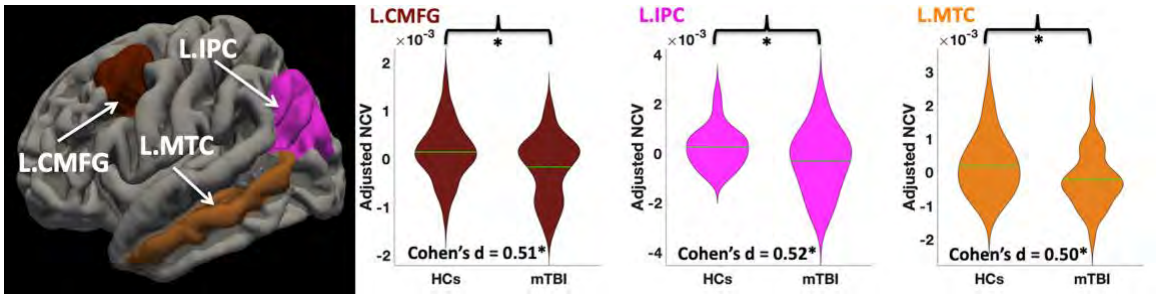


Figure 2.

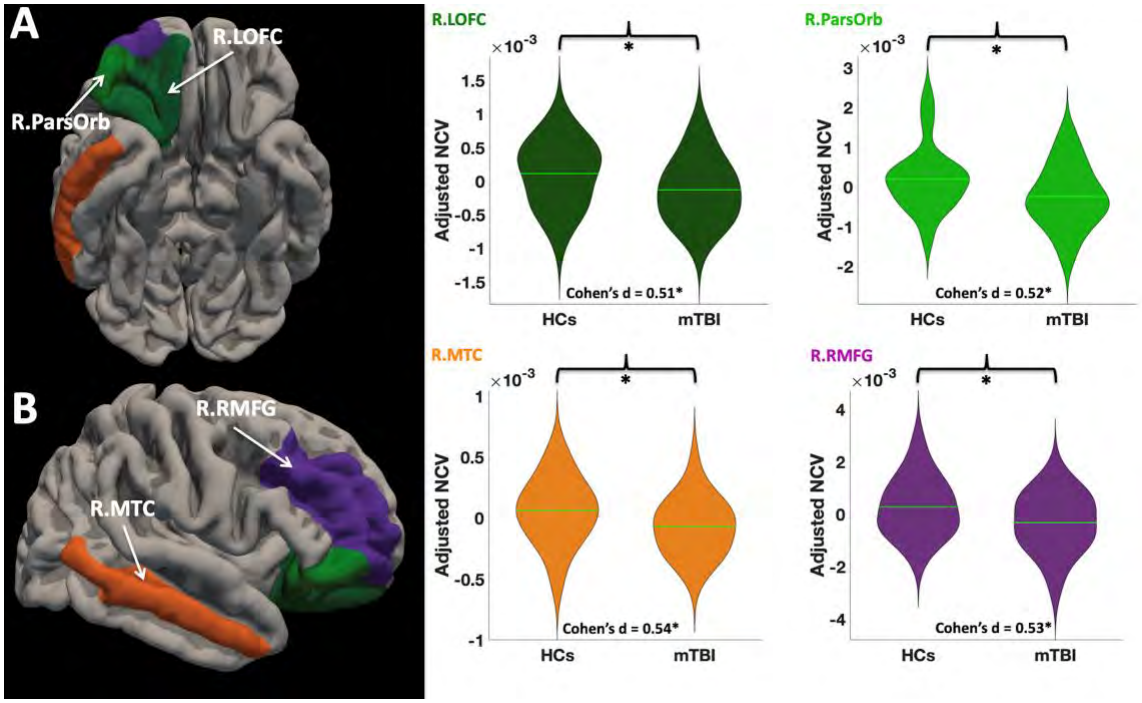


Figure 3.

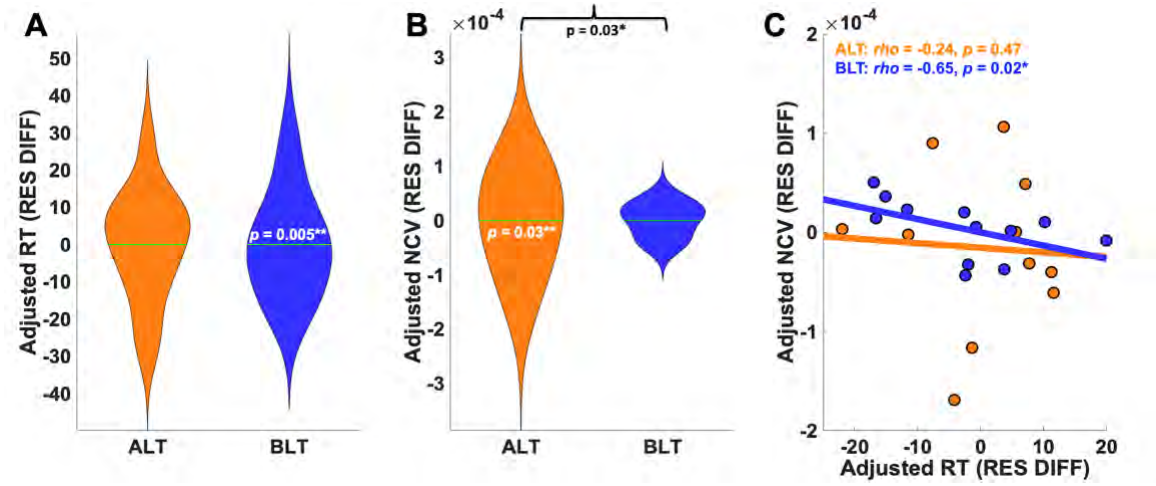


Figure 4.

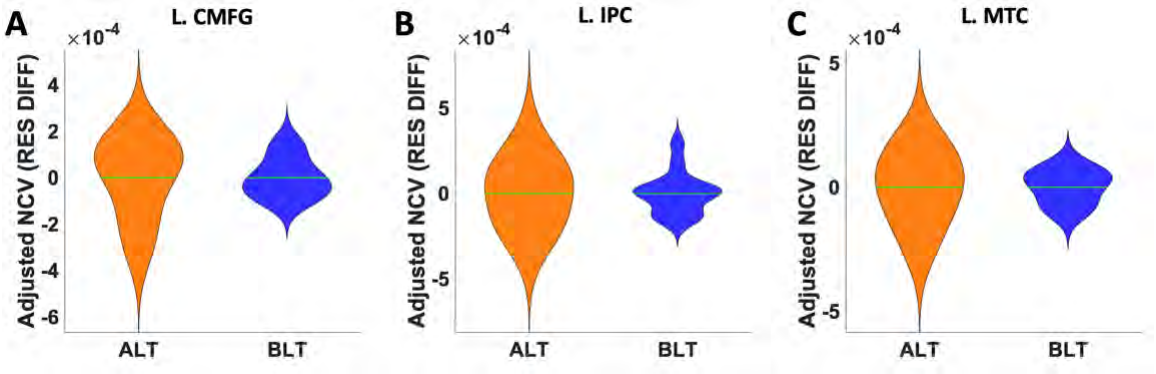


Figure 5.

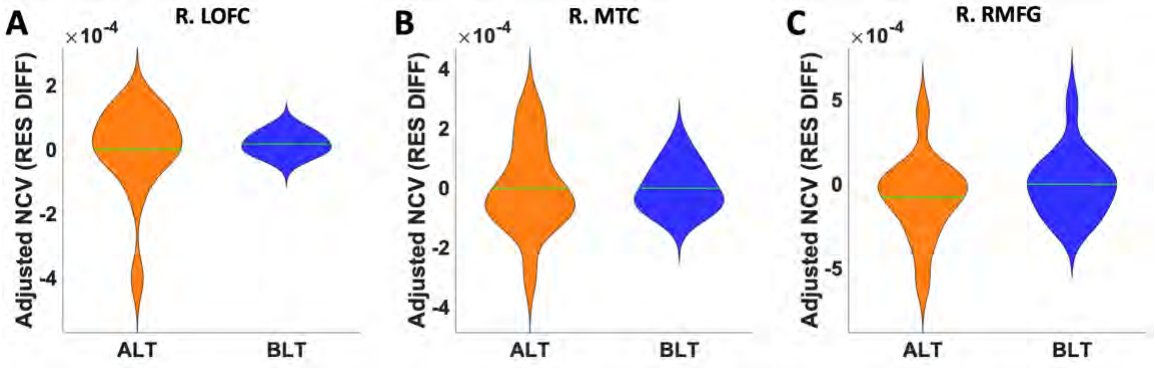


Table 1

Demographics	Healthy Controls (N = 34)	MTBI (Overall) (N = 28)	MTBI (ALT Group) (N = 14)	MTBI (BLT Group) (N = 14)	Significance (Independent sample t-test/ Chi-square)
Mean age (S.D.) (in years)	25.19 (3.38)	21.50 (3.76)	-	-	T (60) = 4.07, p = 0.00*
Sex (% female)	59	54	-	-	$\chi_2(1) = 0.17$, p = 0.68
Head size (ICV) (in cm_3)	1526.68 (176.22)	1607.29 (149.73)	-	-	T (60) = -1.92, p = 0.06
Mean age (S.D.) (in years)	-	-	21.21 (3.09)	21.78 (4.42)	T (26) = -0.40, p = 0.69
Sex (% female)	-	-	50	57	$\chi_2(1) = 0.16$, p = 0.69
Head size (ICV) (in cm_3)	-	-	1648.97 (114.03)	1586.39 (178.22)	T (26) = 1.11, p = 0.28
Mean TSI (S.D.) (in months)	-	-	7.11 (3.53)	6.57 (4.57)	T (26) = 0.35, p = 0.73
Days light used (S.D.)	-	-	34.78 (9.17)	37.85 (4.36)	T (26) = -1.13, p = 0.27

MTBI: Mild Traumatic Brain Injury; S.D.: Standard Deviation; TSI: Time since injury; ICV: Intracranial volume.
*Significant at $p < 0.05$

Table 2.

Within-Subjects Effects (ANCOVA)					
Interaction					
Source	Parameter	Mean Square	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Time (Pre and Post) x Group (ALT/BLT) (Sphericity Assumed)	RT	186.90	F (1, 21) = 1.11	0.30	0.05
	NCV within the R. ParsOrb	1.62×10^{-8}	F (1,23) = 5.05	0.03*	0.18
Pairwise Comparisons (Pre versus Post)					
Effect of treatment	Parameter	Groups	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Pre versus Post	RT	ALT BLT	F (1,21) = 2.66 F (1,21) = 9.90	0.12 0.005**	0.11 0.32
	NCV within the R. ParsOrb	ALT BLT	F (1,23) = 5.37 F (1,23) = 0.81	0.03** 0.38	0.19 0.03

RT: Reaction time; NCV: Normalized Cortical Volume;
*Interaction is significant at $p < 0.05$
**Mean difference between post and pre-treatment is significant at $p < 0.05$.

Table 3.

Within-Subjects Effects (ANCOVA) for NCV					
Interaction					
Source	Region	Mean Square	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Time (Pre and Post) x Group (ALT/BLT) (Sphericity Assumed)	L. CMFG	1.14×10^{-9}	F (1,23) = 0.10	0.75	0.004
	L. IPC	3.0×10^{-9}	F (1,23) = 0.15	0.70	0.01
	L. MTC	4.6×10^{-9}	F (1,23) = 0.53	0.47	0.02
Pairwise Comparisons (Pre versus Post)					
Effect of treatment	Region	Groups	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Pre versus Post	L. CMFG	ALT BLT	F (1,23) = 0.31 F (1,23) = 1.04	0.58 0.32	0.013 0.043
	L. IPC	ALT BLT	F (1,23) = 0.12 F (1,23) = 0.04	0.73 0.83	0.005 0.002

	L. MTC	ALT BLT	F (1,23) = 2.44 F (1,23) = 0.27	0.13 0.61	0.10 0.01

NCV: Normalized Cortical Volume; L. CMFG: Left caudal middle frontal gyrus; L. IPC: Left inferior parietal cortex; L. MTC: Left middle temporal cortex.

Table 4.

Within-Subjects Effects (ANCOVA) for NCV					
Interaction					
Source	Region	Mean Square	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Time (Pre and Post) x Group (ALT/BLT) (Sphericity Assumed)	R. LOFC	2.27×10^{-8}	F (1,22) = 3.12	0.09	0.12
	R. MTC	2.48×10^{-9}	F (1,23) = 0.28	0.60	0.01
	R. RMFG	2.80×10^{-8}	F (1,22) = 1.16	0.29	0.05
Pairwise Comparisons (Pre versus Post)					
Effect of treatment	Region	Groups	Statistics	Significance (*p*-value)	Effect size (Partial Eta Squared)
Pre versus Post	R. LOFC	ALT BLT	F (1,22) = 2.95 F (1,22) = 0.69	0.10 0.41	0.12 0.03
	R. MTC	ALT BLT	F (1,23) = 1.03 F (1,23) = 0.07	0.32 0.80	0.04 0.003
	R. RMFG	ALT BLT	F (1,22) = 2.37 F (1,22) = 0.00	0.14 0.99	0.1 0.0

NCV: Normalized Cortical Volume; R. LOFC: Right lateral orbitofrontal cortex; R. MTC: Right middle temporal cortex; R. RMFG: Right rostral middle frontal gyrus.

Review

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Concussion

Potential for the development of light therapies in mild traumatic brain injury

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Light affects almost all aspects of human physiological functioning, including circadian rhythms, sleep–wake regulation, alertness, cognition and mood. We review the existing relevant literature on the effects of various wavelengths of light on these major domains, particularly as they pertain to recovery from mild traumatic brain injuries. Evidence suggests that light, particularly in the blue wavelengths, has powerful alerting, cognitive and circadian phase shifting properties that could be useful for treatment. Other wavelengths, such as red and green may also have important effects that, if targeted appropriately, might also be useful for facilitating recovery. Despite the known effects of light, more research is needed. We recommend a personalized medicine approach to the use of light therapy as an adjunctive treatment for patients recovering from mild traumatic brain injury.

First draft submitted: 29 June 2018; Accepted for publication: 1 August 2018; Published online: 15 October 2018

Keywords: blue light • brain injury • circadian rhythm • concussion • fatigue • mild TBI • phototherapy • sleep–wake disruption

Mild traumatic brain injuries (mTBIs) are currently among the most socially, medically and academically talked-about issues today. The annual mTBI incidence is at least 1.5 million reported injuries in the USA [1–3]. However, this number fails to capture the untold number of such injuries that likely go unreported [4,5]. The long-term consequences – plausibly including neurodegenerative conditions [6–10], impaired cognitive abilities [11–13] and altered psychosocial functioning [14–20] – necessitate the need for efficacious treatments following injury and proactive preventative methods for reducing injury risk and consequence.

Despite significant job-, school- and economic-related burdens associated with the medical management of mTBIs [1], there is no currently accepted gold standard treatment for mTBIs [21,22]. Historically, the treatment of choice was total rest to allow the brain to heal. However, recent research advances are giving way to more active treatments, with an emphasis on early intervention [23–25]. While early reports are promising for short-term management, the long-term impact of these active interventions is not well established. Additionally, there is little information on methods of optimizing these active approaches or complementary treatments that may enhance recovery in both the short and long term.

One complementary treatment method involves the use of light exposure. Light, both visible and invisible, can have powerful effects on numerous neurological and physiological systems [26–29]. Additionally, light is potentially a modifiable aspect of the environment in which one exists to allow for optimal healing, recovery and a return to homeostatic states following mTBI. The purpose of this narrative review is to provide a focused overview of the role and effect of light on neurological processes and to connect these effects with potential areas of intervention with respect to mTBI.

The fate of ambient light: image-forming & nonimage-forming pathways

The primary sensory function of the eyes is to translate information contained in light into images [30]. This is accomplished primarily through two classes of retinal photoreceptors. Cones are color-sensitive photoreceptors

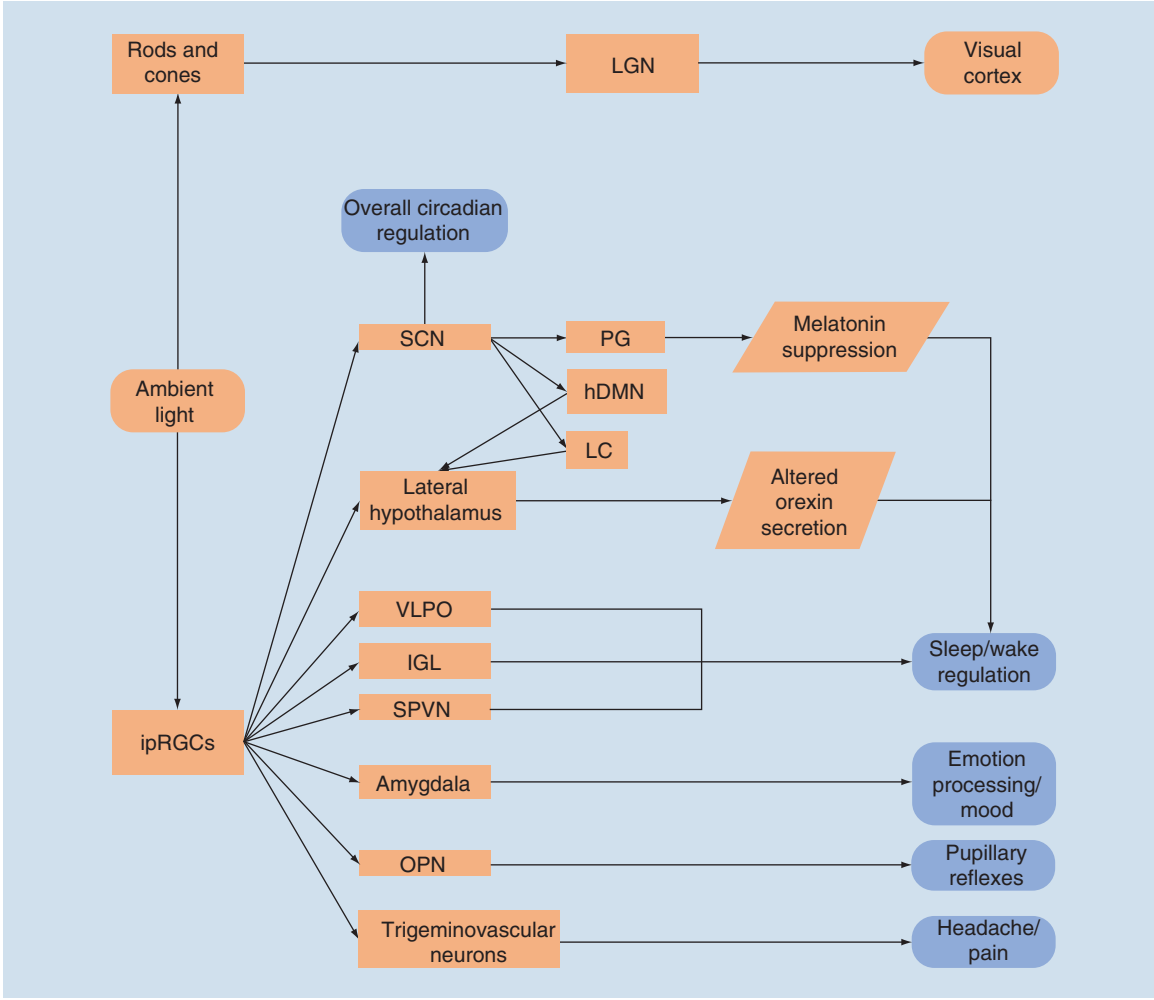


Figure 1. Schematic representation of the destinations for ambient light entering the eye.
hDMN: Hypothalamic dorsomedial nucleus; IGL: Intergeniculate leaflet; ipRGC: Intrinsically photosensitive retinal ganglion cell; LC: Locus coeruleus; LGN: Lateral geniculate nucleus; OPN: Olivary pretectal nucleus; PG: Pineal gland; SCN: Suprachiasmatic nucleus; SPVN: Supraparaventricular nucleus; VLPO: Ventrolateral preoptic nucleus.

while rods respond to changes in brightness and are particularly sensitive to dim light. Light information is converted by these photoreceptors, resulting in the stimulation of retinal ganglion cells (RGCs) that project to subcortical nuclei, including the lateral geniculate nucleus of the thalamus, ultimately terminating in the primary visual cortex and visual attention networks (Figure 1). These pathways provide the sensory information for vision and terminate in areas that process and interpret those sensory signals. For a complete review of the transformation from light information to visual interpretation, please see reference [30].

An additional class of photoreceptor was discovered in the early 2000s and is the starting point for the nonimage-forming (NIF) pathway [31–34]. This third type of photoreceptor is expressed directly by a small proportion of RGCs (termed intrinsically photosensitive RGCs; ipRGCs). These ipRGCs are maximally sensitive to blue light (λ = 460–480 nm) and less so to longer wavelengths including green, amber and red [31]. ipRGCs, combined with information regarding illuminance and color from the rods and cones, then directly project to regions involved in the regulation of or influence the actions of (Figure 1):

- Circadian rhythms. Projections from the ipRGCs to the suprachiasmatic nucleus (SCN), the primary biological clock for all circadian processes, can directly induce entrainment of either expected or aberrant circadian rhythms [31,35].

- Melatonin suppression. Stimulation of ipRGCs results in melatonin suppression via the SCN's projections to the pineal gland as well as the paraventricular nucleus of hypothalamus and superior cervical ganglion [34,36–38].
- Sleep–wake cycle regulation. In conjunction with the above-mentioned melatonin suppression pathways, direct projections from the ipRGCs go to the ventrolateral preoptic nucleus, subparaventricular nucleus and lateral hypothalamus [34]. The SCN may additionally influence the action of the hypothalamus's dorsomedial nucleus, and locus coeruleus, affecting the lateral hypothalamus secretion of orexin [33,34].
- Cognition. The aforementioned pathways regulating circadian rhythms, melatonin suppression and sleep–wake cycles additionally exert both direct and indirect influences on cognition and alertness [26].
- Emotional processing and mood. The amygdala, a primary site of emotional processing and integration, receives direct ipRGC projection [34,39].
- Intracranial nociception. ipRGCs project to the trigeminovascular neurons of the thalamus that transmit nociceptive information from the dura to the cortex [40].
- Pupillary constriction. ipRGCs directly project to the olivary pretectal nucleus [32–34], which in turn project to the Edinger–Westphal nucleus. The cumulative action of this pathway is pupillary constriction. For a complete review of the effects of mTBI on the pupillary light reflex, including NIF pathway contributions, please see [41].

As can be seen, light has the powerful potential to alter numerous biological and cognitive processes through this NIF pathway. Given the complex interactions between circadian timekeepers, hormone and neurotransmitter secretion pathways, cognition, and emotions, light has the potential to positively or negatively influence how individuals function at a very basic level. Consequently, using light as a therapeutic intervention has the potential to directly influence recovery and function following mTBI. In the following sections, we review potential areas of intervention and, where possible, expected outcomes from using light as a therapy.

mTBIs & their consequences

mTBIs are a change or disruption in the normal functioning of the brain subsequent to an external force applied to the head or body [42,43]. Typical guidelines for distinguishing mTBIs from more severe TBIs include a mechanism indicative of mTBI; loss of consciousness <30 min (if at all); post-traumatic amnesia <24 h; Glasgow Coma Scale scores 13–15; and lack of gross abnormalities on traditional neuroimaging [42,44,45]. The effects of a single mTBI are often viewed as transient and may include somatic symptoms, sleep–wake disturbances, and cognitive and behavioral disruptions. However, while these effects are common, the individual manifestations of these are highly individualized and may depend on premorbid functioning and the location and mechanism of injury [46]. Additionally, many individuals experience persistent symptoms associated with an mTBI, and recent findings indicate that the incidence of long-lasting mTBI-related functional decrements may be underestimated [42]. Here we provide an overview of mTBI-related consequences that may be positively affected by light therapy, with an emphasis on sleep and sleep-related consequences given the previously identified NIF-pathway effects.

Sleepiness & fatigue

High-quality sleep is an essential component of all aspects of human performance. Current recommendations for adequate sleep recommend 7–9 h of sleep per night for adults. Despite these recommendations, chronic sleep loss (<5.5 h/night of sleep) in the USA is reaching epidemic levels [47]. For individuals with chronic sleep loss, the consequences are numerous including increased somatization [48,49], poor emotional processing and responsiveness (e.g., increased incidence of depression and anxiety) [50–52], impaired cognition (vigilant attention, executive function, working and long-term memory) [53–56] and poor motor performance [57–59], as well as increased risk for general health issues including diabetes [60–62], cardiovascular disease [60,63], neurodegeneration [64,65] and overall poorer quality of life [66]. While the exact nature of this trend toward chronically undersleeping is not fully understood, work–life stress (e.g., increased expectations for high job-related hours, social stress) as well as the highly prevalent use of fluorescent lighting and blue-shifted light-emitting diode screens at night [67–69] are all implicated.

Compounding the endemic social issue of chronic sleep loss, detrimentally altered sleep is among the most common short- and long-term consequences of mTBI [70–74]. Indeed subjectively perceived traumatic brain injury (TBI)-related sleep–wake disruption is reported by plausibly as many as 70% of all individuals who sustain a TBI (regardless of severity) [70,74,75]. Individuals with mTBI commonly self report insomnia [74–79] and hypersomnolence (excessive sleepiness) [71,75,80–86], though hypersomnia [80,85,87,88] and circadian rhythm sleep disorders [82,89] are

also reported. Objectively, these reports are often corroborated by poor sleep efficiency, higher than usual wake after sleep onset and sleep latency, as well as more fragmented sleep and changes in sleep architecture [87,90–95]. Clinically, it is important to recognize that post-mTBI insomnia may be misdiagnosed as a circadian phase issue, specifically delayed sleep phase syndrome [89]. Consequently, individuals sustaining an mTBI may be at an increased risk for all of the aforementioned sleep-related health and performance outcomes without treatment for mTBI-related alterations.

The mechanisms by which mTBI induces altered sleep are not fully understood. However, there are implications from both human studies and animal models that suggest any combination of possible mechanisms including altered circadian hormone regulation (e.g., melatonin release) [96–98] and reductions in neurotransmitter function (e.g., loss of or damage to wake-promoting, orexin-secreting neurons in the hypothalamus) [99–101] among others may be responsible.

In addition to these possible mechanisms of post-mTBI sleep changes, sleep loss or low-quality sleep may impede and impair healing following mTBI. There is considerable evidence indicating that decreases in sleep quantity and quality, both in humans and animals as well as apart from and in relation to mTBI, may impair hippocampal neurogenesis, disrupt ATP production thereby extending the mTBI-initiated neurometabolic cascade [102,103], prolong neuroinflammation [104], impede metabolic waste removal in the brain [105], alter cerebrovascular responsiveness and compromise glymphatic removal of phosphorylated tau [105–107]. Collectively, these effects of sleep disruption may contribute to the short- and long-term clinical presentation of mTBI as well as precipitate the neurodegenerative conditions, particularly tau-related pathologies (e.g., chronic traumatic encephalopathy), commonly thought to be associated with repetitive head trauma.

Alertness

As noted, an mTBI may induce a sequela whereby disrupted circadian rhythms lead to sleep dysfunction, culminating in daytime sleepiness or fatigue. Broadly, daytime fatigue is associated with decreased alertness and vigilant attention capabilities. Indeed, a recent study demonstrates that evidence of increased fatigue and decreased alertness in an mTBI sample are closely related concepts that are difficult to disentangle [86]. Furthermore, mTBI is associated with degraded alertness and vigilance in both the short and long term [86,108,109]. With regards to daytime alertness, phototherapy may provide a nonpharmacological route for improving daytime functioning in post-mTBI individuals.

Cognition

mTBIs additionally exert a substantial, negative impact on various cognitive functions, including working memory, attention, executive function and visuospatial processing [20,110–117]. While deficits in these cognitive domains are generally resolved soon after injury (e.g., most within a month, many within 3 months postinjury), there is evidence to suggest subtle, persistent deficits that linger well beyond this clinically accepted time course. Additionally, there are individuals in whom the full impact of these deficits does not resolve quickly.

Apart from mTBI, increasing sleep need as well as sleep deprivation conditions induce marked deterioration in the cognitive capabilities of individuals [53,118–120]. Given the impact of mTBI on sleep, daytime sleepiness and fatigue, it is reasonable to posit that many of the observed cognitive deficits, particularly those that linger beyond the general clinical time course, may be mediated by sleep-related changes.

Depression

Depression and increased reporting of depressive symptoms are common following mTBI. The incidence of post-mTBI depression may be as high as 42% in adults and 22% in children and adolescents [121–124]. Premorbid depression is a risk factor for prolonged recovery from mTBI and may be associated with postconcussion symptoms, as well as sleep disruption, impaired cognition and other post-mTBI psychiatric symptoms (e.g., anxiety) [17,20,125–129]. Therefore, ameliorating post-mTBI depression may improve overall symptom presentation and be associated with improvements in sleep and cognitive function.

Post-traumatic headache & pain

Post-traumatic headaches (PTH) and chronic pain are among the most common symptoms experienced by individuals recovering from mTBI. The incidence of PTH likely may be as high 90% [130–135], and the incidence of chronic pain may be as high as 75% [136]. Additionally, both PTH and chronic pain may mediate, or be mediated

by, post-mTBI poor sleep, daytime sleepiness, cognitive deficits and depression [122,137–142]. Consequently, the aforementioned benefits of bright or blue light therapy for sleep, cognitive performance and depression may have positive effects on PTH and pain.

The effects of different types of light & applications to mTBI

Given the range of deficits and changes observed following mTBIs, as well as the known NIF pathways for light, light therapy has the potential to positively influence a wide range of cognitive, emotional and physiological functions. Below, we discuss the known effects of various aspects (colors, intensities) of light across the range of human performance. These findings are additionally summarized in Table 1.

Polychromatic white light

Polychromatic white light is essentially a broad-spectrum light. Because white light includes nearly all wavelengths, it also encompasses the blue light portion of the spectrum (~460–448 nm) that selectively activates ipRGCs and therefore has important circadian and hormone-secreting properties [31]. Consequently, it could be expected that white or bright light therapy would induce changes in post-mTBI circadian rhythms, sleep and alertness.

A recent meta-analysis indicates that light therapy in general is effective in the treatment of sleep disorders that include circadian rhythm sleep disorders, insomnia, and sleep problems associated with Alzheimer's disease and dementia [27]. This meta-analysis included randomized controlled trials and within-subject design studies utilizing polychromatic white light, and blue-enriched white light, as well as several studies utilizing monochromic blue light. Overall, positive effects for light therapy were observed for circadian shifts, bed and wake times, sleep onset latency, total sleep time, wake after sleep onset, sleep efficiency, sleepiness and alertness, sleep quality, insomnia symptoms and fatigue [27]. The authors additionally report that light intensity (ranging from 2000 to 10,000 lux in the majority of included studies) had positive effects on individuals with insomnia, with greater intensity increasing the beneficial effects of light therapy [27]. In estimating effect sizes, the authors did not distinguish the effects of bright light from those of blue light; however, only 9% of the included studies specifically examined blue light.

An additional systematic review by Souman *et al.* examined the effects of light therapy on alertness. Across the reviewed literature, there is the indication that increasing the intensity of polychromatic white light significantly increases subjective alertness [28]. However, this does not appear to translate into improved vigilance or reaction. Additionally, there is limited evidence for significant improvements in subjective or performance-based measures of alertness with blue-shifted polychromatic white light [28]. Cumulatively, these findings suggest that the intensity of polychromatic white light may have positive effects on subjective alertness.

Furthermore, polychromatic white light therapy has been shown to be effective in reducing depressive symptoms in individuals with diagnosed depression, including major depressive disorder. Recent meta-analyses indicate that light therapy, especially polychromatic white light, reduces depressive symptoms at post treatment compared with control participants and this effect is more pronounced for standalone light therapy than for studies using light as an adjunctive therapy [29,143]. The effect is additionally stronger when light therapy is used in the morning than any other time [29]. These effects were observed over studies including polychromatic white, green and pale blue light [29,143].

Monochromatic blue & blue-shifted white light

As previously noted with polychromatic white light, blue light therapy – including monochromatic blue and blue-enriched white light – alters circadian rhythms, particularly the timing of melatonin release, in individuals with a variety of sleep-disrupted conditions [27,144]. These studies demonstrate that short amounts (30 min or more) of focused and intentional daily light therapy in the morning effectively advances individuals' circadian rhythms, evidenced by the timing of melatonin secretion. In general, the effects of phototherapy are condition dependent, but may include changes in circadian rhythm and improvements in sleep duration, self-reported sleep quality, insomnia symptoms and fatigue [27].

In addition to the direct effects of monochromatic blue light therapy on sleep quantity and quality, the appropriate timing of melatonin secretion is essential for maintaining normal daytime arousal and minimizing fatigue. There is robust evidence that blue-wavelength light is effective in acutely decreasing sleepiness and fatigue [145–152] as well as increasing concentrations of arousal-promoting hormones (e.g., cortisol) [153]. Furthermore, blue light therapy has positive effects on increasing alertness [145,147,149,152,154–169]. This phenomenon is present both during the day (e.g., morning blue light exposure) and night.

Prior work has additionally demonstrated that blue light therapy increases activation in cognition-related, task-specific brain regions [157,159,170–176]. However, while light affects brain activation, the actual behavioral effects of blue light exposure are not quite as clear. Individual studies have demonstrated improvements in cognitive performance on working memory, digit recall, sustained attention and arithmetic tasks while others have shown no improvements or even reduced performance in response to light exposure [145,158,169,176–184]. It is thus unclear the extent to which blue light therapy may directly affect cognitive performance beyond those conferred by improvements or alterations in sleep, fatigue or overall alertness.

With respect to mood and affect, blue or blue-shifted light can variously cause [143,185] or improve [29,186] depressive symptoms depending on the timing of therapy (e.g., when timing coincides with or in opposition to naturally expected patterns). Mood disorders, including depression, are associated with the homeostatic maintenance of circulating stress hormones. Among these, glucocorticoids like cortisol exhibit circadian rhythmicity, with a night-time accumulation period and clearance during the day [187,188]. Thus, blue light that influences circadian rhythms, as previously described for sleep and melatonin, may impart a beneficial effect on glucocorticoid expression when utilized in circadian-optimal timings or may induce or worsen mood disorders when mistimed (e.g., night-time use of light-emitting diode screens).

However, one potential pitfall in the application of blue light therapy as described to this point is the exacerbation of PTH. The blue light-sensitive ipRGCs directly project to the trigeminovascular neurons in the thalamus [40]. Prior research related to migraine indicates that these neurons transmit nociceptive signals originating in the dura to cortex, thereby contributing to the perception of intracranial pain during a migraine [40]. Furthermore ipRGC inputs onto the trigeminovascular neurons may modulate the response to light by migraineurs. This neural mechanism may explain why individuals feel worse when exposed to light and preferentially seek dark rooms for relief (photophobia) when experiencing a migraine. While the overarching neural mechanisms of mTBI-related PTH resemble, but may not be exactly the same as those for migraine [140], light-based exacerbation of PTH and/or photophobic responses by individuals post-mTBI may likely have the same neural underpinning. Thus it is plausible that, despite the numerous potential benefits of blue light on circadian rhythms, fatigue, alertness and cognition following mTBI, blue-light or blue-shifted white light treatments may be poorly tolerated and may indeed worsen PTH in some individuals. At present, this specific possibility has not been directly explored in treatment studies using blue light for treating symptoms of mTBI, but research on this topic would be a welcome addition to the literature.

Monochromatic red light

For individuals seeking to enhance alertness without modifying their circadian rhythm (e.g., increasing daytime alertness in the presence of a normal circadian rhythm), utilizing blue light therapy may have unintended and unwanted effects, primarily on melatonin secretion. Interestingly, prior work has shown that longer wavelength light (e.g., red light) may have equally powerful alerting effects [157,160–164]. Red light is detected by L-cones in the retina, and the ipRGCs that are sensitive to blue light are not sensitive to the longer wavelengths (~630 nm) of red light [31,33]. In some preliminary work, the alerting effects of red light were present both in the late afternoon and at night, and were comparable to the effects of blue light. While the mechanisms by which red light has an alerting effect are not fully understood, a plausible explanation is that it may influence the actions of subcortical regions apart from SCN resulting in alerting effects unrelated to melatonin secretion or suppression [159,170].

Monochromatic green light

While the use of blue light may exert its most profound effects on circadian phase advancement or resetting circadian rhythms that mediate sleep, blue light specifically suppresses melatonin secretion thereby inhibiting or delaying the actual onset of sleep. Though possibly beneficial for altering post-mTBI sleep timing or reducing daytime sleepiness and fatigue, this effect on melatonin does nothing for actually promoting night-time sleep. On the other hand, preliminary evidence from animal models suggests that green light (~530 nm) indeed has a sleep-promoting function [189]. This has not yet been confirmed in human studies and the specific mechanisms are not described as yet, though multisynaptic M-cone projections to the ventrolateral preoptic area (involved in sleep promotion) and lateral hypothalamus (where wake-promoting orexin is secreted) may plausibly create this relationship [189,190].

As previously noted, blue light may also have the unintended consequence of aggravating PTHs. However, further research with migraineurs demonstrates that the use of green light has a positive effect on migraine symptoms, including at a minimum no exacerbation of the headache and at best a decrease in the intensity of symptoms [191].

This effect is observed relative to the use of white, blue, amber and red light. Additionally, animal models have demonstrated that green light confers antinociceptive benefits, both at the sensory threshold and with neuropathic pain [192]. Therefore, individuals with mTBI-related PTH or pain may benefit either from environments bathed in green light or from glasses, which preferentially filter the spectra of incoming light to preferentially include green light.

Light therapy following mTBI

To date, two published studies have specifically examined the effects of light therapy following mTBI. Sinclair *et al.* exposed participants to 45 min of morning blue or yellow light for 4 weeks [193]. They demonstrated that individuals receiving blue light, as opposed to yellow light or no treatment, reported less daytime fatigue and sleepiness, faster response times on a sustained psychomotor vigilance task, less self-reported sleep disruption and lower self reports of depression symptoms at 2 and 4 weeks than at baseline. These findings suggest that, for post-mTBI individuals who do self-report fatigue, daytime sleepiness or sleep disruption, daily blue light therapy may be an effective nonpharmacological method for improving function in these areas. It is unclear, however, whether these effects persist after treatment cessation.

Additionally, a study by Bajaj *et al.* had mTBI participants use blue-wavelength light therapy or an amber-wavelength placebo light for 30 min every morning for 6 weeks and found that it was associated with significant changes in white matter integrity (as measured by water diffusion along axonal tracts) within the corpus collosum, corona radiata and thalamus [194]. Moreover, for those receiving blue-light treatment, the magnitude of white matter changes was associated with greater sleep latency on the multiple sleep latency test, which is an objective measure of biological sleepiness. Additionally, they found that the increases in white matter integrity were associated with an improvement in delayed memory performance, but only among those receiving the blue light treatment. These associations were not significant among those receiving the amber light placebo condition. In other words, 6 weeks of blue light therapy appeared to increase the integrity of axonal white matter, and this change was associated with decreased tendency to fall asleep during the day as well as improved delayed memory performance.

Furthermore there is some evidence suggesting that there may be positive effects of blue light exposure on anxiety following mTBI [195,196]. In fact, even a single 30-min exposure to blue-wavelength light appears to increase activation of the anterior cingulate cortex when anticipating positive stimuli compared with an amber placebo light, which might help explain the mood and anxiety improvements that follow blue light exposure [196]. Thus, limited evidence suggests that blue-wavelength light may be effective for some aspects of recovery from mTBI, but more research is needed before the benefits of this approach are fully understood.

Extrapolating the findings from both healthy individuals and those with other neurological conditions as well as animal studies, there may be additional unidentified benefits of light therapy for mTBI beyond those that have been specifically identified. Both polychromatic white and blue lights may be useful for resetting aberrant circadian rhythms, improving sleep, decreasing daytime sleepiness and fatigue, increasing alertness, and decreasing depressive symptoms. Red light may be beneficial for improving alertness without inducing circadian shifts, but more work is needed. Green light may help to promote night-time sleep, minimize PTH and reduce pain. However, given the paucity of studies on post-mTBI light therapy, these applications are speculative at best. Though there is the indication of positive effects on both neural and behavioral outcomes, these findings require further corroboration with larger studies and diverse mTBI populations. Future research objectives are presented in Box 1.

Additional uses of light

In addition to the potential benefits of using visible light as a treatment method, low-level laser therapy (LLLT) has noted wound healing and anti-inflammatory properties, particularly in the near-infrared spectral range. While LLLT is beyond the scope of the present discussion, we encourage readers to see [197] for a recent review on the use of LLLT for TBI.

Current limitations to using phototherapy for mTBI

As has been indicated in the preceding sections, there are numerous potential benefits to using light as an adjunctive therapy in the management of mTBIs. However, there are some limitations that currently limit the scale and scope of the inference that can be made regarding the effects of phototherapy in the recovery from mTBI. Notably, there is significant heterogeneity in light characteristics, timing, duration and illuminance of light therapy between studies that may all influence the outcomes of these studies [26,27,29,198]. Thus considerably more work is required,

Box 1. Future research objectives in the development of light therapy for mild traumatic brain injury recovery.

In light of the potential benefits of light therapy in mild traumatic brain injury recovery as well as the physiological nonimage-forming light pathways, the following research objectives are reasonable targets for exploration:

Sleep-related research

- Expanding current efforts to identify the effects of monochromatic blue light to correct aberrant circadian rhythms, improve sleep, reduce daytime fatigue and improve white matter integrity
- Identifying the optimal dosage and timing of blue light
- Identifying positive effects and differences between polychromatic white light and monochromatic blue light as pertains to circadian rhythms and sleep metrics
- Identifying the optimal dosage and timing for the use of green light to improve night-time sleep onset
- Identifying the optimal dosage and timing for the use of red light to improve alertness without circadian shifting

Cognition

- Identifying the optimal color, timing and dosage of light to improve short-term activation related to cognitive function

Somatic

- Identifying whether green light reduces the presentation of post-traumatic headache
- Identifying whether green light reduces comorbid pain

Precision medicine

- Identifying the personal characteristics that will lead to responsiveness to light treatment (e.g., *PER3* polymorphisms, degree of circadian dysrhythmia, level of daytime sleepiness/fatigue)
- Development and refinement of treatment parameters throughout the day (i.e., timing of blue vs red vs green light therapy based on current symptoms and needs)

particularly for mTBI-related applications, to identify the optimal parameters that maximize the benefit to the individual.

Additionally, there is evidence that polymorphisms in the *PER3* clock gene may additionally explain interindividual differences in the relationship between light exposure and cognition [175]. Consequently, future studies and clinical applications of bright or blue light therapy, particularly for improving cognitive performance, should take genetic variations into account.

Furthermore, many studies employ some form of light box to deliver the phototherapy. These boxes are portable and allow individuals to be treated at home, which is a tremendous benefit. However, an unavoidable drawback to at-home treatments of this nature is compliance and adherence. Additionally, these boxes have limited spatial effectiveness and require the user to be within a certain distance from the light source in order to be effective. Consequently, treatment may be challenging or even impossible in individuals who are unable to remain in front of the light box for the treatment duration. Alternative light presentation methods, such as goggle-mounted light systems are currently being tested, and may afford greater ambulation and flexibility of use. At present, these devices have only been tested with a limited range of wavelengths and will require further research to determine their effectiveness.

Finally, safety concerns are always critical in deciding whether to use a particular treatment, and light therapy is no different. Some safety concerns have been raised for blue light, in particular. There is some evidence to suggest that retinal damage is possible with prolonged exposure to short-wavelength light. Though the optimal wavelength to stimulate ipRGCs (~480 nm) is considerably greater than violet and ultraviolet wavelengths where damage is more certain, it is a plausible concern [199]. However, there is no evidence in the published literature of such damage from the types of therapy described here [200]. Some companies who manufacture blue-wavelength light-box devices have had their products independently evaluated for blue-light retinal hazard and have reported the exposure hazard to be minimal at the distance, intensity and duration of light emitted for those devices. Another consideration is that the amount of blue-wavelength light emitted by most light-box devices is considerably less than that obtained by an equal duration of exposure to midday outdoor sunlight. Additionally, as noted with photophobia and PTH, many individuals do report headaches and other somatic symptoms with the use of light boxes [200]. Although there is no compelling evidence at this time that standard light therapy devices pose a significant optical hazard when used according to manufacturer's instructions, further research into the long-term safety and side effects of light exposure treatment is warranted. As with any treatment, decisions to engage in light therapy should involve judicious evaluation of the benefits and potential risks involved.

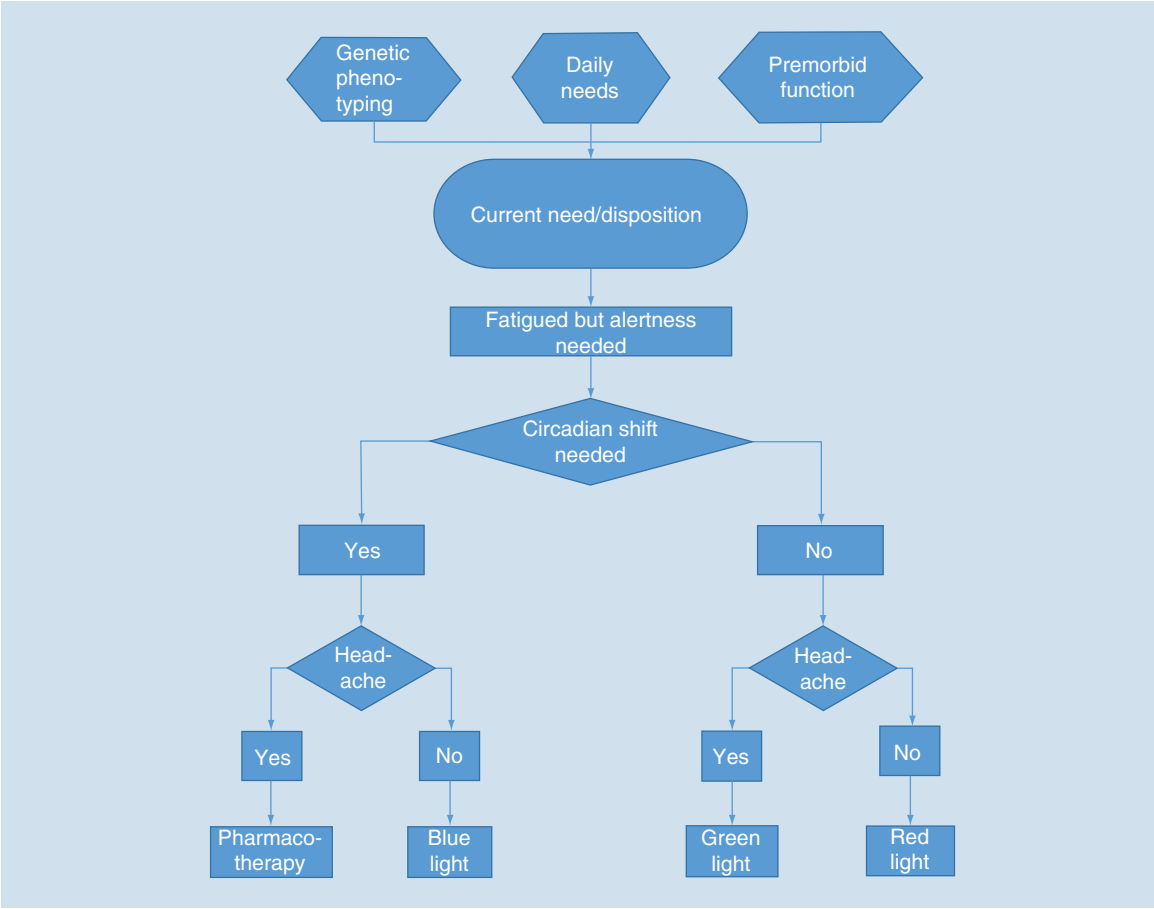


Figure 2. Example decision tree for a precision medicine, needs-based approach to light therapy.

Conclusions

Light is all around us and is an ingrained natural part of our biological rhythms and daily functioning. It is essential for image-forming vision and our ability to interact with the environment. The NIF impacts of light on physiology make it a powerful tool as well as a potent inhibitor of function. While considerable in-roads are being made to understand how early and active intervention may improve the outcomes from mTBIs, the individual's environment is an oft-ignored but important consideration. Light is a critical feature of our environment that has a powerful influence on our biology. There are numerous, interconnected systems that are impaired or altered by mTBIs and whose function can be influenced by exposure to light. Outcomes from two small-scale trials indicate that daily blue-wavelength light therapy may be effective for reducing daytime fatigue and improving sleep and efforts are underway to corroborate these findings. Further evidence from other populations indicates that other wavelengths may confer additional therapeutic benefits (e.g., green light for improving post-traumatic headache) and such findings require future research specific to mTBI.

Future perspective

We believe that significant advances in the use of light therapy can and will be made in the decade ahead to leverage these advantages and minimize the drawbacks. It is our position, though, that in order for light therapies to be effective for mTBI, or any condition, they must be specifically tailored to the individual (i.e., personalized medicine) and account for the uncontrollable aspects of the environment (e.g., sunlight during commuting, work environments with limited capacity to be modified). Accordingly, this requires a complete and ongoing needs assessment of the individual as well as an understanding of those aspects of the environment that can be adapted or modified to meet these needs.

For example, technological control of circadian lighting will require smart lights that shift dominant or active wavelengths throughout the day to mimic lighting patterns that more closely reflect sunlight while indoors (e.g., more blue light in the morning that gives way to more amber wavelengths in the late afternoon). These types of lights do not require a light box, but instead would completely replace existing ambient lighting methods. This technology could be leveraged at the home, or potentially the workplace, to ensure that ambient light maximizes the circadian benefit for the individual, and indeed entrains appropriate rhythms given individual needs. Furthermore, many of these circadian lighting systems could be internet connected. Therefore, tuning of ambient colors in response to an individual's daily needs could be accomplished through needs and symptom reporting via an internet-ready device (e.g., tablet, cellular phone).

Such a scenario would enable fine tuning the environment to meet daily, and even moment by moment, presentation of individualized mTBI-related symptoms. This may mean more blue in the morning for a person on a normal sleep–wake schedule, but for someone regularly engaged in shiftwork, this may mean more blue is presented in the evening as they prepare for work. Likewise, lighting could be manipulated to address symptom expression and behavioral needs, such as shifting to a more green-lit room if the individual reports pain or a headache on a given day or when falling asleep is a goal (Figure 2). Additionally, individuals could conceivably maximize cognitive performance and alertness by shifting to red light during the afternoon, evening or night for improved alertness without inducing an unwanted or unnecessary circadian shift that is associated with blue light.

In these scenarios, lighting patterns could be altered on a daily basis to reflect not only the individual's unchangeable physiology (e.g., *PER3* phenotype, which may limit the effect of blue light on sleep and cognition) and overarching needs (e.g., necessary wake times), but also day-to-day changes in mTBI-related symptoms, fatigue and cognitive demands. In so doing, and in conjunction with other medical management, we can leverage the environment to maximize recovery following mTBI and return biological systems to homeostatic states rapidly to facilitate full returns to work, school, sport and life.

Executive summary

Mild traumatic brain injury, sleepiness & fatigue

- Blue light is selectively absorbed by intrinsically photosensitive retinal ganglion cells. These cells project directly the suprachiasmatic nucleus and influence circadian rhythms and melatonin secretion.
- There is some evidence suggesting that mild traumatic brain injuries (mTBIs) induced circadian dysrhythmias.
- Targeted use of blue light can be used to shift circadian rhythms and improve nighttime sleeping and daytime fatigue.
- Emerging evidence suggests that green light may be an effective sleep promoter.

mTBI & alertness

- Blue light improves daytime fatigue and sleepiness, leading to greater alertness.
- Red light also improves alertness and may be useful when affecting circadian rhythms is undesired.

mTBI & cognition

- Blue light potentiates activation in areas associated with multidomain cognition. Further work is needed to more completely understand these mechanisms.

mTBI & depression

- Depression is a common post-mTBI complaint. Prior work demonstrates that blue light is effective in improving both seasonal and nonseasonal depression.

mTBI, post-traumatic headache & pain

- Despite the positive effects of blue light, the intrinsically photosensitive retinal ganglion cells also project to thalamic neurons that receive input from dural nociceptors that are active during migraine headaches. Blue light therapy may exacerbate post-traumatic headaches.
- Green light does not exacerbate migraine headaches and in some cases improves symptom presentation.

Future perspective

- Phototherapy has the potential to modify the brain's functioning across a wide range of affected systems following mTBI.
- Technology exists that enables ambient lighting to be modified on demand to change the visible spectrum to meet needs.
- A personalized medicine approach – combining genetic phenotyping, injury characteristics, current symptoms and current needs to create an optimal ambient light profile – could make phototherapy a potent, ever-present aspect of mTBI management and recovery.

Financial & competing interests disclosure

This work was supported by multiple grants from the US Army Medical Research and Materiel Command (USAMRMC) to W D S Killgore, including W81XWH-14-1-0570 and W81XWH-14-1-0571. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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References

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006 [Internet]. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Atlanta, USA Available from: http://origin.glb.cdc.gov/traumaticbraininjury/pdf/blue_book.docx
2. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. *Clin. Sports Med.* 30(1), 1–17 (2011).
3. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J. Head Trauma Rehabil.* 21(5), 375–378 (2006).
4. Kerr ZY, Register-Mihalik JK, Kroshus E, Baugh CM, Marshall SW. Motivations associated with nondisclosure of self-reported concussions in former collegiate athletes. *Am. J. Sports Med.* 44(1), 220–225 (2016).
5. Register-Mihalik JK, Guskiewicz KM, McLeod TCV, Linnan LA, Mueller FO, Marshall SW. Knowledge, attitude, and concussion-reporting behaviors among high school athletes: a preliminary study. *J. Athletic Training* 48(5), 645–653 (2013).
6. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nature Rev. Neurol.* 9(4), 211–221 (2013).
7. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. *Alzheimers Dement.* 10(3, Suppl.), S242–S253 (2014).
8. McKee AC, Alosco ML, Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurg. Clin. N. Am.* 27(4), 529–535 (2016).
9. Harris MA, Shen H, Marion SA, Tsui JK, Teschke K. Head injuries and Parkinson's disease in a case–control study. *Occup. environ. Med.* 70(12), 839–844 (2013).
10. Chiò A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 128(3), 472–476 (2005).
11. Martini DN, Broglio SP. Long-term effects of sport concussion on cognitive and motor performance: a review. *Int. J. Psychophysiol.* (2017). www.sciencedirect.com/science/article/pii/S0167876017305779
12. Dalecki M, Albines D, Macpherson A, Sergio LE. Prolonged cognitive-motor impairments in children and adolescents with a history of concussion. *Concussion* 1, CNC14 (2016).
13. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological profile of lifetime traumatic brain injury in older veterans. *J. Int. Neuropsychol. Soc.* 23(1), 56–64 (2017).
14. Goswami R, Dufort P, Tartaglia MC *et al.* Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct. Funct.* 221(4), 1911–1925 (2016).
15. Esopenko C, Chow TW, Tartaglia MC *et al.* Cognitive and psychosocial function in retired professional hockey players. *J. Neurol. Neurosurg. Psychiatry* 88(6), 512–519 (2017).
16. Rao V, Syeda A, Roy D, Peters ME, Vaishnavi S. Neuropsychiatric aspects of concussion: acute and chronic sequelae. *Concussion* 2(1), CNC29 (2017).
17. Guskiewicz KM, Marshall SW, Bailes J *et al.* Recurrent concussion and risk of depression in retired professional football players. *Med. Sci. Sports Exerc.* 39(6), 903–909 (2007).
18. Stein E, Howard W, Rowhani-Rahbar A, Rivara FP, Zatzick D, McCarty CA. Longitudinal trajectories of post-concussive and depressive symptoms in adolescents with prolonged recovery from concussion. *Brain Inj.* 31(13–14), 1736–1744 (2017).
19. Kontos AP, Deitrick JM, Reynolds E. Mental health implications and consequences following sport-related concussion. *Br. J. Sports Med.*50(3), 139–140 (2015).
20. Kontos AP, Covassin T, Elbin RJ, Parker T. Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. *Arch. Phys. Med. Rehabil.* 93(10), 1751–1756 (2012).

21. Maas AIR, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics* 7(1), 115–126 (2010).
22. Dobney DM, Miller MB, Tufts E. Non-pharmacological rehabilitation interventions for concussion in children: a scoping review. *Disabil. Rehabil.* 1–13 (2017).
23. Kontos AP, Collins MW, Holland CL *et al.* Preliminary evidence for improvement in symptoms, cognitive, vestibular, and oculomotor outcomes following targeted intervention with chronic mTBI patients. *Mil Med.* 183(Suppl. 1), 333–338 (2018).
24. Collins MW, Kontos AP, Reynolds E, Murawski CD, Fu FH. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surg. Sports Traumatol. Arthrosc.* 22(2), 235–246 (2014).
25. Dobney DM, Grilli L, Kocilowicz H *et al.* Evaluation of an active rehabilitation program for concussion management in children and adolescents. *Brain Inj.* 31(13/14), 1753–1759 (2017).
26. Gaggioni G, Maquet P, Schmidt C, Dijk D-J, Vandewalle G. Neuroimaging, cognition, light and circadian rhythms. *Front. Syst. Neurosci.* 8 (2014). www.frontiersin.org/articles/10.3389/fnsys.2014.00126/full
27. van Maanen A, Meijer AM, van der Heijden KB, Oort FJ. The effects of light therapy on sleep problems: a systematic review and meta-analysis. *Sleep Med. Rev.* 29, 52–62 (2016).
28. Souman JL, Tinga AM, te Pas SF, van Ee R, Vlaskamp BNS. Acute alerting effects of light: a systematic literature review. *Behav. Brain Res.* 337, 228–239 (2018).
29. Perera S, Eisen R, Bhatt M *et al.* Light therapy for non-seasonal depression: systematic review and meta-analysis. *BJPsych. Open* 2(2), 116–126 (2016).
30. Nassi JJ, Callaway EM. Parallel processing strategies of the primate visual system. *Nat. Rev. Neurosci.* 10(5), 360–372 (2009).
31. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295(5557), 1070–1073 (2002).
32. Dacey DM, Liao H-W, Peterson BB *et al.* Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature* 433(7027), 749–754 (2005).
33. Hattar S, Liao H-W, Takao M, Berson DM, Yau K-W. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295(5557), 1065–1070 (2002).
34. Hattar S, Kumar M, Park A *et al.* Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J. Comp. Neurol.* 497(3), 326–349 (2006).
35. Dewan K, Benloucif S, Reid K, Wolfe LF, Zee PC. Light-induced changes of the circadian clock of humans: increasing duration is more effective than increasing light intensity. *Sleep* 34(5), 593–599 (2011).
36. Klein DC, Smoot R, Weller JL *et al.* Lesions of the paraventricular nucleus area of the hypothalamus disrupt the suprachiasmatic→ spinal cord circuit in the melatonin rhythm generating system. *Brain Res. Bull.* 10(5), 647–652 (1983).
37. Moore RY, Lenn NJ. A retinohypothalamic projection in the rat. *J. Comp. Neurol.* 146(1), 1–14 (1972).
38. Pickard GE, Silverman A-J. Direct retinal projections to the hypothalamus, piriform cortex, and accessory optic nuclei in the golden hamster as demonstrated by a sensitive anterograde horseradish peroxidase technique. *J. Comp. Neurol.* 196(1), 155–172 (1981).
39. Vandewalle G, Schwartz S, Grandjean D *et al.* Spectral quality of light modulates emotional brain responses in humans. *PNAS* 107(45), 19549–19554 (2010).
40. Noseda R, Kainz V, Jakubowski M *et al.* A neural mechanism for exacerbation of headache by light. *Nat. Neurosci.* 13(2), 239–245 (2010).
41. Ciuffreda KJ, Joshi NR, Truong JQ. Understanding the effects of mild traumatic brain injury on the pupillary light reflex. *Concussion* 2(3), CNC36 (2017).
42. McCrory P, Meeuwisse W, Dvorak J *et al.* Consensus statement on concussion in sport – The 5th international conference on concussion in sport held in Berlin, October 2016. *Br. J. Sports Med.* 51, 838–847 (2017).
43. Basic information about traumatic brain injury and concussion | Concussion | Traumatic brain injury | CDC Injury Center [Internet]. www.cdc.gov/traumaticbraininjury/basics.html
44. O'Neil ME, Carlson K, Storzbach D *et al.* Definition of MTBI from the VA/DOD clinical practice guideline for management of concussion/mild traumatic brain injury (2009) [Internet]. Department of Veterans Affairs (US) www.ncbi.nlm.nih.gov/books/NBK189784/
45. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* 8(3), 86 (1993).
46. Makdissi M, Schneider KJ, Feddermann-Demont N *et al.* Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review. *Br. J. Sports Med.* 51(12), 958–968 (2017).
47. Institute of Medicine (US) Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation: an unmet public health problem [Internet]. National Academies Press, WA (DC), USA www.ncbi.nlm.nih.gov/books/NBK19960/
48. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J. Pain* 14(12), 1539–1552 (2013).

49. Schlarb AA, Claßen M, Hellmann SM, Vögele C, Gulewitsch MD. Sleep and somatic complaints in university students. *J. Pain Res.* 10, 1189–1199 (2017).
50. Minkel JD, Banks S, Htaik O *et al.* Sleep deprivation and stressors: evidence for elevated negative affect in response to mild stressors when sleep deprived. *Emotion* 12(5), 1015–1020 (2012).
51. Prather AA, Vogelzangs N, Penninx BWJH. Sleep duration, insomnia, and markers of systemic inflammation: results from the Netherlands Study of Depression and Anxiety (NESDA). *J. Psychiatr. Res.* 60, 95–102 (2015).
52. Samaranayake CB, Arroll B, Fernando AT. Sleep disorders, depression, anxiety and satisfaction with life among young adults: a survey of university students in Auckland, New Zealand. *N. Z. Med. J.* 127(1399), 13–22 (2014).
53. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136(3), 375–389 (2010).
54. Renn RP, Cote KA. Performance monitoring following total sleep deprivation: effects of task type and error rate. *Int. J. Psychophysiol.* 88(1), 64–73 (2013).
55. Nankar M, Szturm T, Marotta J, Shay B, Beauchet O, Allali G. The interacting effects of treadmill walking and different types of visuospatial cognitive task: discriminating dual task and age effects. *Arch. Gerontol. Geriatr.* 73, 50–59 (2017).
56. Heaton KJ, Maule AL, Maruta J, Kryskow EM, Ghajar J. Attention and visual tracking degradation during acute sleep deprivation in a military sample. *Aviat. Space Environ. Med.* 85(5), 497–503 (2014).
57. Furtado F, Gonçalves B da SB, Abranches ILL, Abrantes AF, Forner-Cordero A. Chronic low quality sleep impairs postural control in healthy adults. *PLoS ONE* 11(10), e0163310 (2016).
58. Martin T, Gauthier A, Ying Z *et al.* Effect of sleep deprivation on diurnal variation of vertical perception and postural control. *J. Appl. Physiol.* (2018). www.physiology.org/doi/abs/10.1152/japplphysiol.00595.2017
59. Watson AM. Sleep and athletic performance. *Curr. Sports Med. Rep.* 16(6), 413 (2017).
60. Altman NG, Izci-Balserak B, Schopfer E *et al.* Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. *Sleep Med.* 13(10), 1261–1270 (2012).
61. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. *Best Pract. Res. Clin. Endocrinol. Metab.* 24(5), 731–743 (2010).
62. Zizi F, Jean-Louis G, Brown CD, Ogedegbe G, Boutin-Foster C, McFarlane SI. Sleep duration and the risk of diabetes mellitus: epidemiologic evidence and pathophysiologic insights. *Curr. Diab. Rep.* 10(1), 43–47 (2010).
63. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens. Res.* 36(11), 985–995 (2013).
64. Tranah GJ, Blackwell T, Stone KL *et al.* Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann. Neurol.* 70(5), 722–732 (2011).
65. Stern AL, Naidoo N. Wake-active neurons across aging and neurodegeneration: a potential role for sleep disturbances in promoting disease. *SpringerPlus* 4, 25 (2015).
66. Tan SL, Storm V, Reinwand DA, Wienert J, de Vries H, Lippke S. Understanding the positive associations of sleep, physical activity, fruit and vegetable intake as predictors of quality of life and subjective health across age groups: a theory based, cross-sectional web-based study. *Front. Psychol.* 9 (2018). Available from: www.frontiersin.org/articles/10.3389/fpsyg.2018.00977/full
67. Figueiro M, Overington D. Self-luminous devices and melatonin suppression in adolescents. *Lighting Res. Technol.* 48(8), 966–975 (2016).
68. Gooley JJ. Light resetting and entrainment of human circadian rhythms [Internet]. In: *Biological Timekeeping: Clocks, Rhythms and Behaviour*. Springer, New Delhi, India, 297–313 (2017). https://link.springer.com/chapter/10.1007/978-81-322-3688-7_14
69. Zietzer JM, Dijk D-J, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J. Physiol.* 526(3), 695–702 (2004).
70. Wickwire EM, Williams SG, Roth T *et al.* Sleep, sleep disorders, and mild traumatic brain injury. what we know and what we need to know: findings from a National Working Group. *Neurotherapeutics* 13(2), 403–417 (2016).
71. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J. Head Trauma Rehabil.* 21(3), 199–212 (2006).
72. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Sleep–wake disturbances after traumatic brain injury. *Lancet Neurol.* 14(7), 746–757 (2015).
73. Wiseman-Hakes C, Colantonio A, Gargaro J. Sleep and wake disorders following traumatic brain injury: a systematic review of the literature. *Crit. Rev. Phys. Rehabil. Med.* 21(3–4), 317–374 (2009).
74. Gosselin N, Lassonde M, Petit D *et al.* Sleep following sport-related concussions. *Sleep Med.* 10(1), 35–46 (2009).
75. Theadom A, Cropley M, Parmar P *et al.* Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med.* 16(8), 926–932 (2015).

76. Sullivan KA, Edmed SL, Allan AC, Karlsson LJE, Smith SS. Characterizing self-reported sleep disturbance after mild traumatic brain injury. *J. Neurotrauma* 32(7), 474–486 (2014).

77. Hinds A, Jungquist CR, Leddy JJ, Seemant F, Baker JG, Willer B. Sleep disturbance in patients with chronic concussive effects. *Concussion* 1(3), CNC15 (2016).

78. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. *Brain Inj.* 16(3), 197–206 (2002).

79. Fichtenberg NL, Putnam SH, Mann NR, Zafonte RD, Millard AE. Insomnia screening in postacute traumatic brain injury: utility and validity of the Pittsburgh Sleep Quality Index. *Am. J. Phys. Med. Rehabil.* 80(5), 339–345 (2001).

80. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep–wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* 130(7), 1873–1883 (2007).

81. Theadom A, Rowland V, Levack W *et al.* Exploring the experience of sleep and fatigue in male and female adults over the 2 years following traumatic brain injury: a qualitative descriptive study. *BMJ Open.* 6(4), e010453 (2016).

82. Kempf J, Werth E, Kaiser PR, Bassetti CL, Baumann CR. Sleep-wake disturbances 3 years after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 81(12), 1402–1405 (2010).

83. Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. Prevalence and consequences of sleep disorders in traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 349–356 (2007).

84. Imbach LL, Büchele F, Valko PO *et al.* Sleep–wake disorders persist 18 months after traumatic brain injury but remain underrecognized. *Neurology* 86(21), 1945–1949 (2016).

85. Imbach LL, Valko PO, Li T *et al.* Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. *Brain* 138(3), 726–735 (2015).

86. Mollayeva T, Shapiro CM, Cassidy JD, Mollayeva S, Colantonio A. Assessment of concussion/mild traumatic brain injury-related fatigue, alertness, and daytime sleepiness: a diagnostic modelling study. *Neuropsychiatry* 7(2), 86–104 (2017).

87. Sommerauer M, Valko PO, Werth E, Baumann CR. Excessive sleep need following traumatic brain injury: a case–control study of 36 patients. *J. Sleep Res.* 22(6), 634–639 (2013).

88. Watson NF, Dikmen S, Machamer J, Doherty M, Temkin N. Hypersomnia following traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 363–368 (2007).

89. Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders following mild traumatic brain injury. *Neurology* 68(14), 1136–1140 (2007).

90. Verma A, Anand V, Verma NP. Sleep disorders in chronic traumatic brain injury. *J. Clin. Sleep Med.* 3(4), 357–362 (2007).

91. Schreiber S, Barkai G, Gur-Hartman T *et al.* Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Med.* 9(5), 481–487 (2008).

92. Williams BR, Lazic SE, Ogilvie RD. Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clin. Neurophysiol.* 119(2), 429–438 (2008).

93. Khoury S, Chouchou F, Amzica F *et al.* Rapid EEG activity during sleep dominates in mild traumatic brain injury patients with acute pain. *J. Neurotrauma* 30(8), 633–641 (2013).

94. Lu W, Cantor JB, Aurora RN *et al.* The relationship between self-reported sleep disturbance and polysomnography in individuals with traumatic brain injury. *Brain Inj.* 29(11), 1342–1350 (2015).

95. Mollayeva T, Colantonio A, Cassidy JD, Vernich L, Moineddin R, Shapiro CM. Sleep stage distribution in persons with mild traumatic brain injury: a polysomnographic study according to American Academy of Sleep Medicine standards. *Sleep Med.* 34, 179–192 (2017).

96. Shekleton JA, Parcell DL, Redman JR, Phipps-Nelson J, Ponsford JL, Rajaratnam SMW. Sleep disturbance and melatonin levels following traumatic brain injury. *Neurology* 74(21), 1732 (2010).

97. Paparrigopoulos T, Melissaki A, Tsekou H *et al.* Melatonin secretion after head injury: a pilot study. *Brain Inj.* 20(8), 873–878 (2006).

98. Seifman MA, Gomes K, Nguyen PN *et al.* Measurement of serum melatonin in intensive care unit patients: changes in traumatic brain injury, trauma, and medical conditions. *Front. Neurol.* 5 (2014). http://journal.frontiersin.org/article/10.3389/fneur.2014.00237/abstract

99. Valko PO, Gavrilov YV, Yamamoto M *et al.* Damage to histaminergic tuberomammillary neurons and other hypothalamic neurons with traumatic brain injury. *Ann. Neurol.* 77(1), 177–182 (2015).

100. Baumann CR, Stocker R, Imhof H *et al.* Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology* 65(1), 147–149 (2005).

101. Baumann CR, Bassetti CL, Valko PO *et al.* Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann. Neurol.* 66(4), 555–559 (2009).

102. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J. Athl. Train.* 36(3), 228–235 (2001).

103. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery* 75(4), S24–S33 (2014).

104. Zielinski MR, Dunbrasky DL, Taishi P, Souza G, Krueger JM. Vagotomy attenuates brain cytokines and sleep induced by peripherally administered tumor necrosis factor-α and lipopolysaccharide in mice. *Sleep* 36(8), 1227–1238 (2013).

105. Xie L, Kang H, Xu Q *et al.* Sleep drives metabolite clearance from the adult brain. *Science* 342(6156), 373–377 (2013).

106. Lucke-Wold BP, Smith KE, Nguyen L *et al.* Sleep disruption and the sequelae associated with traumatic brain injury. *Neurosci. Biobehav. Rev.* 55, 68–77 (2015).

107. Iliff JJ, Chen MJ, Plog BA *et al.* Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J. Neurosci.* 34(49), 16180–16193 (2014).

108. Beaulieu C, Turcotte-Giroux A, Carrier-Toutant F, Brisson B, Jolicoeur P, De Beaumont L. Long-term effects of concussions on psychomotor speed and cognitive control processes during motor sequence learning. *J. Psychophysiol.* 1–13 (2018).doi:10.1027/0269-8803/a000213 .

109. Beaulieu-Bonneau S, Fortier-Brochu É, Ivers H, Morin CM. Attention following traumatic brain injury: neuropsychological and driving simulator data, and association with sleep, sleepiness, and fatigue. *Neuropsychol. Rehabil.* 27(2), 216–238 (2017).

110. Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J. Neurol. Neurosurg. Psychiatry* 77(2), 241–245 (2006).

111. McCrea M. Mild traumatic brain injury and postconcussion syndrome: the new evidence base for diagnosis and treatment [Internet]. Oxford University Press, NY, USA https: //books.google.com/books?hl=en&lr=&id=Y0M9LOL40EMC&oi=fnd&pg=PR5&dq=(%E2%80%9Cconcuss*%E2%80%9D+OR+%E2%80%9CmTBI%E2%80%9D+OR+%E2%80%9Cmild+traumatic+brain+injury%E2%80%9D+OR+%E2%80%9Cclosed+head+injury%E2%80%9D)+*cognitive+OR+%22*cognitive+test%22&ots=O-7Hb_xFz3&sig=5bYbyWPNwzegDkNwGnYlSloUQ5M

112. McCrea M, Guskiewicz K, Doncevic S *et al.* Day of injury cognitive performance on the Military Acute Concussion Evaluation (MACE) by US military service members in OEF/OIF. *Mil. Med.* 179(9), 990–997 (2014).

113. McCrea M, Guskiewicz KM, Marshall SW *et al.* Acute effects and recovery time following concussion in collegiate football players: The NCAA Concussion Study. *JAMA* 290(19), 2556–2563 (2003).

114. Gaines KD, Soper HV, Berenji GR. Executive functioning of combat mild traumatic brain injury. *Appl. Neuropsychol. Adult* 23(2), 115–124 (2016).

115. Sim A, Terryberry-Spohr L, Wilson KR. Prolonged recovery of memory functioning after mild traumatic brain injury in adolescent athletes. *J. Neurosurg.* 108(3), 511–516 (2008).

116. Covassin T, Elbin RJ, Nakayama Y. Tracking neurocognitive performance following concussion in high school athletes. *Phys. Sportsmed.* 38(4), 87–93 (2010).

117. Covassin T, Elbin RJ, Harris W, Parker T, Kontos A. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. *Am. J. Sports Med.* 40(6), 1303–1312 (2012).

118. Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Ann. N. Y. Acad. Sci.* 1129(1), 305–322 (2008).

119. Killgore WDS. Effects of sleep deprivation on cognition [Internet]. In: *Progress in Brain Research*. Kerkhof GA, van Dongen HPA (Eds). Elsevier, CambridgeMA. 105–129 (2010) www.sciencedirect.com/science/article/pii/B9780444537027000075

120. Killgore WD, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ. Sustaining executive functions during sleep deprivation: a comparison of caffeine, dextroamphetamine, and modafinil. *Sleep* 32(2), 205–216 (2009).

121. Yrondi A, Brauge D, LeMen J, Arbus C, Pariente J. Depression and sports-related concussion: a systematic review. *La Presse Médicale* 46(10), 890–902 (2017).

122. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N. Engl. J. Med.* 358(5), 453–463 (2008).

123. Decq P, Gault N, Blandeau M *et al.* Long-term consequences of recurrent sports concussion. *Acta Neurochir.* 158(2), 289–300 (2016).

124. Stazyk K, DeMatteo C, Moll S, Missiuna C. Depression in youth recovering from concussion: correlates and predictors. *Brain Inj.* 31(5), 631–638 (2017).

125. Vargas G, Rabinowitz A, Meyer J, Arnett PA. Predictors and prevalence of postconcussion depression symptoms in collegiate athletes. *J. Athl. Train.* 50(3), 250–255 (2015).

126. Yang J, Peek-Asa C, Covassin T, Torner JC. Post-concussion symptoms of depression and anxiety in division I collegiate athletes. *Dev. Neuropsychol.* 40(1), 18–23 (2015).

127. Theadom A, Parag V, Dowell T *et al.* Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand. *Br. J. Gen. Pract.* 66(642), e16–e23 (2016).

128. Chaput G, Giguère J-F, Chauny J-M, Denis R, Lavigne G. Relationship among subjective sleep complaints, headaches, and mood alterations following a mild traumatic brain injury. *Sleep Med.* 10(7), 713–716 (2009).

129. Kerr ZY, Marshall SW, Harding HP, Guskiewicz KM. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. *Am. J. Sports Med.* 40(10), 2206–2212 (2012).

130. Packard RC. Chronic post-traumatic headache: associations with mild traumatic brain injury, concussion, and post-concussive disorder. *Curr. Pain Headache Rep.* 12(1), 67–73 (2008).

131. Packard RC. Epidemiology and pathogenesis of posttraumatic headache. *J. Head Trauma Rehabil.* 14(1), 9 (1999).

132. Faux S, Sheedy J. A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Med.* 9(8), 1001–1011 (2008).

133. Stovner LJ, Schrader H, Mickevičiene D, Surkiene D, Sand T. Headache after concussion. *Eur. J. Neurol.* 16(1), 112–120 (2009).

134. Terrio H, Brenner LA, Ivins BJ *et al.* Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J. Head Trauma Rehabil.* 24(1), 14–23 (2009).

135. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache* 50(8), 1262–1272 (2010).

136. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* 300(6), 711–719 (2008).

137. Mollayeva T, Cassidy JD, Shapiro CM, Mollayeva S, Colantonio A. Concussion/mild traumatic brain injury-related chronic pain in males and females: a diagnostic modelling study. *Medicine* 96(7), e5917 (2017).

138. Kjeldgaard D, Forchhammer H, Teasdale T, Jensen RH. Chronic post-traumatic headache after mild head injury: a descriptive study. *Cephalalgia* 34(3), 191–200 (2014).

139. Grandhi R, Tavakoli S, Ortega C, Simmonds MJ. A review of chronic pain and cognitive, mood, and motor dysfunction following mild traumatic brain injury: complex, comorbid, and/or overlapping conditions? *Brain Sci.* 7(12), 1–8 (2017).

140. Ruff RL, Blake K. Pathophysiological links between traumatic brain injury and post-traumatic headaches. *F1000Res.* 5 (2016). www.ncbi.nlm.nih.gov/pmc/articles/PMC5007746/

141. Ruff RL, Ruff SS, Wang X-F. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. *J. Rehabil. Res. Dev.* 46(9), 1071–1084 (2009).

142. Ruff RL, Riechers RG II, Wang X-F, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *J. Rehabil. Res. Dev.* 49(9), 1305 (2012).

143. Mårtensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: a critical review of the evidence. *J. Affect. Disord.* 182, 1–7 (2015).

144. Najjar RP, Wolf L, Taillard J *et al.* Chronic artificial blue-enriched white light is an effective countermeasure to delayed circadian phase and neurobehavioral decrements. *PLoS One* 9(7), e102827 (2014).

145. Phipps-Nelson J, Redman JR, Dijk D-J, Rajaratnam SMW. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep* 26(6), 695–700 (2003).

146. Phipps-Nelson J, Redman JR, Schlangen LJM, Rajaratnam SMW. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiol. Int.* 26(5), 891–912 (2009).

147. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand. J. Work Environ. Health.* 34(4), 297–306 (2008).

148. Mills PR, Tomkins SC, Schlangen LJ. The effect of high correlated colour temperature office lighting on employee wellbeing and work performance. *J. Circadian Rhythms* 5, 2 (2007).

149. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS ONE* 6(1), e16429 (2011).

150. Münch M, Linhart F, Borisuit A, Jaeggi SM, Scartezzini J-L. Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. *Behav. Neurosci.* 126(1), 196–203 (2012).

151. Gordijn MC, Beerma DGM, Rüger M, Daan S. The effects of blue light on sleepiness. *Annu. Proc. Dutch Sleep-Wake Soc.* 16, 67–70 (2005).

152. Lockley SW, Evans EE, Scheer FAJL, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep* 29(2), 161–168 (2006).

153. Figueiro MG, Rea MS. Short-wavelength light enhances cortisol awakening response in sleep-restricted adolescents. *Int. J. Endocrinol.* 2012, 7 (2012).

154. Beaven CM, Ekström J. A comparison of blue light and caffeine effects on cognitive function and alertness in humans. *PLoS One* 8(10), e76707 (2013).

155. Rodríguez-Morilla B, Madrid JA, Molina E, Correa A. Blue-enriched white light enhances physiological arousal but not behavioral performance during simulated driving at early night. *Front. Psychol.* 8 (2017). www.frontiersin.org/articles/10.3389/fpsyg.2017.00997/full

156. Rodríguez-Morilla B, Madrid JA, Molina E, Pérez-Navarro J, Correa Á. Blue-enriched light enhances alertness but impairs accurate performance in evening chronotypes driving in the morning. *Front. Psychol.* 9 (2018). www.frontiersin.org/articles/10.3389/fpsyg.2018.00688/full

157. Łaszewska K, Goroncy A, Weber P *et al.* Daytime acute non-visual alerting response in brain activity occurs as a result of short- and long-wavelengths of light. *J. Psychophysiol.* 1–25 (2017).doi: 10.1027/0269-8803/a000199 .

158. Smolders KCHJ, de Kort YAW, Cluitmans PJM. A higher illuminance induces alertness even during office hours: findings on subjective measures, task performance and heart rate measures. *Physiol. Behav.* 107(1), 7–16 (2012).

159. Vandewalle G, Balteau E, Phillips C *et al.* Daytime light exposure dynamically enhances brain responses. *Curr. Biol.* 16(16), 1616–1621 (2006).

160. Figueiro MG, Bierman A, Plitnick B, Rea MS. Preliminary evidence that both blue and red light can induce alertness at night. *BMC Neurosci.* 10, 105 (2009).

161. Figueiro MG, Sahin L, Wood B, Plitnick B. Light at night and measures of alertness and performance: implications for shift workers. *Biol. Res. Nurs.* 18(1), 90–100 (2016).

162. Plitnick B, Figueiro M, Wood B, Rea M. The effects of red and blue light on alertness and mood at night. *Lighting Res. Technol.* 42(4), 449–458 (2010).

163. Sahin L, Figueiro MG. Alerting effects of short-wavelength (blue) and long-wavelength (red) lights in the afternoon. *Physiol. Behav.* 116–117, 1–7 (2013).

164. Sahin L, Wood BM, Plitnick B, Figueiro MG. Daytime light exposure: effects on biomarkers, measures of alertness, and performance. *Behav. Brain Res.* 274, 176–185 (2014).

165. Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 290(5), R1413–R1420 (2006).

166. Myers BL, Badia P. Immediate effects of different light intensities on body temperature and alertness. *Physiol. Behav.* 54(1), 199–202 (1993).

167. Chang A-M, Santhi N, St Hilaire M *et al.* Human responses to bright light of different durations. *J. Physiol.* 590(13), 3103–3112 (2012).

168. Cajochen C, Zeitzer JM, Czeisler CA, Dijk D-J. Dose–response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. *Behav. Brain Res.* 115(1), 75–83 (2000).

169. Badia P, Myers B, Boecker M, Culpepper J, Harsh JR. Bright light effects on body temperature, alertness, EEG and behavior. *Physiol. Behav.* 50(3), 583–588 (1991).

170. Vandewalle G, Schmidt C, Albouy G *et al.* Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. *PLoS ONE* 2(11), e1247 (2007).

171. Alkozei A, Smith R, Pisner DA *et al.* Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* 39(9), 1671–1680 (2016).

172. Perrin F, Peigneux P, Fuchs S *et al.* Nonvisual responses to light exposure in the human brain during the circadian night. *Current Biol.* 14(20), 1842–1846 (2004).

173. Vandewalle G, Gais S, Schabus M *et al.* Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cereb. Cortex.* 17(12), 2788–2795 (2007).

174. Okamoto Y, Nakagawa S. Effects of daytime light exposure on cognitive brain activity as measured by the ERP P300. *Physiol. Behav.* 138, 313–318 (2015).

175. Vandewalle G, Archer SN, Wuillaume C *et al.* Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *J. Biol. Rhythms* 26(3), 249–259 (2011).

176. Killgore WDS, Kent HC, Knight SA, Alkozei A. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. *Neuroreport* 29(6), 488–494 (2018).

177. Kretschmer V, Schmidt K-H, Griefahn B. Bright light effects on working memory, sustained attention and concentration of elderly night shift workers. *Lighting Res. Technol.* 44(3), 316–333 (2012).

178. Boyce PR, Beckstead JW, Eklund NH, Strobel RW, Rea MS. Lighting the graveyard shift: the influence of a daylight-simulating skylight on the task performance and mood of night-shift workerst. *Int. J. Lighting Res. Technol.* 29(3), 105–134 (1997).

179. Gabel V, Maire M, Reichert CF *et al.* Effects of artificial dawn and morning blue light on daytime cognitive performance, well-being, cortisol and melatonin levels. *Chronobiol. Int.* 30(8), 988–997 (2013).

180. Gabel V, Maire M, Reichert CF *et al.* Dawn simulation light impacts on different cognitive domains under sleep restriction. *Behav. Brain Res.* 281, 258–266 (2015).

181. Santhi N, Groeger JA, Archer SN, Gimenez M, Schlangen LJM, Dijk D-J. Morning sleep inertia in alertness and performance: effect of cognitive domain and white light conditions. *PLoS ONE* 8(11), e79688 (2013).

182. Smolders KCHJ, de Kort YAW. Investigating daytime effects of correlated colour temperature on experiences, performance, and arousal. *J. Environ. Psychol.* 50, 80–93 (2017).

183. Smolders KCHJ, de Kort YAW. Bright light and mental fatigue: effects on alertness, vitality, performance and physiological arousal. *J. Environ. Psychol.* 39, 77–91 (2014).

184. Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS ONE* 12(9), e0184884 (2017).

185. Bedrosian TA, Nelson RJ. Timing of light exposure affects mood and brain circuits. *Transl. Psychiatry* 7(1), e1017 (2017).

186. Golden RN, Gaynes BN, Ekstrom RD *et al.* The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *AJP* 162(4), 656–662 (2005).

187. Wolkowitz Owen M, Burke Heather, Epel Elissa S, Reus Victor I. Glucocorticoids. Mood, memory, and mechanisms. *Ann. N. Y. Acad. Sci.* 1179(1), 19–40 (2009).

188. Son GH, Chung S, Kim K. The adrenal peripheral clock: glucocorticoid and the circadian timing system. *Front. Neuroendocrinol.* 32(4), 451–465 (2011).

189. Pilorz V, Tam SKE, Hughes S *et al.* Melanopsin regulates both sleep-promoting and arousal-promoting responses to light. *PLoS Biol.* 14(6), e1002482 (2016).

190. Cajochen C, Chellappa SL. Commentary: melanopsin regulates both sleep-promoting and arousal-promoting responses to light. *Front. Neural Circuits* 10 (2016). www.frontiersin.org/articles/10.3389/fncir.2016.00094/full

191. Noseda R, Bernstein CA, Nir R-R *et al.* Migraine photophobia originating in cone-driven retinal pathways. *Brain* 139(7), 1971–1986 (2016).

192. Ibrahim MM, Patwardhan A, Gilbraith KB *et al.* Long-lasting antinociceptive effects of green light in acute and chronic pain in rats. *Pain* 158(2), 347 (2017).

193. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SMW. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil. Neural Repair* 28(4), 303–313 (2014).

194. Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore WDS. Blue-light therapy following mild traumatic brain injury: effects on white matter water diffusion in the brain. *Front. Neurol.* 8 (2017). www.frontiersin.org/articles/10.3389/fneur.2017.00616/full

195. Vanuk J, Shane B, Bajaj S, Millan M, Killgore WDS. 538. Blue light therapy following a mild traumatic brain injury improves MPFC-amygdala functional connectivity and mood. *Biol. Psychiatry* 81(10), S218 (2017).

196. Alkozei A, Smith R, Killgore WDS. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neurosci. Lett.* 616, 5–10 (2016).

197. Hamblin MR. Photobiomodulation for traumatic brain injury and stroke. *J. Neurosci. Res.* 96(4), 731–743 (2017).

198. Xu Q, Lang CP. Revisiting the alerting effect of light: a systematic review. *Sleep Med. Rev.* (2017). www.sciencedirect.com/science/article/pii/S1087079217300989

199. International Commission on Non-Ionizing Radiation Protection. ICNIRP guidelines on limits of exposure to incoherent visible and infrared radiation. *Health Physics.* 105(1), 74 (2013).

200. Brouwer A, Nguyen H-T, Snoek FJ *et al.* Light therapy: is it safe for the eyes? *Acta Psychiatrica Scandinavica* 136(6), 534–548 (2017).

Accepted Manuscript



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PII: S1389-9457(18)30496-9

DOI: 10.1016/j.sleep.2018.09.018

Reference: SLEEP 3836

To appear in: *Sleep Medicine*

Received Date: 31 July 2018

Revised Date: 6 September 2018

Accepted Date: 26 September 2018

Please cite this article as: Raikes AC, Satterfield BC, Killgore WDS, Evidence of Actigraphic and Subjective Sleep Disruption Following Mild Traumatic Brain Injury, *Sleep Medicine* (2018), doi: https://doi.org/10.1016/j.sleep.2018.09.018.

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Evidence of Actigraphic and Subjective Sleep Disruption Following Mild Traumatic Brain Injury

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Word Count: 3846

Tables: 2 (including 1 supplemental table)

Figures: 3

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Abstract

Objective/Background: Mild traumatic brain injuries (mTBI) are frequently associated with long-term, self-reported sleep disruption. Objective corroboration of these self-reports is sparse and limited by small sample sizes. The purpose of this study was to report on actigraphically-measured sleep outcomes in individuals with and without a history of recent mTBI in two U.S. cities (Boston, MA and Tucson, AZ).

Patients/Methods: 58 individuals with a recent (within 18 months) mTBI and 35 individuals with no prior mTBI history were recruited for one of four studies across two sites. Participants completed a minimum of one week of actigraphy. Additionally, mTBI participants self-reported daytime sleepiness, sleep disruption, and functional sleep-related outcomes.

Results: In Boston, mTBI participants obtained less average sleep with shorter sleep onset latencies (SOL) than healthy individuals. In Tucson, mTBI participants had greater SOL and less night-to-night SOL variability compared to healthy individuals. Across mTBI participants, SOL was shorter and night-to-night SOL variability was greater in Boston than Tucson. Sleep efficiency (SE) variability was greater in Tucson than Boston across both groups. Only SOL variability was significantly associated with daytime sleepiness ($r = 0.274$) in the mTBI group after controlling for location.

Conclusion: Sleep quality, SOL and SE variability, are likely affected by mTBIs. Between-group differences in each site existed but went in opposite directions. These findings suggest the possibility of multiple, rather than a singular, profiles of sleep disruption following mTBI. Precision medicine models are warranted to determine whether multiple sleep disruption profiles

22 do indeed exist following mTBI and the predisposing conditions that contribute to an
23 individual's experience of sleep disruption.

24

25 **Keywords:** actigraphy; daytime sleepiness; coefficient of variation; sleep disruption; mild
26 traumatic brain injury; mTBI; sleep onset latency; sleep efficiency; sleep quality

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1. Introduction

Each year, at least 1.5 million documented and undocumented mild traumatic brain injuries (mTBIs) occur in the United States each year.[1,2] mTBIs are the result of external forces to the head or body resulting in the disruption of normal brain function, with or without short-term loss of consciousness, and the absence of gross abnormalities on conventional diagnostic neuroimaging.[3,4] These injuries result in a wide range of somatic symptoms, as well as changes and impairments in cognitive, motor, and behavioral functioning.[3,5,6] Some of these changes appear to be transient, naturally recovering to preinjury levels within 1-3 months.[5,7–9] However many others – including depression, pain, and increased daytime fatigue and poor sleep – may have long-term sequelae that do not resolve without intervention.[10–15]

Post-mTBI sleep changes are a common complaint, with 30-70% of individuals reporting some form of sleep disruption.[10,16] The most frequent of these complaints are self-reported sleep disruption, insomnia, and daytime sleepiness or fatigue.[15,17–22] However, these self-reports are generally not corroborated by objective findings.[11,23–25] Objective findings of sleep disruption specific to mTBI are limited. Several studies employing polysomnography have demonstrated that individuals with a history of mTBI get poorer sleep (lower sleep efficiency, more frequent and longer nocturnal wakefulness) and have higher overall physiological arousal compared to either population norms or control participants.[26–29] However, these findings are inconsistent[11,24,30,31] and a recent meta-analysis suggests that such findings may not persist into the chronic phase (> 6 months post-injury).[32]

Additional studies employing actigraphy have corroborated findings of lower sleep efficiency and increased nighttime awakenings.[33–35] Actigraphy-based studies have further identified circadian rhythm sleep disorders following mTBI,[36] as well as findings indicating that total 24-

hour sleep time may be greater in individuals immediately after a mTBI, and that this recovers over time.[33,34] However, these findings are also not consistently observed,[37,38] and higher intra-individual variability following mTBI than in controls may partially explain inconsistent findings across both PSG and actigraphy studies.[34,37]

Two major challenges in post-mTBI sleep-related research are overall small sample sizes and the reliance on mixed severity TBI samples.[39] Consequently, the findings across the literature require further corroboration and exploration in order to more completely describe the generalizability. The purpose of this study was to compare individuals with a recent mTBI (< 18 months prior) to healthy controls with no prior history of mTBI on seven days of at-home actigraphy. We hypothesized that both sleep quantity and sleep quality (e.g., greater nighttime awakening, lower sleep efficiency) would be worse in those with a recent mTBI. We additionally hypothesized that post-mTBI individuals would exhibit greater night-to-night variability in these actigraphy-based sleep metrics than controls.

2. Material and Methods

Study procedures were evaluated and approved by the Institutional Review Boards of Partners Healthcare, the University of Arizona College of Medicine, and the U.S. Army's Human Research Protections Office. All participants provided written informed consent prior to participation.

2.1. Participants

Data for the present study were acquired from four samples of individuals enrolled in four separate studies that employed similar methodology for recruitment and collection of actigraphy.

Two of these studies were completed in Boston, MA and two are on-going in Tucson, AZ. Participant demographics are summarized in Table 1.

2.1.1. Mild traumatic brain injury participants

A total of 58 individuals with a recent mTBI (time since injury: 8 ± 4.74 months; male/female: 23/35) were recruited from the greater Boston (n = 28) and Tucson (n = 29) areas. In both locations, individuals were recruited via community fliering and were required to provide documentation indicating either direct observation of the injury and immediate sequalae (e.g., by a coach) or the diagnosis of a concussion by a qualified professional (e.g., physician, athletic trainer). For both locations, mild traumatic brain injury was defined according to criteria consistent with the American Congress of Rehabilitation Medicine[40] and VA/DoD Guidelines.[41] Specifically, a mTBI was defined as a physiological disruption of brain function caused by a traumatic injury to the head, resulting in a Glasgow Coma Scale (if obtained) between 13-15 within 24 hours of injury, loss of consciousness lasting no more than 30 minutes, posttraumatic amnesia lasting less than 24 hours, altered mental state lasting less than 24 hours, and/or focal neurological damage that may be transient.[40,41] Unrelated neuroimaging findings from these samples have been reported elsewhere[42,43] but the use of actigraphy in the present paper is novel and has not been previously published.

2.1.2. Healthy controls

Sleep-related data were additionally available from two separate groups of healthy control participants. 24 individuals were recruited in Boston. These healthy controls met the following criteria: no history of psychological, neurological, sleep, or other medical disorders; self-reported sleep duration within the top or bottom quartile of the population; no history of head injury with loss of consciousness or post-traumatic amnesia; daily caffeine intake less than 300 mg per day;

no drug or alcohol abuse in the past 6 months; no history of smoking; no use of medications with drowsiness as a side effect; and not pregnant. Unrelated results from the primary study for these participants have previously been published[44] or are currently under review. However, their use in this study provides novel insights.

An additional 11 healthy individuals were recruited in Tucson. These healthy controls met the following criteria: no history of psychological, neurological, sleep, or other medical disorders; no history of concussion or TBI; no history of cardiac conditions; no presence of excessive daytime sleepiness; no presence of irregular circadian schedule (e.g., shift work); daily caffeine intake less than 300 mg per day; no current use of medications (except birth control), recreational drugs, or tobacco; and not pregnant.

2.2. Actigraphy

All participants completed a minimum 7 days of actigraphy using either a Philips Respironics Actiwatch Spectrum (mTBI groups) or the Philips Respironics Actiwatch-2 (healthy control groups). Data for the Tucson mTBI and healthy controls groups were collected using 1 min epochs. Data for the Boston mTBI group was collected using 2 min epochs.

Actigraphy data were processed in the Philips Actiware 6 software. All data were scored automatically in the software using the default scoring algorithm, with sleep time scored based on minutes of immobility. The algorithm analysis criteria were set as follows for all subjects: wake threshold value of 40 activity counts, 10 immobile minutes for sleep onset and sleep end; white light threshold of 1,000 lux. Automatic scoring was visually inspected by a trained technician and scores were modified as needed based on sleep diary data to reconcile unclear recordings. Sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (total sleep time / total time-in-bed; SE), and total nighttime sleep duration were extracted. The

coefficient of variation (standard deviation/mean; CV) as a measure of intra-individual variation for each individual was calculated for each measure.

2.3 Self-reported outcomes

Participants in each of the parent studies completed comprehensive battery of neuropsychological exams and self-reported questionnaires. Here we report the outcomes from three of these self-report questionnaires only.

2.3.1. The Epworth Sleepiness Scale (ESS)

All participants completed the ESS, a self-report measure of daytime sleepiness.[45] Scores range from 0-24 and a cutoff score of 10 has been identified to indicate excessive daytime sleepiness.[46]

2.3.2. The Pittsburgh Sleep Quality Index (PSQI)

Participants in the mTBI groups completed the PSQI, a self-report measure regarding overall sleep quality.[47] Lower scores indicate better sleep quality. Total scores greater than 5 indicate poor sleep in the general public,[47] though scores greater than 8 have been identified as more sensitive in TBI samples.[48] The PSQI has both good test-retest reliability ($r > 0.80$)[47] and post-mTBI sleep disruption sensitivity.[15,49]

2.3.3 The Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a self-report questionnaire designed to identify the impact of sleep, particularly excessive daytime sleepiness on activities of daily living.[50] Scores on the FOSQ range from 5-20, and higher scores are better (greater overall function).[51]

2.3. Statistical Analyses

All statistical analyses were conducted in R (including the tidyverse,[52–54] lmerTest,[55] and rsq[56] packages) with *a priori* significance set at $p < 0.05$. Group differences in demographic and

personal characteristics were computed using two-sample *t*-tests a χ^2 tests as appropriate. To identify differences in sleep measures over the seven days of actigraphy, we fit individual linear mixed effects models using the lmerTest package. Main effects included mTBI group (healthy vs. mTBI) and location (Boston vs. Tucson) as well as the interaction term. These models utilized all available days of actigraphy for each individual, as between-group differences in weekly means may be obscured by high intra-individual variability.[28,34,37] Planned post-hoc comparisons were made within site (e.g., healthy vs. mTBI in Boston) and within group (e.g., Boston vs. Tucson mTBI) but not fully crossed (e.g., not Boston healthy vs. Tucson mTBI). We also computed group x location ANOVAs on the CV data to identify intra-individual variability differences. We further report Cohen's d as a measure of effect size for reported post-hoc comparisons. For the linear mixed models, these effect sizes were computed on the estimated marginal means after adjusting for the random effects in the models,

We additionally performed exploratory analyses within the mTBI participant group to evaluate the relationship between sleep and self-reported outcomes. First, to assess whether sleep parameters improve over time since injury, we fit a linear model to the weekly mean and CV data with months since injury as the independent variable and controlled for location. We also fit individual linear models to the ESS, PSQI, and FOSQ scores with mean and CV data from the preceding week while controlling for location. These models allowed us to determine the extent to which prior sleep predicts self-reported sleep quality and sleep-related outcomes.

3. Results

3.1. Demographic data

Demographic and self-report outcomes are presented in Table 1. Healthy controls in Tucson were significantly younger than both the Boston healthy controls and Tucson mTBI participants.

ESS total scores were higher in the mTBI groups than the matched controls in each respective location.

3.2. Linear mixed effects models of actigraphy

3.2.1. Total nighttime sleep

Post-hoc analyses revealed that healthy control participants in Boston slept approximately 30 minutes more on average per night than both mTBI participants in Boston ($t = 2.716$, $p = 0.007$, $d = 0.76$; Figure 1A) and healthy controls in Tucson ($t = 1.915$, $p = 0.056$, $d = 0.70$).

3.2.2 Sleep quality measures

SOL data required transformation ([$y = \ln(x + 1)$]) prior to model fitting in order to reduce positive skewness in the residuals. SOL was shorter for the Boston mTBI subgroup than for the Boston healthy controls ($t = 5.060$, $p < 0.0001$, $d = 1.41$; Figure 1B) and Tucson mTBI participants ($t = 8.275$, $p < 0.0001$, $d = 2.28$). Additionally, SOL was longer in the Tucson mTBI subgroup than the Tucson healthy controls ($t = 4.238$, $p < 0.0001$, $d = 1.5$).

Nightly WASO data required fourth root transformation to reduce positive skewness in the residuals. No statistically significant differences were observed for any post-hoc comparisons (Figure 1C).

Sleep efficiency data required fourth power transformation to reduce negative skewness in the residuals. Post-hoc analyses demonstrated greater SE for mTBI participants in Boston compared to those in Arizona ($t = 3.428$, $p = 0.001$, $d = 0.91$) as well as healthy controls in Boston ($t = 2.568$, $p = 0.01$, $d = 0.71$).

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3.3. Intra-individual variability

All CV data required log transformation prior to model fitting to address non-normality in the residuals. mTBI participants in Tucson had less variable SOL ($t = 3.137$, $p = 0.002$, $d = 0.83$; Figure 2B) and more variable SE ($t = 2.866$, $p = 0.005$, $d = 0.76$; Figure 2D) than mTBI participants in Boston. Additionally, Tucson mTBI participants had less variable SE than the Tucson healthy controls ($t = 2.616$, $p = 0.011$, $d = 0.93$; Figure 2D). Finally, overall SE variability was greater in Tucson than Boston ($t = 2.628$, $p = 0.010$, $d = 0.55$; Figure 2D) No other statistically significant pairwise comparisons were observed (Figure 2A-D).

3.4. Relationship between Actigraphy and Self-reported outcomes

After controlling for location, SOL coefficient of variation significantly predicted ESS (Figure 3). No other sleep measures were related to time since injury or self-reported outcomes.

4. Discussion

The purpose of this study was to identify differences in actigraphically-measured sleep characteristics between individuals with and without a history of mild traumatic brain injury. We hypothesized that individuals with a recent mTBI would have greater nighttime sleep duration and worse sleep quality, as well as greater night-to-night variability, than healthy controls, regardless of data collection location. These hypotheses were partially confirmed.

4.1 Objective sleep findings

Our initial hypotheses concerned the differences between healthy individuals and mTBI participants. Given the multi-site nature of our data, we included location in the models to address potentially systematic between-site differences. While not hypothesized, we found differing patterns of actigraphic sleep outcomes between the two sites. Individuals in the Boston

mTBI group obtained, on average, 32 fewer minutes of sleep per night than their location-matched healthy controls. By contrast, the Tucson mTBI participants slept approximately 18 minutes longer per night than their location-matched healthy controls, though this finding was not statistically significant. Importantly, the healthy controls in Tucson slept approximately 32 minutes less than the Boston healthy control group, putting them at a similar level as the Boston mTBI group. Thus, no consistent pattern of findings was observed for total sleep time between those with a prior mTBI and healthy controls, although this may have been obscured by the between-location variability.

We observed similarly conflicting within and cross-location findings for average SOL (longer for mTBI in Tucson; shorter for mTBI in Boston), as well as intra-individual variability in SOL (more for mTBI in Boston; less for mTBI in Tucson). Collectively, average SE was lower in Tucson than in Boston while intra-individual variability was higher. However, there were no between group (mTBI vs. control) differences.

4.1.1 Potentially multiple profiles of post-mTBI sleep disturbance

Taken individually, the findings from the Boston subgroups showing reduced sleep in the mTBI sample would stand in opposition to other actigraphy-based studies indicating no differences or greater sleep duration in those with mTBI compared to population norms or controls.[23,33,34,37] However, the Tucson sub-samples would seem to confirm the no difference findings.[37,38] Additionally, no between-group differences were observed in night-to-night sleep duration variability, in contrast to prior findings.[37] Similarly, prior work generally reports no differences in actigraphically-measured SOL following mTBI,[25,38,57] though one report suggests SOL may be decreased.[33] Our present findings suggest that SOL may be affected after mTBI, though the direction is unclear.

Taken together with the inconsistently reported effects of mTBI on sleep across the literature, these seemingly conflicting findings yield a critical observation on post-mTBI sleep. To date, studies in this area have employed small sample sizes from a single location and may or may not include a control group. As evident in the patterns of differences between healthy individuals and mTBI participants across the two sites, as well as the differences between the two groups of mTBI participants reported here, it is likely that, similar to the heterogeneity of mTBI mechanisms and individual responses to injury,[6,58,59] self-reported and actigraphic sleep findings are highly individualized. Recent reports highlight the fact that there are multiple divergent clinical profiles of mTBI (i.e., cognitive fatigue; oculomotor).[6,60–63] Sleep disruption of all kinds, however, is considered a sub-component modifier of these clinical profiles, but not in itself a primary profile.

The findings in the present study suggest that there may likewise be multiple profiles of sleep disruption (e.g., long latency vs. short latency; increased night-to-night variability vs. no change in variability; shorter sleep duration vs. unaffected sleep duration but longer onset latency). In light of the individually small sample sizes in each of our groups, this explanation is speculative at present. However multiple sleep disruption profiles, rather than a one-size-fits-all approach, are consistent with emerging clinical views of mTBI and would explain the inconsistent findings resulting from single, small cohorts of individuals following injury. The possibility of multiple sleep outcome profiles following mTBI merits further investigation with larger samples of not only individuals following mTBI but also reference cohorts.

4.1.2 Additional explanations for the observed patterns of responses.

There are several other possible explanations for the pattern of findings in the present study. As stated, there are multiple mTBI clinical profiles.[6,60–63] Given the various mechanisms of injury

leading to the most recent mTBI in the present participants, the clinical profiles in the present study may have varied significantly. We were unable to retrospectively create these profiles for our mTBI participants. As the relationship between current views of clinical profiles and sleep is unknown, there may be sleep effects driven by differences in injury mechanism and potentially varied clinical presentations leading to inconsistent between- and within-group findings, particularly the between-site differences in SE and SOL for the mTBI participants.

Second, a recent meta-analysis of sleep architecture in chronic (> 6 months) TBI identified no overall differences in sleep architecture (measured via PSG) for those with mTBI compared to control participants. The authors, however, suggest caution when interpreting these findings in light of several limitations including inconsistent definitions of mTBI and the possibility that injury-related changes may resolve within six months.[32] Thus our inconsistent pattern of findings may be driven by the varied time since injury for our participants. However, we find this explanation unlikely because of A.) the lack of relationship between time since injury (in months) and any of the reported measures, even after accounting for location differences; and B.) post-hoc assessments of our models including time since injury as a covariate did not significantly improve the fits of any of our models.

Finally, in light of the between-site differences, particularly in both average SE and intra-individual variability, it is possible that location matters when interpreting actigraphy results. Prior work has shown that perceptions of sleep quality differ by geographic region.[64,65] Furthermore, sleep-related circadian rhythms are influenced by the amount of exposure to blue wavelength light, of which sunlight is a major contributor.[66,67] Given the seasonal differences between Boston and Tucson (e.g., year-round availability of sunlight in Tucson) as well as a difference of just over 10 degrees in latitude, the amount of daily light exposure may have

differed significantly across sites and between individuals. Consequently, geographic and seasonal variation in sunlight exposure may exert influences on sleep timing, quantity, and quality that affect the findings of individual studies.[68,69] However, the implications of strictly geographic and seasonal influences on the outcomes reported here are not identified or well-supported by any extant literature and therefore require further exploration.

Regardless, this is the first multi-site mTBI-specific analysis of actigraphically-measured sleep with location-matched controls of which we are aware. Further work using tightly controlled geographic and season-matched samples is needed to identify the extent to which geographic location and seasonal variation may impact sleep-related outcomes.

4.2 Relationship between subjective and objective findings

An additional important finding from the present study is the further corroboration of prior studies identifying a discrepancy between perceived and objective sleep quality following mTBI. Across both mTBI groups, 50.9% (n = 29/57) of participants reported excessive daytime sleepiness (ESS score ≥ 10), 84.2% (n = 48/57) reported clinically significant PSQI total scores ≥ 5,[47] and 47.4% (n = 27/57) reported PSQI scores ≥ 8.[48] Collectively, these self-reports indicate a high prevalence of *perceived* sleep disruption and daytime sleepiness in the mTBI group. However, only intra-individual variability in SOL significantly predicted ESS total scores. Higher variability in SOL was associated with greater daytime sleepiness, though the model including CV and location explained very little overall variance in ESS scores (R^2 = 0.1). Thus, individuals *perceive* poorer sleep and greater daytime fatigue, despite no relationship between objective and subjective measures. As previous authors have suggested, it may be that these objective and subjective measures are capturing differing aspects of the sequelae of post-mTBI recovery, and therefore provide complementary rather than conflicting outcomes.[23]

4.3 Limitations

The findings from this study should be interpreted in light of several limitations. First, the participants in all of our groups were recruited for different studies, each with individually small sample sizes. This is particularly true of the Tucson healthy control group (n = 11). Consequently, these findings should be conservatively viewed as preliminary results that require further corroboration.

Second, as noted previously, geographic and seasonal, as well as genetic, sociodemographic, and cross-cultural effects on actigraphically-quantified sleep remain largely unclear and, with the exception of geographic location, were not accounted for in these analyses. While the month (as a proxy for season) of participation is available, there were too few individuals at any given time point to adequately model the across-season variability. Future work should address these considerations in larger multi-site samples with seasonally-matched controls.

Third, the four samples reported here were recruited for four different studies with varied methods and goals. Consequently, there were between-sample differences in the actigraph models used as well as the epoch length for the Boston mTBI sample was longer than any of the other groups. To minimize the effects of these differences, all of the data were analyzed using the same software, visually inspected by similarly trained technicians, and verified against sleep diary data. It is possible that between-model differences account for some variability in the data. Additionally, the differing epoch length for the Boston mTBI sample may have reduced the sensitivity of the automatic scoring algorithm to sleep-wake transitions. We were unable to statistically control for these differences in the models (this variance is already captured by the group x location interaction term) and this remains a potential confound to these findings. Future

multi-site studies employing consistent hardware and epoch lengths are needed in order address these concerns.

Finally, we were unable to capture any pre-injury data from the mTBI participants. Consequently, it is unclear what their level of premorbid sleep was. In spite of these important limitations, this study is the first reported multi-site actigraphy-based sleep study with an mTBI-only (rather than mixed severity) sample. These findings provide critical insight into the need for multi-site post-mTBI sleep related research that additionally addresses diverse clinical profiles of mTBI presentation, geographic and seasonal variation in sleep, and the relationship between objective measurement and subjective perceptions of sleep.

5. Conclusions

Sleep quality, particularly night-to-night sleep onset latency and sleep efficiency variability, are likely affected by mTBIs. While between-group differences in each site were apparent for these measures, the patterns of differences were not consistent across the two sites in this study. This highlights the fact that post-mTBI sleep outcomes reported from a single cohort may be insufficient to capture the spectrum of sleep disruption following injury. Furthermore, these findings suggest the possibility of multiple, rather than a singular, profile of sleep disruption following mTBI. Additionally, these results further confirm that self-reported and objectively quantified sleep quantity and quality following mTBI are largely unrelated. Precision medicine models derived from large cohorts across multiple sites are warranted to determine whether multiple sleep disruption profiles do indeed exist following mTBI and the conditions (e.g., injury mechanism, other symptom presentation, social pressures) that may predispose or contribute to an individual's experience of sleep disruption.

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Acknowledgements

We are grateful to Bradley R. Shane and Melissa Millan for their work on scoring the actigraphy.

Funding

This research was supported by multiple grants from the US Army Medical Research and Materiel Command (USAMRMC) to Dr. William D. S. Killgore, including W81XWH-11-1-0056, W81XWH-14-1-0571, W81XWH-17-C-008, and D12AP00241. The content, opinions, interpretations, conclusions, and recommendations are solely the responsibility of the authors and do not necessarily represent the views of Partners Healthcare, the University of Arizona College of Medicine, the Department of Defense, or the U.S. Army Medical Research and Materiel Command.

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354 **References**
355

356 1. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States:*
357 *Emergency Department Visits, Hospitalizations and Deaths 2002-2006*. Atlanta (GA): Centers
358 for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
359 http://origin.glb.cdc.gov/traumaticbraininjury/pdf/blue_book.docx. Accessed April 25, 2015.

360 2. Kerr Z, Roos K, Dompier T, et al. Estimating concussion incidence in college sports:
361 Rates, risks, average per team and proportion of teams with concussions. In: *BRAIN INJURY*.
362 Vol 30. TAYLOR & FRANCIS INC 530 WALNUT STREET, STE 850, PHILADELPHIA, PA
363 19106 USA; 2016:504–504.

364 3. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport -
365 The 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports*
366 *Med*. 2017;51:838-847. doi:10.1136/bjsports-2017-097699

367 4. Basic Information about Traumatic Brain Injury and Concussion | Concussion |
368 Traumatic Brain Injury | CDC Injury Center.
369 https://www.cdc.gov/traumaticbraininjury/basics.html. Accessed July 17, 2018.

370 5. McCrea M, Guskiewicz KM, Randolph C, et al. Incidence, clinical course, and predictors
371 of prolonged recovery time following sport-related concussion in high school and college
372 athletes. *J Int Neuropsychol Soc*. 2013;19(1):22–33. doi:10.1017/S1355617712000872

373 6. Collins MW, Kontos AP, Okonkwo DO, et al. Statements of Agreement From the
374 Targeted Evaluation and Active Management (TEAM) Approaches to Treating Concussion
375 Meeting Held in Pittsburgh, October 15-16, 2015. *Neurosurgery*. 2016;79(6):912-929.
376 doi:10.1227/NEU.0000000000001447

377 7. Kontos AP, Braithwaite R, Dakan S, Elbin RJ. Computerized Neurocognitive Testing
378 within 1 Week of Sport-Related Concussion: Meta-analytic Review and Analysis of Moderating
379 Factors. *Journal of the International Neuropsychological Society*. 2014;20(3):324-332.
380 doi:10.1017/S1355617713001471

381 8. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time
382 following concussion in collegiate football players: The NCAA Concussion Study. *JAMA*.
383 2003;290(19):2556-2563.

384 9. Nelson LD, Guskiewicz KM, Barr WB, et al. Age differences in recovery after sport-
385 related concussion: a comparison of high school and collegiate athletes. *Journal of athletic*
386 *training*. 2016;51(2):142–152.

387 10. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Sleep-wake disturbances after traumatic
388 brain injury. *The Lancet Neurology*. 2015;14(7):746-757. doi:10.1016/S1474-4422(15)00068-X

389 11. Gosselin N, Lassonde M, Petit D, et al. Sleep following sport-related concussions. *Sleep*
390 *Medicine*. 2009;10(1):35-46. doi:10.1016/j.sleep.2007.11.023

12. Stein E, Howard W, Rowhani-Rahbar A, Rivara FP, Zatzick D, McCarty CA. Longitudinal trajectories of post-concussive and depressive symptoms in adolescents with prolonged recovery from concussion. *Brain Injury*. 2017;31(13-14):1736-1744. doi:10.1080/02699052.2017.1380843

13. Martini DN, Broglio SP. Long-term effects of sport concussion on cognitive and motor performance: A review. *International Journal of Psychophysiology*. October 2017. doi:10.1016/j.ijpsycho.2017.09.019

14. McMahon P, Hricik A, Yue JK, et al. Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. *J Neurotrauma*. 2014;31(1):26-33. doi:10.1089/neu.2013.2984

15. Theadom A, Cropley M, Parmar P, et al. Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Medicine*. 2015;16(8):926-932. doi:10.1016/j.sleep.2015.04.013

16. Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: A meta-analysis. *Sleep Medicine*. 2012;13(7):898-905. doi:10.1016/j.sleep.2012.04.006

17. Towns SJ, Silva MA, Belanger HG. Subjective sleep quality and postconcussion symptoms following mild traumatic brain injury. *Brain Injury*. 2015;29(11):1337-1341. doi:10.3109/02699052.2015.1045030

18. Sullivan KA, Berndt SL, Edmed SL, Smith SS, Allan AC. Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. *Applied Neuropsychology: Adult*. 2016;23(6):426-435. doi:10.1080/23279095.2016.1172229

19. Mollayeva T, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. Insomnia in workers with delayed recovery from mild traumatic brain injury. *Sleep Medicine*. 2016;19:153-161. doi:10.1016/j.sleep.2015.05.014

20. Mollayeva T, Pratt B, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. The relationship between insomnia and disability in workers with mild traumatic brain injury/concussion: Insomnia and disability in chronic mild traumatic brain injury. *Sleep Medicine*. 2016;20:157-166. doi:10.1016/j.sleep.2015.09.008

21. Sullivan KA, Edmed SL, Allan AC, Karlsson LJE, Smith SS. Characterizing Self-Reported Sleep Disturbance after Mild Traumatic Brain Injury. *Journal of Neurotrauma*. 2015;32(7):474-486. doi:10.1089/neu.2013.3284

22. Farrell-Carnahan L, Barnett S, Lamberty G, et al. Insomnia symptoms and behavioural health symptoms in veterans 1 year after traumatic brain injury. *Brain Injury*. 2015;29(12):1400-1408. doi:10.3109/02699052.2015.1063161

ACCEPTED MANUSCRIPT

23. Berger I, Obeid J, Timmons BW, DeMatteo C. Exploring Accelerometer Versus Self-Report Sleep Assessment in Youth With Concussion. *Global Pediatric Health*. 2017;4:2333794X17745973. doi:10.1177/2333794X17745973

24. Mantua J, Mahan KM, Henry OS, Spencer RMC. Altered sleep composition after traumatic brain injury does not affect declarative sleep-dependent memory consolidation. *Frontiers in Human Neuroscience*. 2015;9. doi:10.3389/fnhum.2015.00328

25. Sinclair KL, Ponsford JL, Rajaratnam SM. Actigraphic assessment of sleep disturbances following traumatic brain injury. *Behavioral Sleep Medicine*. 2014;12(1):13-27. doi:10.1080/15402002.2012.726203

26. Mollayeva T, Colantonio A, Cassidy JD, Vernich L, Moineddin R, Shapiro CM. Sleep stage distribution in persons with mild traumatic brain injury: a polysomnographic study according to American Academy of Sleep Medicine standards. *Sleep Medicine*. 2017;34:179-192. doi:10.1016/j.sleep.2017.02.021

27. Arbour C, Khoury S, Lavigne GJ, et al. Are NREM sleep characteristics associated to subjective sleep complaints after mild traumatic brain injury? *Sleep Medicine*. 2015;16(4):534-539. doi:10.1016/j.sleep.2014.12.002

28. Williams BR, Lazic SE, Ogilvie RD. Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clinical Neurophysiology*. 2008;119(2):429-438. doi:10.1016/j.clinph.2007.11.003

29. Mantua J, Henry OS, Garskovas NF, Spencer RMC. Mild Traumatic Brain Injury Chronically Impairs Sleep- and Wake-Dependent Emotional Processing. *Sleep*. 2017;40(6). doi:10.1093/sleep/zsx062

30. Modarres MH, Kuzma NN, Kretzmer T, Pack AI, Lim MM. EEG slow waves in traumatic brain injury: Convergent findings in mouse and man. *Neurobiology of Sleep and Circadian Rhythms*. 2017;2:59-70. doi:10.1016/j.nbscr.2016.06.001

31. Schreiber S, Barkai G, Gur-Hartman T, et al. Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Medicine*. 2008;9(5):481-487. doi:10.1016/j.sleep.2007.04.014

32. Mantua J, Grillakis A, Mahfouz SH, et al. A systematic review and meta-analysis of sleep architecture and chronic traumatic brain injury. *Sleep Medicine Reviews*. February 2018. doi:10.1016/j.smrv.2018.01.004

33. Chiu H-Y, Chen P-Y, Chen N-H, Chuang L-P, Tsai P-S. Trajectories of sleep changes during the acute phase of traumatic brain injury: A 7-day actigraphy study. *Journal of the Formosan Medical Association*. 2013;112(9):545-553. doi:10.1016/j.jfma.2013.06.007

34. Sufrinko AM, Howie EK, Elbin RJ, Collins MW, Kontos AP. A Preliminary Investigation of Accelerometer-Derived Sleep and Physical Activity Following Sport-Related

462 Concussion. *The Journal of Head Trauma Rehabilitation*. 2018;Publish Ahead of Print.
463 doi:10.1097/HTR.0000000000000387

464 35. Tham SW, Fales J, Palermo TM. Subjective and Objective Assessment of Sleep in
465 Adolescents with Mild Traumatic Brain Injury. *Journal of Neurotrauma*. 2015;32(11):847-852.
466 doi:10.1089/neu.2014.3559

467 36. Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders
468 following mild traumatic brain injury. *Neurology*. 2007;68(14):1136-1140.
469 doi:10.1212/01.wnl.0000258672.52836.30

470 37. Raikes AC, Schaefer SY. Sleep quantity and quality during acute concussion: A pilot
471 study. *Sleep*. 2016;39(12):2141-2147. doi:10.5665/sleep.6314

472 38. Allan AC, Edmed SL, Sullivan KA, Karlsson LJE, Lange RT, Smith SS. Actigraphically
473 Measured Sleep-Wake Behavior After Mild Traumatic Brain Injury: A Case-Control Study. *The*
474 *Journal of Head Trauma Rehabilitation*. 2017;32(2):E35. doi:10.1097/HTR.0000000000000222

475 39. Wickwire E, Schnyer DM, Germain A, et al. Sleep, sleep disorders, and circadian health
476 following mild traumatic brain injury: Review and research agenda. *Journal of Neurotrauma*.
477 June 2018. doi:10.1089/neu.2017.5243

478 40. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury.
479 *The Journal of Head Trauma Rehabilitation*. 1993;8(3):86.

480 41. STATEMENTS Q. VA/DoD Clinical Practice Guideline for the Management of
481 Concussion - mild Traumatic Brain Injury. 2016.
482 https://www.healthquality.va.gov/guidelines/Rehab/mtbi/mTBICPGFullCPG50821816.pdf.
483 Accessed July 27, 2018.

484 42. Bajaj S, Vanuk JR, Smith R, Dailey NS, Killgore WDS. Blue-Light Therapy following
485 Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. *Front*
486 *Neurol*. 2017;8. doi:10/gcnnrw

487 43. Bajaj S, Dailey NS, Rosso IM, Rauch SL, Killgore WDS. Time-dependent differences in
488 cortical measures and their associations with behavioral measures following mild traumatic brain
489 injury. *Human Brain Mapping*. 2018;39(5):1886-1897. doi:10.1002/hbm.23951

490 44. Cui J, Tkachenko O, Gogel H, et al. Microstructure of frontoparietal connections predicts
491 individual resistance to sleep deprivation. *NeuroImage*. 2015;106:123-133.
492 doi:10.1016/j.neuroimage.2014.11.035

493 45. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness
494 scale. *Sleep*. 1991;14(6):540–545.

495 46. Johns M, Hocking B. Daytime Sleepiness and Sleep Habits of Australian Workers. *Sleep*.
496 1997;20(10):844-847. doi:10.1093/sleep/20.10.844

47. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4

48. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. *Brain Inj*. 2002;16(3):197-206. doi:10.1080/02699050110103940

49. Mani A, Dastgheib SA, Chanor A, Khalili H, Ahmadzadeh L, Ahmadi J. Sleep quality among patients with mild traumatic brain injury: A cross-sectional study. *Bull Emerg Trauma*. 2015;3(3):93-96.

50. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835–843.

51. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis Care & Research*. 63(S11):S287-S296. doi:10.1002/acr.20544

52. Wickham H. *Tidyr: Easily Tidy Data with `spread()` and `gather()` Functions*.; 2016. https://CRAN.R-project.org/package=tidyr.

53. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag; 2009. //www.springer.com/us/book/9780387981413.

54. Wickham H, Francois R. *Dplyr: A Grammar of Data Manipulation*.; 2015. https://CRAN.R-project.org/package=dplyr.

55. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*. 2017;82(13):1–26. doi:10.18637/jss.v082.i13

56. Zhang D. *Rsq: R-Squared and Related Measures*.; 2018. https://CRAN.R-project.org/package=rsq.

57. Chiu H-Y, Lo W-C, Chiang Y-H, Tsai P-S. The effects of sleep on the relationship between brain injury severity and recovery of cognitive function: A prospective study. *International Journal of Nursing Studies*. 2014;51(6):892-899. doi:10.1016/j.ijnurstu.2013.10.020

58. Broglio SP, Collins MW, Williams RM, Mucha A, Kontos AP. Current and emerging rehabilitation for concussion: a review of the evidence. *Clinics in sports medicine*. 2015;34(2):213–231. doi:10.1016/j.csm.2014.12.005

59. Okonkwo D, Brooks J, Kontos A, et al. TEAM-TBI: A MONITORED MULTIPLE INTERVENTIONAL TBI RESEARCH TRIAL. *Journal of Neurotrauma*. 2016;33(13):A-38.

531 60. Kontos AP, Collins MW, Holland CL, et al. Preliminary Evidence for Improvement in
532 Symptoms, Cognitive, Vestibular, and Oculomotor Outcomes Following Targeted Intervention
533 with Chronic mTBI Patients. *Mil Med*. 2018;183(suppl_1):333-338. doi:10.1093/milmed/usx172

534 61. Henry LC, Elbin RJ, Collins MW, Marchetti G, Kontos AP. Examining Recovery
535 Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach.
536 *Neurosurgery*. 2016;78(2):232-241. doi:10/f77kw7

537 62. Sandel N, Reynolds E, Cohen PE, Gillie BL, Kontos AP. Anxiety and Mood Clinical
538 Profile following Sport-related Concussion: From Risk Factors to Treatment. *Sport Exerc*
539 *Perform Psychol*. 2017;6(3):304-323. doi:10.1037/spy0000098

540 63. Reynolds E, Collins MW, Mucha A, Troutman-Ensecki C. Establishing a Clinical
541 Service for the Management of Sports-Related Concussions. *Neurosurgery*.
542 2014;75(suppl_4):S71-S81. doi:10.1227/NEU.0000000000000471

543 64. Dregan A, Armstrong D. Cross-country variation in sleep disturbance among working
544 and older age groups: an analysis based on the European Social Survey. *International*
545 *Psychogeriatrics*. 2011;23(9):1413-1420. doi:10.1017/S1041610211000664

546 65. Soldatos CR, Allaert FA, Ohta T, Dikeos DG. How do individuals sleep around the
547 world? Results from a single-day survey in ten countries. *Sleep Medicine*. 2005;6(1):5-13.
548 doi:10.1016/j.sleep.2004.10.006

549 66. Berson DM, Dunn FA, Takao M. Phototransduction by Retinal Ganglion Cells That Set
550 the Circadian Clock. *Science*. 2002;295(5557):1070-1073. doi:10.1126/science.1067262

551 67. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms,
552 sleep and affect. *Nature Reviews Neuroscience*. 2014;15(7):443-454. doi:10.1038/nrn3743

553 68. Hashizaki M, Nakajima H, Shiga T, Tsutsumi M, Kume K. A longitudinal large-scale
554 objective sleep data analysis revealed a seasonal sleep variation in the Japanese population.
555 *Chronobiology International*. 2018;0(0):1-13. doi:10.1080/07420528.2018.1443118

556 69. Kantermann T, Juda M, Merrow M, Roenneberg T. The Human Circadian Clock's
557 Seasonal Adjustment Is Disrupted by Daylight Saving Time. *Current Biology*.
558 2007;17(22):1996-2000. doi:10.1016/j.cub.2007.10.025

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Figure captions:

Figure 1. Mean values for actigraphically-measured sleep variables by location (Boston, MA and Tucson, AZ) and group (healthy control or mild traumatic brain injury (mTBI)). Bars are presented as estimated marginal means ± standard error based on the linear mixed models. †: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Figure 2. Coefficient of variation (CV) for actigraphically-measured sleep variables by location (Boston, MA and Tucson, AZ) and group (healthy control or mild traumatic brain injury (mTBI)). Bars are presented as estimated marginal means ± standard error based on the linear mixed models. †: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Figure 3. Relationship between sleep onset latency coefficient of variation (CV) and daytime sleepiness scores (Epworth Sleepiness Scale; ESS). A significant positive association between increased sleep onset latency intra-individual variability and self-reported daytime sleepiness was observed in both sites. No between site differences were observed.

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Table 1. Demographic characteristics, self-reported outcomes, and actigraphy measures by site and group				
	Boston		**Tucson**	
	HC	**mTBI**	**HC**	**mTBI**
N	24	28	11	29
Age (years)	25.8 ± 5.33	22.8 ± 7.16	19.9 ± 1.51[a***]	26 ± 8.22[b***]
Sex (M/F)	10/14	13/15	3/8	10/19
BMI (kg/m^2)	24.0 ± 3.72	25.4 ± 3.67	21.8 ± 3.66[a]	25.4 ± 6.26[b*]
Months post-injury		6.77 ± 3.97		9.21 ± 5.30
Mechanism of Injury (n)				
SRC[c]	-	17	-	7
MVA	-	5	-	13
Environmental[d]	-	4	-	4
Bicycle	-	1	-	2
Violence[e]	-	1	-	3
Participation month (n)				
January	2	1		1
February	4	4	3	1
March	4	6	6	2
April	1		2	3
May				1
June	1	6		4
July		3		3
August	1	1		1
September	1	2		7
October	4	2		2
November	5	2		2
December	1	1		2
Self-report Measures				
ESS Score	5.92 ± 3.82	10.2 ± 3.19 [f***]	5.55 ± 3.39	8.62 ± 3.24 [b*]
PSQI Total Score	-	7.14 ± 2.27	-	7.76 ± 3.24

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FOSQ Total Score	-	16.47 ± 1.95	-	15.90 ± 3.34
Actigraphy Measures				
Sleep duration				
Mean (min)	439.98 ± 38.99	407.51 ± 59.64	405.30 ± 68.59	425.55 ± 53.01
CV	0.16 ± 0.07	0.18 ± 0.08	0.17 ± 0.07	0.18 ± 0.08
SOL				
Mean (min)	8.98 ± 5.59	3.43 ± 2.53	10.13 ± 9.17	20.66 ± 14.27
CV	1.17 ± 0.39	1.40 ± 0.56	1.40 ± 0.44	1.04 ± 0.52
WASO				
Mean (min)	52.23 ± 17.64	56.39 ± 29.60	62.05 ± 37.18	52.36 ± 19.01
CV	0.39 ± 0.16	0.44 ± 0.24	0.43 ± 0.24	0.43 ± 0.37
SE				
Mean (%)	85.31 ± 3.78	85.94 ± 6.43	82.21 ± 7.93	82.24 ± 5.34
CV	0.06 ± 0.03	0.05 ± 0.04	0.09 ± 0.08	0.08 ± 0.04

Note. Values are provided as mean ± SD unless otherwise indicated. Two sample *t*-tests were used to identify significant differences between groups for continuous variables. PSQI and FOSQ outcomes were not recorded for the healthy control participants in Boston or Tucson. HC: Healthy Control; mTBI: Mild Traumatic Brain Injury; BMI: Body Mass Index; SRC: Sports-related concussion; MVA: Motor vehicle accident; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; FOSQ: Functional Outcomes of Sleep Questionnaire; CV: Coefficient of Variation; SOL: Sleep Onset Latency; WASO: Wake After Sleep Onset; SE: Sleep Efficiency

[a]Boston vs. Tucson HC

[b]Tucson mTBI vs HC

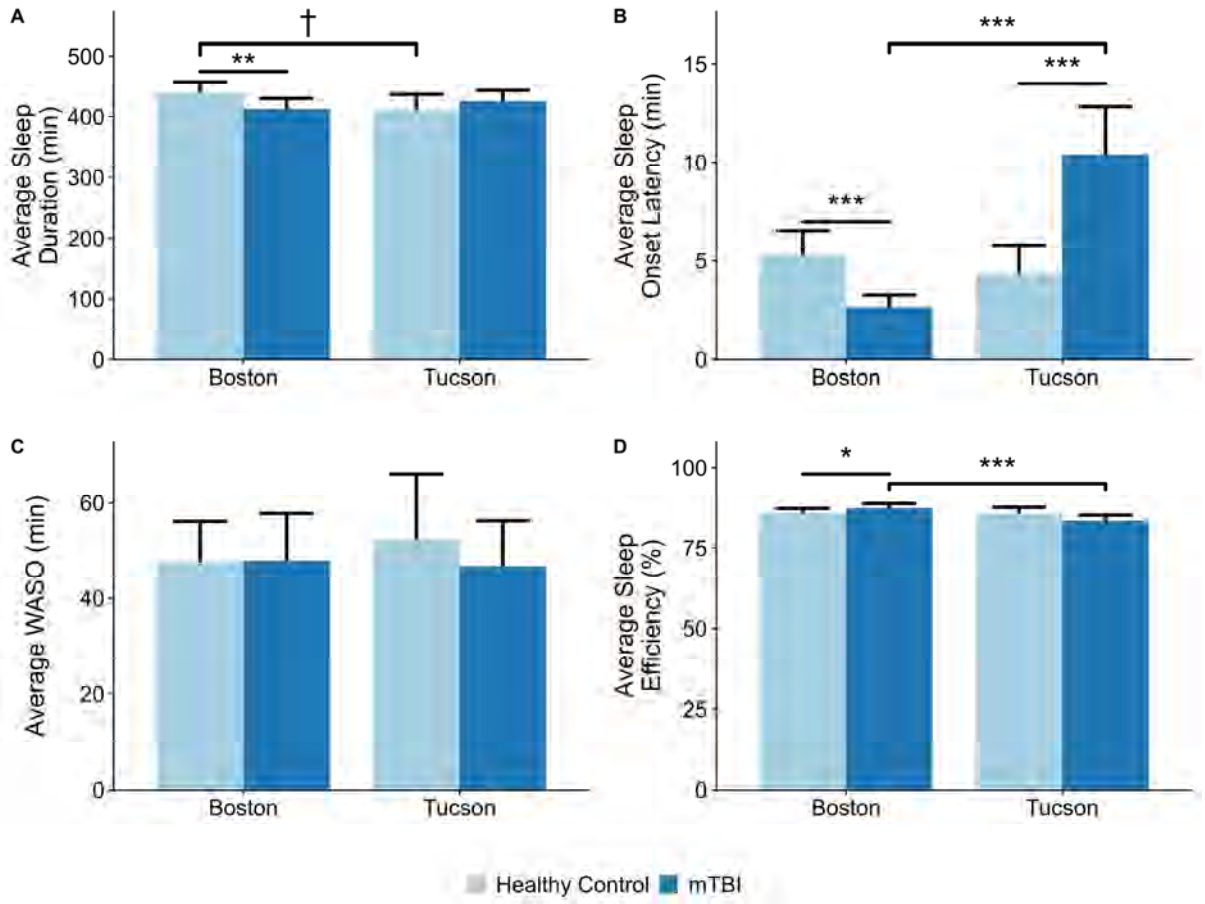
[c]Includes competitive and recreational (i.e. $n = 1$ boating accident) sports

[d]Includes contact with the environment due to slipping/tripping, alcohol-related mTBI, and falling objects

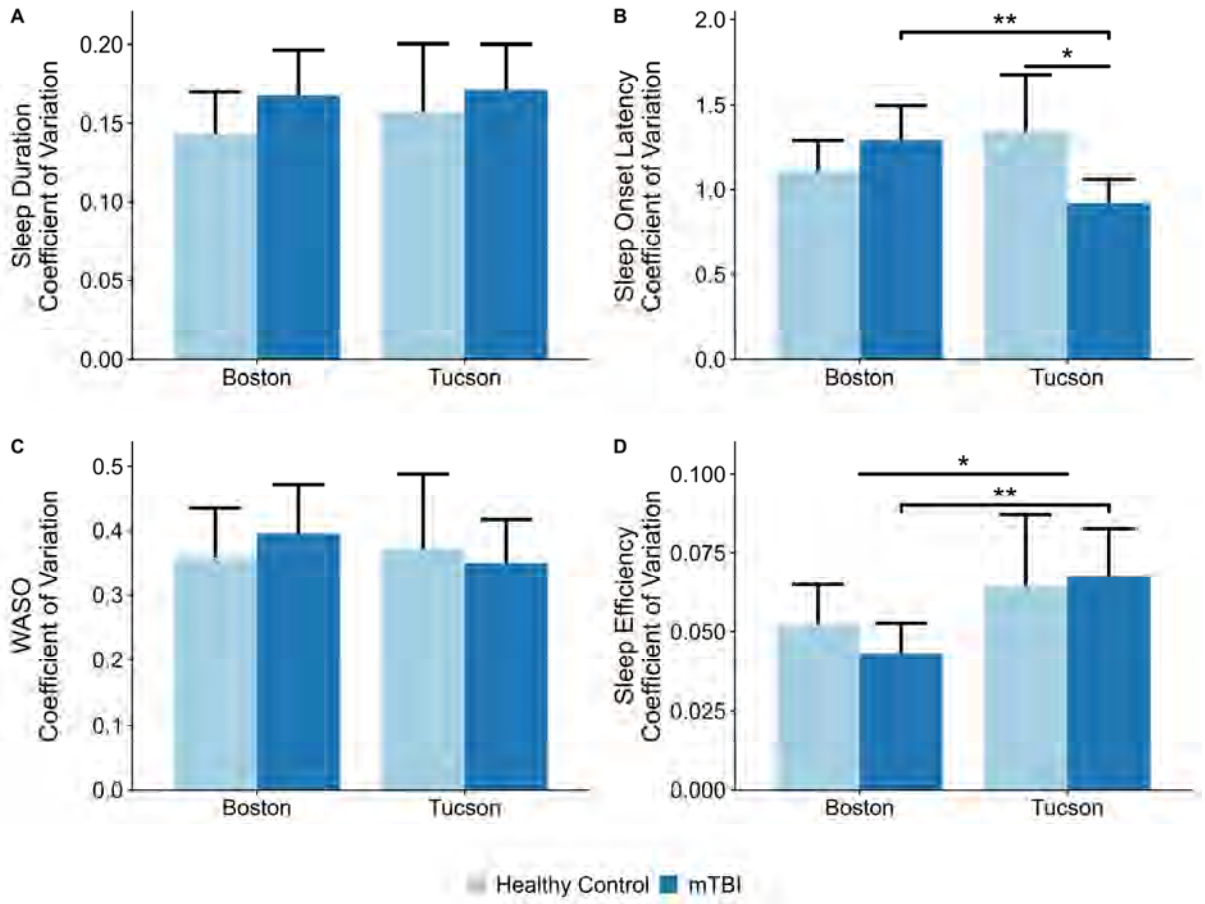
[e]Includes interpersonal violence and animal attacks

[f]Boston mTBI vs HC

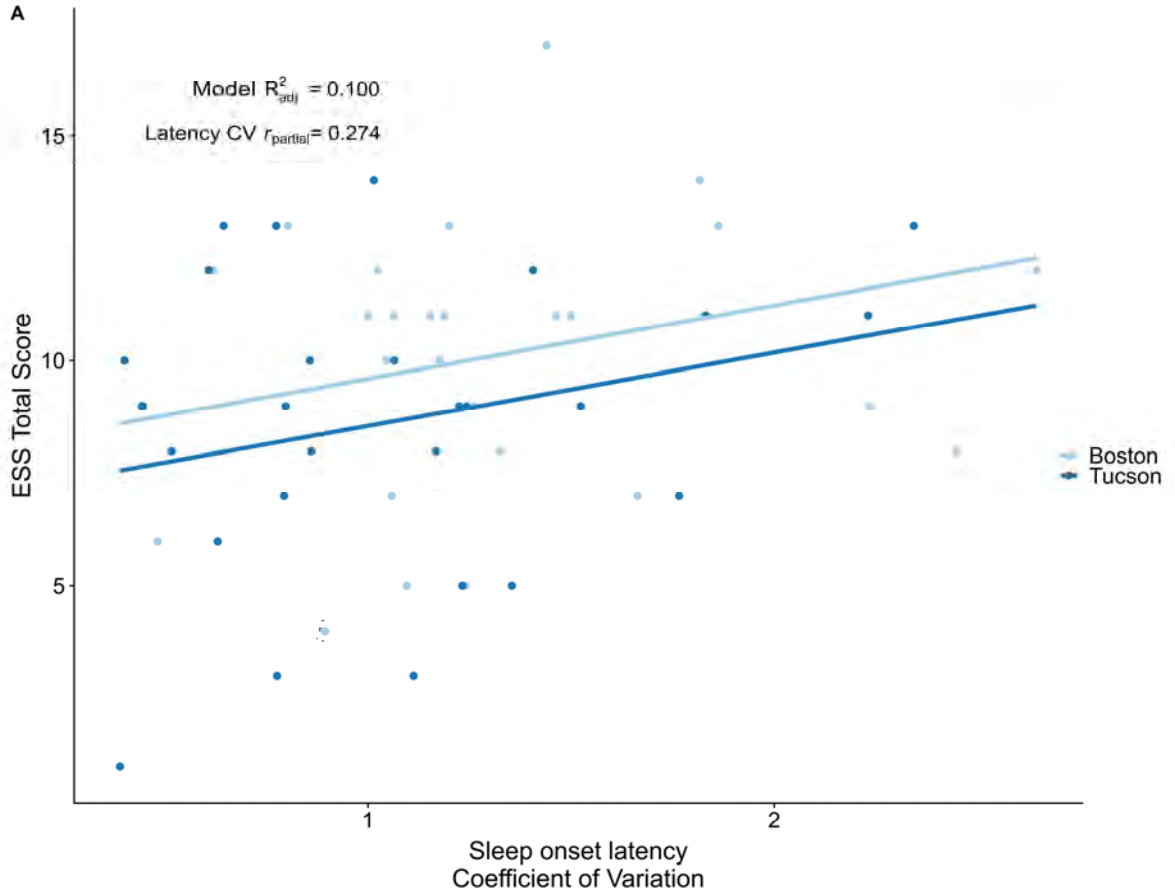
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$



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Highlights

- Daytime sleepiness and disrupted sleep are common after mild traumatic brain injury
- Sleep onset latency and sleep efficiency were susceptible to disruption after mTBI
- mTBIs were also associated with altered night-to-night sleep quality variability
- Consistent disruption patterns across independent samples were not evident
- Post-mTBI sleep disruption may not have a one-size-fits-all interpretation

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Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance

William D.S. Killgore, Haley C. Kent, Sara A. Knight and Anna Alkozei

Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle, with profound increases in circulating levels during the nighttime and nearly nonexistent levels during daylight hours. Although melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and executive function. We measured the change in salivary melatonin from mid-morning to late-morning in 26 healthy young adults who were also exposed to a 30-min period of blue or amber light followed by functional MRI during a working memory task (*N*-back). Brain activation was regressed on the change in melatonin scores from the mid-morning to late-morning saliva samples and the role of light exposure was also assessed. Although overall melatonin levels did not change significantly over the morning at the group level, individual declines in salivary melatonin were associated with significant increases in activation within the left dorsomedial and right inferior lateral prefrontal cortex during the 2-back condition ($P < 0.05$, cluster corrected). Medial prefrontal activation also correlated modestly with better vigilance performance during the 0-back ($P < 0.05$), but not the 1-back or 2-back conditions. The light condition did not affect the outcomes. These findings suggest declining melatonin levels in the morning are associated with increased prefrontal cortex functioning and may play a role in the increased frontal activation that occurs following awakening. *NeuroReport* **29:488–494** **Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

NeuroReport 2018, **29**:488–494

Keywords: functional magnetic resonance imaging, lateral prefrontal cortex, light exposure, medial prefrontal cortex, melatonin, neuroimaging, vigilance

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Received 12 February 2018 **accepted** 14 February 2018

Introduction

Nearly all living organisms demonstrate an innate biological rhythm that is closely entrained to the 24-h light/dark cycle produced by the Earth's rotation. Among mammals, this pattern is particularly notable in terms of the circadian rhythm of the circulating neurohormone melatonin [1]. For humans, melatonin secretion closely tracks the normal light/dark cycle, increasing in the evening near sunset and declining during the early morning hours before awakening, leading it to be dubbed the 'hormone of darkness' [2]. Although melatonin does not directly induce sleep, it appears to play a key role in preparing the brain for the sleep period [3]. Indeed, sleep onset is facilitated when melatonin levels are high, and there is evidence that increased melatonin is associated with more rapid sleep onset and longer sleep duration [4]. The circadian regulation of melatonin is directly tied to light exposure, and melatonin levels normally drop quickly in the early morning and remain at low to nonexistent levels throughout the light period of the day [1,3]. In fact, exposure to bright light, especially in the blue wavelengths, has been shown to actively suppress melatonin when administered soon after awakening in the morning, a finding that has been associated with improved alertness and vigilance [5].

The neurocognitive effects of melatonin are unclear and may depend on the time of day and body temperature. Early evidence suggested that circulating endogenous melatonin levels alone may not have a significant direct effect on cognition, but may have an indirect effect on logical reasoning, serial add/subtract, mental rotation, and choice reaction time by reductions in core body temperature [6]. Daytime administration of exogenous melatonin has been shown to increase self-rated sleepiness [7–9], and produce mild neurocognitive declines in psychomotor vigilance and attention [9,10], visual tracking speed, and spatial working memory [8]. The neural underpinnings of these effects, however, are still largely unknown. As melatonin is important for preparing the brain for sleep, we hypothesized that greater declines in salivary melatonin levels after awakening in the morning would be associated with increased functional activation responses and improved performance during a sustained working memory task using functional MRI (fMRI). Although any number of cognitive tasks could have been chosen for this study, we selected the classic *N*-back

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working memory task because it is one of the most widely used cognitive tasks in neuroimaging studies [11] and has previously been investigated for its association with cognitive processes associated with melatonin production, such as light exposure [12,13].

Participants and methods

Participants

Twenty-five (12 male; 13 female) right-handed, primary English speaking, healthy adults ranging in age from 18 to 32 years (mean = 22.2, SD = 3.7) provided multiple saliva samples and completed a neuroimaging scan (26 participants initially provided full data, but one male participant was dropped as an extreme outlier because of baseline melatonin levels exceeding 3 SDs from the sample mean). Participants were recruited from the metropolitan area of Tucson, Arizona, USA through posted flyers and internet advertisements and were screened to exclude any history of severe medical, neurological, or psychiatric conditions, head injury, alcohol or drug treatment, or current use of psychoactive drugs. Participants had obtained an average of 14.1 years (SD = 1.9) of formal education, and described themselves as normal sleepers, averaging 7.3 h (SD = 1.0) on weeknights, and 8.3 h (SD = 0.8) on weekends. The night before testing, participants self-reported sleeping an average of 7.0 h (SD = 0.4). Although we have published other data from this sample previously [12,14], the current paper presents novel data on a subset of participants who also provided salivary melatonin data. The analyses reported herein linking change in melatonin levels with brain activation are novel and have not been reported previously. This project was reviewed and approved by the University of Arizona College of Medicine Institutional Review Board and the US Army Human Research Protections Office.

Materials and procedure

A detailed description of the study methods is provided elsewhere [12]. Briefly, participants began the study at 0945 by sitting in a dimly lit room for 30-min (i.e. light washout), with ambient lighting provided by two amber light exposure devices, which were activated on the desk in front of participants and located 45° to the left and right of center, ~80 cm from the participant's nasion (Fig. 1). The light devices consisted of a plastic table-mounted chassis with a 10 × 6 array of light emitting diodes peaking at λ of 578 nm, at 188 Lx, and total irradiance (mW/cm^2) of 0.35, encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover (i.e. the housing was the same as the Philips goLITE BLU Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, Connecticut, USA). At the outset of this light washout session, participants also provided a saliva sample (MEL1).

At 1015, while seated in same location, participants completed an additional 30-min bright light exposure period (Fig. 1) in which they were exposed to an array of four devices fitted with either amber (n = 11), or four identical appearing fitted with blue wavelength light emitting diodes (peaking at λ = 469 nm, at 214 Lx, and panel irradiance (mW/cm^2) = 1.23 at 20 cm; n = 14). At 1045, the light period ended and participants provided a second saliva sample (MEL2), donned amber colored glasses (to block ambient blue light), and were escorted to the MRI scanner room next door, where they underwent fMRI while completing an *N*-back working memory task. At the completion of the fMRI scan, participants exited the scanner and provided a third saliva sample (MEL3) at 1245.

Melatonin assay and analysis

All materials for salivary melatonin collection were acquired from Salimetrics (State College, Pennsylvania, USA). Saliva was collected by passive drool method and stored in a 2 ml cryovial made of polypropylene. Within 3 min of collection, samples were placed in a Styrofoam cooler with ice packs and subsequently transferred to and stored in a freezer set and monitored to maintain sample storage at a temperature of −20°C. Samples were analyzed using Salimetrics Salivary Melatonin EIA kits according to standard procedures (*https://www.salimetrics.com/assets/documents/1-3402n.pdf*).

Neuroimaging

N-back task

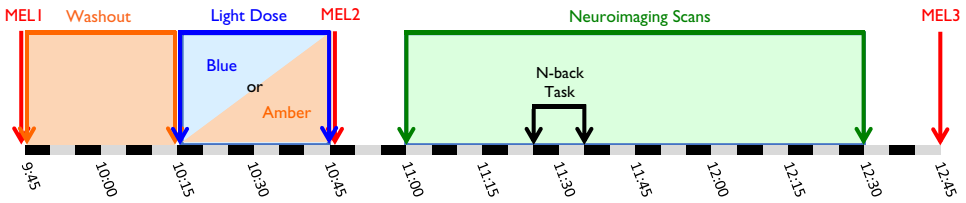
We used a variant of the visually presented *N*-back task [15] to assess working memory. Participants were presented with a black screen with centered white letters, appearing one at a time and were required to use the index or middle finger of their right hand to indicate whether the current letter presented was identical to the letter presented during the immediately preceding trial (1-back) or was identical to the letter presented two trials previously (2-back), or a control condition (i.e. 0-back), whereby they were asked to identify whether the letter on the screen matched a predetermined letter (e.g. 'P'). Each condition lasted 52 s and was repeated in a pseudorandom order. During each block, a crosshair fixation point was shown for 10 s, followed by the instructions for the next block (0-back, 1-back, or 2-back) for 6000 ms. During each trial, each letter was presented for 500 ms with a total of 1750 ms provided to respond to each item. The task concluded with a final crosshair screen for 10 s. The entire task lasted 7 min and 58 s.

Neuroimaging parameters

Neuroimaging data were collected on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were acquired using a T1-weighted three-dimensional MPRAGE sequence (TR/TE/flip angle = 2.1 s/2.33 ms/12°) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted fMRI scans were collected over 32 transverse slices and a

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Fig. 1



Overview of the study procedure. Between 9:45 a.m. and 10:15 a.m., participants completed 30 min of amber light 'washout' exposure period, followed by an additional 30 min of either amber placebo light or blue light exposure (i.e. between 10:15 a.m. and 10:45 a.m.). The neuroimaging scan began at 11:00 a.m. and the *N*-back task was initiated at 11:25 a.m., and ended at 11:33 a.m. Neuroimaging ended at 12:30 p.m. Participants provided a salivary melatonin sample (MEL) three times during the procedure, including just before the start of the washout period, immediately after the light exposure, and at 12:45 a.m. after exiting the functional MRI scanner.

slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/25.0 ms/90°) with 239 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

Image processing and statistical analysis

Processing and analysis was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; *http://www.fil.ion.ucl.ac.uk/spm*) following standard procedures [12], including realignment, unwarping, co-registration, normalization to Montreal Neurological Institute (MNI) coordinate space, spatial smoothing (6 mm full-width at half maximum), and reslicing to 2 × 2 × 2 mm voxels. Low-frequency confounds were removed with a high pass filter (128 s cutoff period). Motion artifacts were removed using the Artifact Detection Tool (*http://www.nitrc.org/projects/artifact_detect/*). Individual general linear models were specified to contrast activation relevant to working memory (i.e. 2-back > 0-back condition) and simple alertness and vigilance (i.e. 1-back > 0-back, 1-back > cross-hair fixation, and 0-back > cross-hair fixation point) for each participant.

Our interest was to examine the brain activation responses predicted by changes in salivary melatonin from prelight to postlight exposure. Therefore, melatonin data from the 0945 (MEL1) sample were subtracted from the mean of the 1045 (MEL2) and 1245 (MEL3) samples [i.e. (MEL2 + MEL3)/2 − MEL1] to derive a melatonin change score (MEL change). The individual contrast images for the *N*-back task, as described above, were entered as the dependent variable in an SPM12 linear regression analysis with MEL change as the independent variable. Significant clusters were identified by initially thresholding the statistical maps at *P* less than 0.001, and then applying a *P* less than 0.05 false discovery rate (FDR) cluster extent threshold. The data from significant clusters were extracted and transferred for further analysis in IBM SPSS 20 (IBM Corp., IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, New York, USA). Further regression analyses were conducted to determine the individual and combined effects of light exposure, MEL change, and their interaction on brain activation.

Results

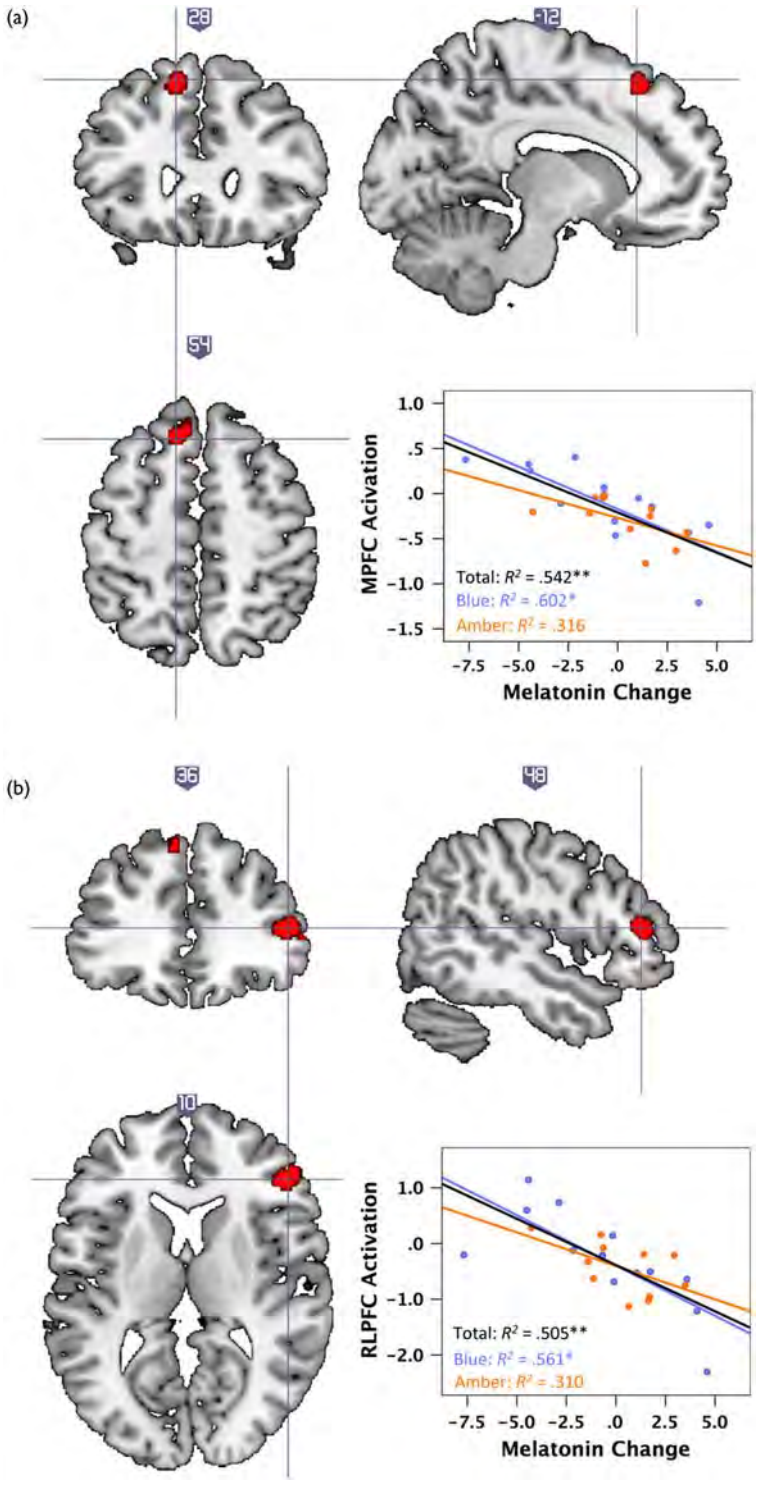
There was considerable individual variability in the magnitude and direction of change in melatonin across the morning, with 14 individuals showing a decline and 11 showing an increase from mid-morning to late-morning. Consequently, when the sample was considered as a whole, salivary melatonin levels did not decline significantly during the study period [MEL change, mean = −0.18, SD = 3.01, $t(24) = -0.31$, $P = 0.76$], and this change did not differ significantly between the blue (mean = −0.59, SD = 3.53) and amber (mean = 0.33, SD = 2.24) light groups, $t(23) = 0.75$, $P = 0.46$. Behaviorally, greater decline in melatonin levels was associated with marginally better throughput [i.e. the number of correct responses per second; (% correct/RT) × 1000] for the 0-back ($r = -0.32$. $P = 0.055$, one tailed), but not for the 1-back ($r = -0.22$, $P = -0.14$, one tailed) or 2-back ($r = -0.15$, $P = 0.23$, one tailed) conditions, suggesting that declines in melatonin were associated with improved vigilance.

Our primary hypothesis focused on the association between changes in melatonin and brain activation associated with working memory. However, it was first important to rule out any potential effects of melatonin change on simple vigilance performance. Thus, we first conducted three correlational analyses to examine the relation between melatonin change and brain activation for the pure vigilance (0-back > fixation), and low working memory load (1-back > fixation), and low working memory minus vigilance conditions (1-back > 0-back). At our a priori statistical threshold of *P* less than 0.001, with cluster correction of *P* less than 0.05, we found no activations that survived in any of these correlation analyses.

However, for our primary hypothesis regarding activation during high working memory load, the decline in melatonin levels during the morning was associated with increased task-related activation in two clusters within the prefrontal cortex for the 2-back > 0-back contrast

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Fig. 2



Three-dimensional views of the cortical regions showing significant ($P < 0.05$, false discovery rate cluster corrected) correlation with melatonin change for the contrast of interest (i.e. 2-back > 0-back), including (a) the left superior medial frontal gyrus (x, y, z: −12, 28, 54, respectively), and (b) the right inferior frontal gyrus (trigone region) (x, y, z: 48, 36, 10, respectively). The scatterplots show the association between melatonin change from baseline to the time of the scan and its association with prefrontal activation for the group as a whole (black line), and the blue and amber light conditions separately. *$P < 0.005$, **$P < 0.001$. MPFC, medial prefrontal cortex; RLPFC, rostrolateral prefrontal cortex.

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(Fig. 2). The first was a cluster ($k=75$) located within the left medial superior frontal gyrus (MNI coordinates: $x=-12$, $y=28$, $z=54$, $T=5.21$, $P=0.046$, FDR cluster corrected, Fig. 2a), and the second was a cluster ($k=76$) located within the right inferior frontal gyrus (MNI coordinates: $x=48$, $y=36$, $z=10$, $T=4.85$, $P=0.046$, FDR cluster corrected, Fig. 2b). As shown in the scatterplots of Fig. 2, MEL change accounted for more than 50% of the variance in brain responses in these two regions.

Activation within the medial prefrontal cortex cluster was significantly associated with better throughput (i.e. correct responses per second) performance on the 0-back ($r=0.34$, $P=0.047$, one tailed), and marginally so for the 1-back ($r=0.29$, $P=0.08$, one tailed), but not the 2-back ($r=0.22$, $P=0.14$, one tailed) conditions. The activation cluster in the lateral prefrontal cortex was not significantly associated with any level of *N*-back performance (all rs <0.25).

It was also of interest to determine whether the associations between MEL change and brain activation differed as a function of the light exposure. We, therefore, conducted a stepwise multiple linear regression analysis to evaluate the contribution of the light category to the models. For the first cluster, located in the left medial superior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (change in $R^2=0.016$, $P=0.38$) above and beyond the effects of MEL change, and the addition of the light condition × MEL change interaction term also did not contribute significant prediction to the model (change in $R^2=0.013$, $P=0.44$). Similarly, for the second cluster located in the right inferior frontal gyrus, the addition of light category to the model led to no significant improvement in R^2 (change in $R^2<0.001$, $P=0.998$), and the addition of the light condition × MEL change interaction term also did not contribute significantly to the model (change in $R^2=0.012$, $P=0.45$).

Discussion

Changes in morning salivary melatonin over a 3-h period were associated with reliable differences in prefrontal brain activation during a sustained working memory task, even after removing activation associated with simple vigilance. For those individuals showing the greatest decline in melatonin over the course of the morning, there was correspondingly greater brain activation within the left medial superior frontal gyrus, a region involved in vigilance, self-monitoring, conflict monitoring, and response action selection [16–18], and the right inferior frontal gyrus, a region involved in working memory and cognitive control [19]. However, those individuals showing increases in melatonin levels during the same 3-h time period showed correspondingly lower task-related activation responses in these same regions. It is interesting that changes in melatonin levels were not directly associated with brain responses during the simple vigilance components of the task, but were associated with activation specific to the working memory components of the task. It is also interesting that the melatonin-related activation in medial prefrontal cortex, whereas only apparent for the working memory condition, was modestly associated with better performance on the simplest vigilance condition of the *N*-back task, but not for the performance of the more demanding working memory conditions. This suggests that the greater activation of this area may still indirectly play a role in vigilance processes and would be an important topic for further exploration. Finally, we also found that the slopes of these associations were not differentially affected by the administration of an intervening half-hour pulse of blue or amber light, suggesting that the general association between melatonin changes and brain function is robust and reliable regardless of recent light exposure.

Melatonin has long been known as the 'hormone of darkness' [2], and is believed to play a role in preparing the brain for sleep [20]. Acute melatonin administration has a soporific effect, generally reducing vigilance levels [10] and facilitating sleep onset [4,21]. For example, a single 5 mg dose of melatonin administered during the early morning leads to a significant worsening of vigilance performance relative to placebo [10]. Among individuals with a normal sleep/wake rhythm, circulating melatonin levels drop rapidly in the early morning hours, remain near zero during the typical daylight waking period, and rapidly increase in the early evening as natural sunlight recedes and blue wavelengths of light are minimized [1]. There is, however, considerable variation in individual timing of endogenous melatonin onset and offset [22,23], and very little is known about how melatonin levels relate to brain activation. Early work showed that exogenous administration of melatonin led to decreased activation within the visual cortex during a visual search task and decreased activation within the auditory cortex during a music perception task, both of which correlated with self-reported fatigue [20]. A later study by the same group confirmed the association of decreased occipital cortex activation on a visual search task in response to exogenous melatonin administration during the late afternoon [24]. These studies, however, only focused on late day associations between melatonin administration and brain function. A recent study examined the circadian modulation of brain activation across the entire day and night to a psychomotor vigilance task and an *N*-back task similar to the one used here [25]. The *N*-back data from their study showed that cortical responses within the insula were tightly coupled with melatonin levels and showed increased functional brain activation as morning melatonin levels declined, a finding consistent with our results. Here, we expand on those results by showing that the magnitude of the decline in melatonin observed over a 3-h period in the morning is significantly correlated

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with greater task-related activation in the medial prefrontal cortex and right lateral inferior frontal cortex.

We interpret these melatonin-neuroimaging data as reflecting differences in circadian phase among individuals. Specifically, we speculate that those individuals who showed the largest declines in melatonin were those who were the most phase delayed (i.e. late risers whose melatonin was still relatively high at the outset of the study and thus dropped more precipitously relative to the early risers whose melatonin was already at a relatively low point at the start of testing). This interpretation would be consistent with previous work showing that the process of awakening involves increased metabolic activity within the prefrontal cortex [26]. Additional research will be necessary to determine whether the changes in melatonin play a causal role in the pattern of brain activation or are simply correlated with increased prefrontal activation during the awakening process.

Findings from this study need to be considered in the context of potential methodological limitations. First, melatonin samples were collected at only a few time points, so it is not possible to determine the precise circadian phase of the participants. Although all participants self-reported normal bed-times and wake-times, and normal sleep the night before the study, it is possible that some may display extreme chronotypes or arrived more sleep deprived than reported. Second, we found that blue light had no appreciable effect on melatonin, despite considerable evidence that morning short wavelength light exposure suppresses morning melatonin [27]. However, our data collections occurred late in the morning, and melatonin levels are likely to have already dropped close to their nadir, minimizing any appreciable suppressive effect of blue light.

Conclusion

Changes in morning salivary melatonin were associated with functional brain responses during a working memory task. The magnitude of the decline in salivary melatonin during the late-morning hours was associated with increased brain activation within dorsomedial and lateral prefrontal cortex, brain regions involved in vigilance, action selection, and cognitive control. These changes were modestly associated with improved vigilance performance during the task, but not with complex executive function. These findings suggest that changes in morning melatonin levels are associated with differences in prefrontal cortex functioning. We interpret these associations as reflecting individual differences in circadian phase of melatonin and their potential impact on the morning establishment of prefrontal functioning in the hours following awakening.

Acknowledgements

This work was supported by a grant from the US Army Medical Research and Materiel Command to WDSK (W81XWH-14-0571) and an Arizona Area Health Education Centers (AzAHEC) Research Grant to AA.

Conflicts of interest

There are no conflicts of interest.

References

1 Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. *Ann Clin Biochem* 2006; **43** (**Pt 5**): 344–353.
2 Utiger RD. Melatonin – the hormone of darkness. *N Engl J Med* 1992; **327**:1377–1379.
3 Cajochen C, Krauchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 2003; **15**:432–437.
4 Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, *et al*. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev* 2005; **9**:41–50.
5 Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J Clin Endocrinol Metab* 2003; **88**:4502–4505.
6 Slotten HA, Krekling S. Does melatonin have an effect on cognitive performance? *Psychoneuroendocrinology* 1996; **21**:673–680.
7 Arendt J, Borbely AA, Franey C, Wright J. The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neurosci Lett* 1984; **45**:317–321.
8 Rogers NL, Kennaway DJ, Dawson D. Neurobehavioural performance effects of daytime melatonin and temazepam administration. *J Sleep Res* 2003; **12**:207–212.
9 Crowley SJ, Eastman CI. Melatonin in the afternoons of a gradually advancing sleep schedule enhances the circadian rhythm phase advance. *Psychopharmacology (Berl)* 2013; **225**:825–837.
10 Ghattassi K, Hammouda O, Graja A, Boudhina N, Chtourou H, Hadhri S, *et al*. Morning melatonin ingestion and diurnal variation of short-term maximal performances in soccer players. *Physiol Int* 2016; **103**:94–104.
11 Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 2005; **25**:46–59.
12 Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, *et al*. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* 2016; **39**:1671–1680.
13 Munch M, Linhart F, Borisuit A, Jaeggi SM, Scartezzini JL. Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. *Behav Neurosci* 2012; **126**:196–203.
14 Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PLoS ONE* 2017; **12**:e0184884.
15 Gevins A, Cutillo B. Neuroelectric evidence for distributed processing in human working memory. *Electroencephalogr Clin Neurophysiol* 1993; **87**:128–143.
16 Hinds O, Thompson TW, Ghosh S, Yoo JJ, Whitfield-Gabrieli S, Triantafyllou C, *et al*. Roles of default-mode network and supplementary motor area in human vigilance performance: evidence from real-time fMRI. *J Neurophysiol* 2013; **109**:1250–1258.
17 Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, Carter CS. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn* 2004; **56**:129–140.
18 Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proc Natl Acad Sci USA* 1993; **90**:873–877.
19 Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 2004; **8**:170–177.
20 Gorfine T, Assaf Y, Goshen-Gottstein Y, Yeshurun Y, Zisapel N. Sleep-anticipating effects of melatonin in the human brain. *Neuroimage* 2006; **31**:410–418.
21 Pires ML, Benedito-Silva AA, Pinto L, Souza L, Vismari L, Calil HM. Acute effects of low doses of melatonin on the sleep of young healthy subjects. *J Pineal Res* 2001; **31**:326–332.
22 Burgess HJ, Fogg LF. Individual differences in the amount and timing of salivary melatonin secretion. *PLoS One* 2008; **3**:e3055.
23 Crowley SJ, Van Reen E, LeBourgeois MK, Acebo C, Tarokh L, Seifer R, *et al*. A longitudinal assessment of sleep timing, circadian phase, and

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phase angle of entrainment across human adolescence. *PLoS One* 2014; **9**:e112199.
24 Gorfine T, Zisapel N. Late evening brain activation patterns and their relation to the internal biological time, melatonin, and homeostatic sleep debt. *Hum Brain Mapp* 2009; **30**:541–552.
25 Muto V, Jaspar M, Meyer C, Kusse C, Chellappa SL, Degueldre C, *et al*. Local modulation of human brain responses by circadian rhythmicity and sleep debt. *Science* 2016; **353**:687–690.
26 Balkin TJ, Braun AR, Wesensten NJ, Jeffries K, Varga M, Baldwin P, *et al*. The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. *Brain* 2002; **125** (**Pt 10**):2308–2319.
27 West KE, Jablonski MR, Warfield B, Cecil KS, James M, Ayers MA, *et al*. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J Appl Physiol (1985)* 2011; **110**:619–626.

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RESEARCH ARTICLE

Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance

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Citation: Alkozei A, Smith R, Dailey NS, Bajaj S, Killgore WDS (2017) Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. PLoS ONE 12(9): e0184884. https://doi.org/10.1371/journal.pone.0184884

Editor: Etsuro Ito, Waseda University, JAPAN

Received: June 20, 2017

Accepted: September 3, 2017

Published: September 18, 2017

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by a U.S. Army US Army MOMRP Grant (W81XWH-11-1-0056) as well as by an Arizona Health Education Centers (AHEC) Research Grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Acute exposure to light within the blue wavelengths has been shown to enhance alertness and vigilance, and lead to improved speed on reaction time tasks, possibly due to activation of the noradrenergic system. It remains unclear, however, whether the effects of blue light extend beyond simple alertness processes to also enhance other aspects of cognition, such as memory performance. The aim of this study was to investigate the effects of a thirty minute pulse of blue light versus placebo (amber light) exposure in healthy normally rested individuals in the morning during verbal memory consolidation (i.e., 1.5 hours after memory acquisition) using an abbreviated version of the California Verbal Learning Test (CVLT-II). At delayed recall, individuals who received blue light (n = 12) during the consolidation period showed significantly better long-delay verbal recall than individuals who received amber light exposure (n = 18), while controlling for the effects of general intelligence, depressive symptoms and habitual wake time. These findings extend previous work demonstrating the effect of blue light on brain activation and alertness to further demonstrate its effectiveness at facilitating better memory consolidation and subsequent retention of verbal material. Although preliminary, these findings point to a potential application of blue wavelength light to optimize memory performance in healthy populations. It remains to be determined whether blue light exposure may also enhance performance in clinical populations with memory deficits.

Introduction

Short-wavelength light exposure (~480nm, blue light) plays multiple important roles in biopsychological functioning. Specifically, in addition to its role in conscious visual perception through the lateral geniculate nucleus and projection to primary and secondary visual cortex, light exposure can also influence the timing of circadian rhythms, the magnitude of alertness, and quality and duration of sleep through a secondary non-image forming light response system [1, 2]. When light strikes the retina, the blue wavelengths specifically stimulate intrinsically photosensitive retinal ganglion cells (ipRGCs), which respond by transmitting irradiance

signals to a number of sub-cortical nuclei, including the the suprachiasmatic nucleus (SCN) and other nuclei of the hypothalamus. The SCN serves as the body's master clock and regulates the production of melatonin (a hormone secreted by the pineal gland that prepares the brain for sleep) and circadian rhythms of sleep and wake [2]. In addition, the SCN has projections to the locus coeruleus (LC) in the brain stem [3]. Acute short bursts of exposure to blue wavelength light have been shown to increase activation in the brainstem, in an area consistent with the brain coordinates of the LC [4]. Importantly, stimulation of the LC has been shown to promote greater release of norepinephrine throughout the cerebral cortex [5], which in turn influences a variety of brain functions including alertness [6]. It has therefore been proposed that blue light may activate the LC through projections from the SCN, and that such stimulation of the LC may lead to increased norephineprhine release throughout the brain which in turn increases alertness [4].

Blue light exposure (or bright light more generally) at night leads to increases in subjectively and objectively measured alertness and vigilance, likely as a consequence of suppression of melatonin production [7±9]. However, studies have also shown that blue light (or blue-enriched white light) exposure during the day, a time when melatonin levels are naturally low, also leads to an increase in alertness and vigilance, as well as improvements in working memory performance [10±12]. For example, we have recently shown that 30 minutes of exposure to blue versus amber (placebo) wavelength light during the day led to *subsequently* faster performance on a working memory task (i.e., 45 minutes after light exposure) and increased functional brain responses in regions that are important for working memory processes, such as the dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC) [10]. This alerting effect has even been demonstrated in visually blind individuals, further suggesting that it is produced by activation of the non-image forming ipRGCs [13]. The mechanisms underlying this alerting effect remain to be fully elucidated but one potential explanation that has been proposed as a result of these findings involves the potential stimulating effect of blue light on the LC, leading to increased noradrenergic activation within other areas of the brain (i.e., the PFC), resulting in increased alertness and speed of responding [4, 10].

While studies have shown that blue light increases performance in both simple reaction time tasks and in working memory tasks, it is unclear whether other aspects of cognition may also be affected. Long-term memory (LTM), in particular, is a critical aspect of cognition that could potentially be affected above and beyond the simple effects of blue light on alertness. Although the effects of blue light exposure on memory have not been studied, evidence suggests that norepinephrine has a positive effect on memory consolidation (i.e., the period after memory acquisition) [for a review see 14]. In particular, a number of animal studies have shown that increases in norepinephrine (as a result of drug administration) after memory acquisition led to better LTM [14, 15]. Importantly, the timing of norepinephrine administration appears to play a crucial role, but the optimal timing of stimulation to enhance LTM is unclear and may depend specifically on the type of memory studied. However, it appears that noradrenergic influences are particularly prominent during later stage memory consolidation processes. For example, studies have shown that rats who were administered beta blockers 2 hours after memory acquisition showed amnesia 48 hours later, whereas no effect was seen when beta blockers were administered 5 minutes after learning [16, 17].

In summary, daytime exposure to blue light has been shown to activate functional brain responses in brainstem areas consistent with the LC, a region which, when stimulated, has been shown to release norepinephrine throughout the brain. Because increased norepinephrine during memory consolidation is known to improve memory due to neuromodulatory effects on multiple LTM-related brain areas, it follows that blue light exposure may therefore enhance memory performanceÐa prediction that remains untested to date. To fill this critical

gap in knowledge, we therefore tested the hypothesis that daytime exposure to blue wavelength light for 30 minutes during memory consolidation (~1.5 hours after encoding) would lead to better verbal LTM performance when compared to equal exposure to a placebo (amber) light.

Materials and methods

Participants

Thirty healthy 18±32 year olds (17 female; mean age = 21.87± 3.74) took part in the study. Participants were all right handed, native English speakers, free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 10pm and 1am and waking between 6am and 9am. Participants self-reported that they obtained, on average, 6 hours and 45 minutes (SD = 49 minutes) of sleep the night preceding the day of testing.

California Verbal Learning Test, Version II (CVLT-II)

The CVLT-II [18] is an individually administered test of verbal memory and associated cognitive processes. Participants completed the immediate recall, short-delay, and long-delay free recall parts of the CVLT-II. Participants were read a list of words and told they would be asked to repeat as many words as possible. This test-recall procedure was repeated 5 times (*immediate recall*, *trials 1–5*). The list consisted of 15 neutral words evenly divided into the following categories: animals, furniture, vegetables, and modes of transportation. After the 5^{th} trial, participants were read a second list (i.e., distractor list) and asked to repeat only words from the second list. Immediately following recall of the second list, participants were asked to recall only words presented in initial list (*short-delay free recall*). Approximately 1.5 hours after the short-delay free recall subtest, participants were asked to recall as many words from the initial list (*long-delay recall*). Raw scores (i.e., total number of words recalled) as well as standard scores (i.e., raw scores converted to norm-referenced scores) were calculated for each trial.

Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI-II) [19] is a 21-item self-report questionnaire used to assess depressive symptoms over the preceding 2 weeks. The BDI-II has been shown to have good psychometric properties [19]. Scores of 13 or higher have been shown to discriminate well between clinical and non-clinical populations, therefore only participants who scored lower than 13 on the BDI-II were eligible for this study [20]. BDI-II scores were nevertheless included as a covariate in the analysis, as depressive symptoms have consistently been shown to influence CVLT-II performance [18].

Two-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI-FSIQ)

The Full Scale-II Wechsler Abbreviated Scale of Intelligence (WASI-II FSIQ) [21] was used as a measure of intellectual ability or ªIQº. The WASI-II FSQI is one of the most widely used intelligence scales and correlates highly (r = .92) with the Wechsler Adult Intelligence Scale-III (WAIS; Pearson Assessment, Inc., San Antonio, TX) [21]. The instrument yields scores for Full Scale IQ, Verbal IQ, and Performance IQ. The WASI-II FSQI was individually administered by a trained research technician under the supervision of a licensed doctoral level neuropsychologist. WASI-II FSQI scores were used as a covariate in the analysis, as IQ has been shown to influence performance on the CVLT-II [18].

Light exposure protocol

The light exposure protocol is described in detail in Alkozei et al. (2016) [10]. In brief, all participants began with a half-hour blue light Washout Period (described in more detail under Procedure) that involved sitting in a dark room while only exposed to two amber light devices (described below) mounted on a desk at a distance of approximately 80 cm from the participant's nasion, with each light centered at a 45 degree angle from midline (see Fig 1A). During the Exposure Period, light was administered by a similar configuration of four light devices, also centered at 45 degrees to each side of the participant with a distance of approximately 80 cm from the participant's nasion (see Fig 1B). In the Exposure Period, participants were randomly assigned to undergo a half hour of exposure to an array of either blue or amber light devices. Blue light exposure utilized an array four of commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). Each device consisted of a plastic table-mounted chassis with a 10 x 6 array of light emitting diodes (LEDs),

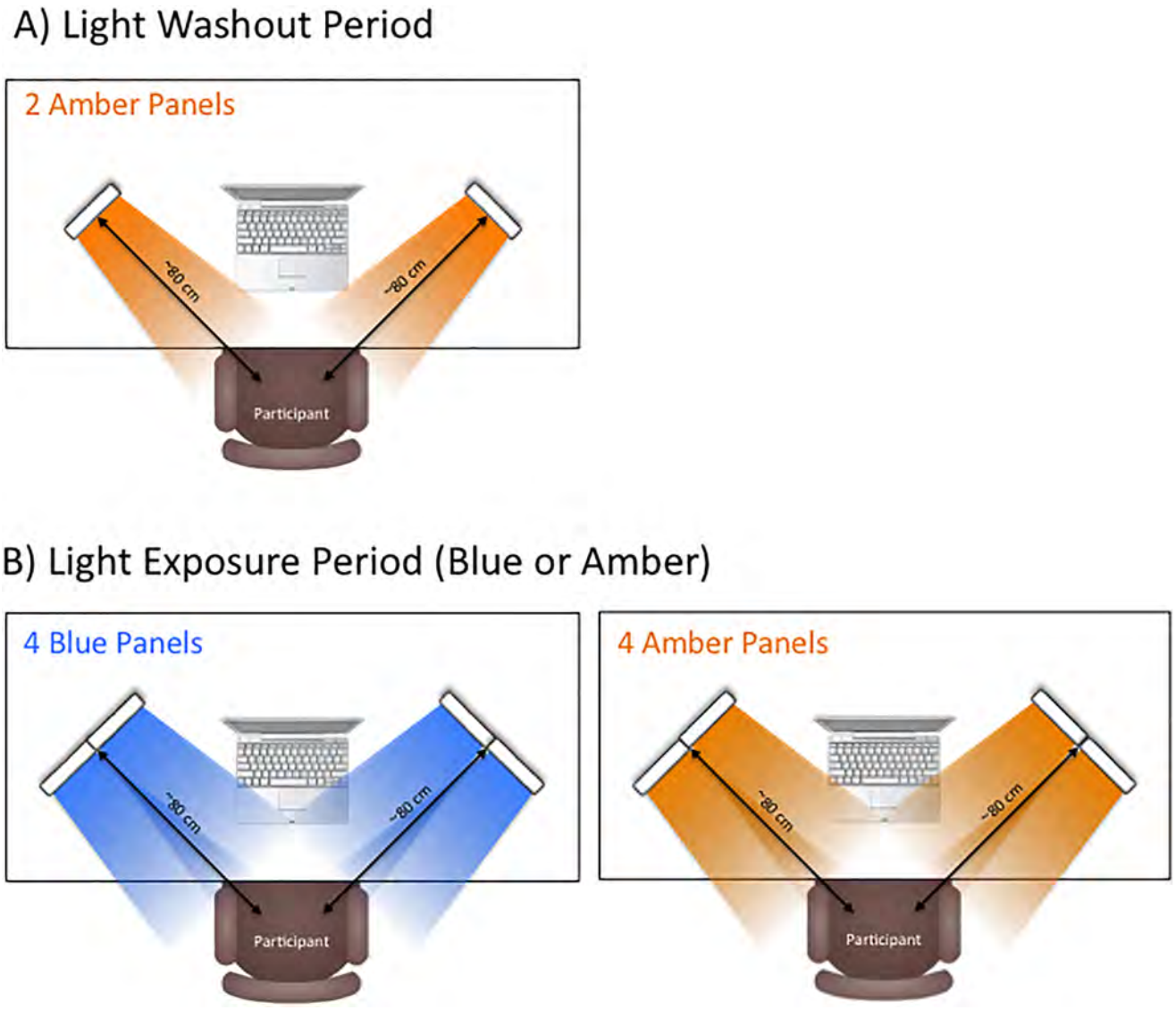


Fig 1. Illustration of the light exposure study design set-up.

https://doi.org/10.1371/journal.pone.0184884.g001

encased in 1 x 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU Energy Light is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and single panel irradiance (mW/cm^2) = 0.11 at 80 cm). The amber placebo devices were provided by the manufacturer for research purposes and were essentially identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and panel irradiance (mW/cm^2) = 0.04 at 80 cm).

Procedure

While participants completed the study on an individual basis, all participants were tested at the same time of day to control for circadian time-of-day effects. To avoid potential caffeine withdrawal effects, participants were asked to consume their normal levels of morning caffeine before arrival for the study at 0745. For the first portion of the day, participants completed the informed consent process, basic information questionnaires, and cognitive tasks. At approximately 0905, participants were administered the first 5 encoding trials and the short-delay recall portion of the CVLT-II. Participants were then randomized to receive either 30 minutes of blue (n = 12) or amber (n = 18) light exposure. At approximately 0945, participants underwent the [a]blue light washout[o] period (see above) for 30 minutes to ensure that residual effects of outdoor and ambient lighting dissipated before the beginning of the light exposure period. At 1015, the two Washout Period light devices were replaced with the four Exposure Period devices (i.e., either blue or amber). During the two light exposure periods, participants completed a number of computerized tasks. The laptop monitors were fitted with an amber colored Plexiglas panel to block blue wavelength light. At approximately 1100, participants were asked to complete the long delay portion of the CVLT-II. Fig 2 illustrates the timeline of the study design.

Ethical considerations

The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office. All participants provided written informed consent.

Data analysis

Change in performance from CVLT-II short-delay free recall to long-delay free recall raw and standard scores between the blue and amber light exposure groups were analyzed using

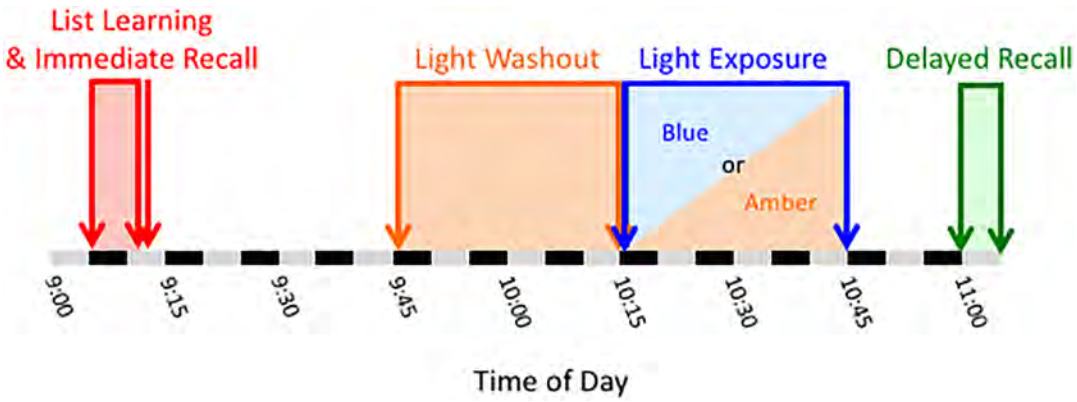


Fig 2. Illustration of the study timeline.

https://doi.org/10.1371/journal.pone.0184884.g002

repeated-measures analysis of covariance (ANCOVA), using WASI-FSQI and BDI-II scores as covariates. As the two groups differed in habitual wake time (see Results section below), we also included habitual wake times as an additional covariate.

Results

Preliminary analyses

In order to rule out any group differences prior to the light exposure, independent samples t-tests were conducted comparing performance on the CVLT-II between the blue and amber light group. There were no differences in standard scores on the CVLT between the two groups at trial 1 ($t(28) = .56$, $p = .57$), trial 5 ($t(28) = -1.29$, $p = .21$), or on total performance standard scores (sum of trials 1±5) ($t(28) = .17$, $p = .87$). These findings suggest that the two groups did not differ in their initial learning or retention of the word list prior to exposure to the light conditions.

In addition, the two groups did not differ in age, sex, sleep duration the night before the day of testing, number of caffeinated products consumed on the morning before testing, WASI-II FSQI total and Vocabulary subscale scores (see Table 1). Participants also did not differ on habitual bedtime, or habitual sleep duration. However, participants in the amber light group did report significantly earlier habitual wake times (7:20 am; SD = 60 min) than participants in the blue light group (8:07 am; SD = 54 min; $t(28) = -2.15$, $p = .04$), and it was therefore included as an additional covariate in the analyses below.

Hypothesis testing

The repeated-measures ANCOVA showed a significant main effect of time ($F(1, 25) = 5.06$, $p = .03$, $d = .09$) as well as a group x time interaction ($F(1, 25) = 4.39$, $p = .05$, $d = .84$). Post-hoc pairwise comparisons showed that while there was no significant difference from pre- to post-light exposure for the blue light group ($p = .13$), there was a significant decline in CVLT standard scores from pre- to post-light exposure for the amber light group ($p < .001$). However,

Table 1. Descriptive statistics.

	Blue light group n = 12	Amber light group n = 18	Statistic
Age	21.50 (3.34)	22.11 (4.07)	$t(28) = .42$
Sex	50% female	61% female	$\chi^2(1) = .36$
Sleep duration the night before (in hours)	6.87 (.71)	6.88 (.90)	$t(28) = .05$
Habitual bedtime	11:33pm (66 min)	11::16pm (55 min)	$t(28) = -.70$
Habitual waketime	8:07am (54 min)	7:20am (60 min)	$t(28) = -2.15$*
Habitual sleep duration (in hours)	7.54 (.78)	7.33 (1.02)	$t(28) = -.59$
Number of caffeinated products	1	3	$\chi^2(1) = .43$
WASI-FSQI	104.75 (12.82)	106.61 (11.50)	$t(28) = .68$
WASI-FSQI Vocabulary Subscale	54.28 (8.92)	54.75(9.62)	$t(28) = -.14$
BDI-II	1.75 (2.00)	2.94 (3.40)	$t(28) = 1.01$
CVLT-II Trial 1 standard score	0.42 (.86)	.28 (1.25)	$t(28) = .57$
CVLT-II Trial 5 standard score	.45 (.97)	.00 (.91)	$t(28) = -1.29$
CVLT Trial 1±5 standard score	55.83 (8.89)	56.39 (8.75)	$t(28) = .16$

WASI-FSQI: Wechsler Abbreviated Scale of Intelligence Full Scale-II; BDI-II: Beck Depression Inventory; CVLT-II: California Verbal Learning Test
*p <.05

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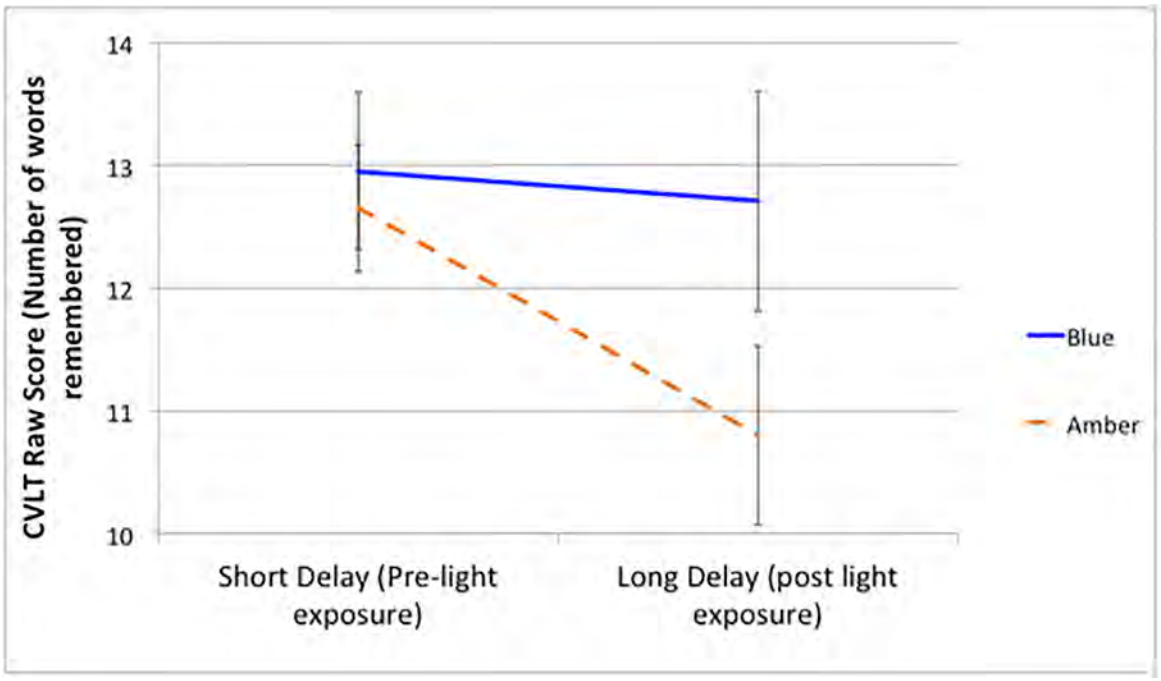


Fig 3. Estimated marginal means and error bars (1SE) for CVLT ±II short-delay and long-delay raw scores for individuals in the blue (n = 12) and amber (n = 18) light groups. CVLT-II: California Verbal Learning Test (Version 2).

https://doi.org/10.1371/journal.pone.0184884.g003

there was no significant difference between the two groups for CVLT long-delay recall scores ($p = .20$).

As standard scores can be difficult to interpret because they include corrections for age and gender, we re-ran the analysis using CVLT raw scores. While, there was no significant main effect of time ($F(1, 25) = 2.45$, $p = .13$, $d = .62$), there was a significant group x time interaction ($F(1, 25) = 4.50$, $p = .04$, $d = .85$). Fig 3 shows participants in the blue light group forgot an average of 0.19 words, whereas participants in the amber light group forgot an average of 1.88 words from short-delay to long-delay recall. This translates to an average decline of only 1.48% in delayed verbal recall for individuals receiving the active blue light treatment, but an average decline of 14.62% for individuals in the amber placebo light group.

Discussion

The aim of the present study was to investigate the effect of blue wavelength light exposure during memory consolidation on later memory performance in healthy participants. As expected, after learning a list of words, individuals who were exposed to 30 minutes of blue wavelength light during the consolidation period (approximately 1.5 hours after learning) showed greater memory retention than individuals who were exposed to an amber wavelength (placebo) light.

This effect of blue light exposure on memory consolidation was predicted based on its role in promoting activation of the LC [4] which, when stimulated, is known to increase norephinephine release throughout the brain [5]. Norephinephrine, in turn, has been shown to have beneficial effects on LTM systems, leading to enhanced recall [14, 22]. However, while our results provide some initial evidence that blue light exposure sustains better memory recall performance relative to placebo, and the previous literature provides a strong basis for our hypothesis regarding the potential underlying mechanisms, it is important to stress that we did

not directly assess neurotransmitter release or brain activation within the noradrenergic system in the present study. It therefore remains necessary for future work to determine whether the beneficial effect of blue light on memory is, in fact, explained by the proposed underlying neural mechanisms.

LTM is the outcome of successful learning and is crucial for normal cognitive functioning. The results from the present study raise the intriguing possibility that blue light exposure during the consolidation period might prove useful as a strategy to optimize the retention of verbal memory. In the present study, we found that those who were exposed to blue light during the consolidation period showed only a 1.48% decline in retention of previously learned words after two hours, compared to a 14.62% decline for those in the placebo group. If confirmed in future work, this strategy could be of potential benefit to nearly any population engaged in active learning, such as school-aged children, college students, vocational students, and those invested in learning even in later adulthood, just to name a few.

While not tested here, it is likely that blue light might also prove beneficial for individuals whose memory is compromised, due to disease or injury. In fact, our results complement a previous longitudinal study (average duration 15 months) that investigated the effects of continuous exposure to either bright light (1000 lux) or dim (300 lux) light in an elderly residential group facility [23]. Older adults who were continually exposed to bright light showed attenuated cognitive deterioration, as measured by the Mini Mental State Examination (MMSE), as well as diminished depressive symptoms when compared to individuals who were exposed to dim light. While the MMSE measures aspects of short-term and long-term memory, it also measures other aspects of cognitive functioning. It is therefore unclear whether bright light influenced learning and memory in particular, or whether other cognitive processes were also positively influenced. In addition, it is unclear how continuous exposure to bright light may influence memory and learning differently when compared to short, targeted exposure to blue wavelength light. Future studies will be necessary to investigate whether the beneficial effects of blue light exposure on memory would also be found using broad spectrum bright light (which contains a large proportion of light within the blue wavelengths), or whether longer durations of bright light exposure would be necessary to achieve the same effect as targeted blue light exposure specifically. However, these results provide promise that using blue (or broad spectrum bright) light may be useful in different settings where learning and memory are important. For example, blue light exposure could be implemented during memory training for elderly individuals, or it could be used selectively by students to improve memory for important test material. In addition, exposure to blue wavelength light from natural sun exposure may have similar beneficial effects on memory; however future research will be necessary to investigate whether the results from this study are also found in such naturalistic settings.

The results from this study focused specifically on the effects of blue wavelength light during memory consolidation (i.e., 1.5 hours after memory acquisition). The present study focused on brief, targeted, blue light exposure within the period where consolidation should be occurring, which resulted in no significant change in word retention and recall after a two hour delay, when compared to an amber placebo group which showed a significant decline in verbal memory performance. It may be that light exposure during memory consolidation is more adventatgeous than light exposure during the learning/encoding phase. However, this is an open question for further research, as it remains unclear whether blue light exposure before, during, or at different time points after learning would lead to similar or enhanced effects. Future studies will be necessary to conduct a systematic comparison of memory performance after blue light exposure at various time points. In addition, this study focused exclusively on verbal memory; thus, the effects of blue light exposure on other types of memory, such as visuo-spatial, temporal, or prospective memory, are unclear and require future investigation.

It has also been shown that gray matter volume changes across the menstrual cycle are associated with changes in verbal memory performance [24]. We did not control specifically for menstrual phase in our analyses, so it is conceivable that exposure to blue wavelength light could potentially have different effects for women at different stages of their menstrual cycle. In addition, while 30 minutes of blue wavelength light has been used as a standard duration of exposure across a number of studies [10, 25], it will be necessary to investigate the duration of exposure that is necessary or sufficient to improve memory performance.

One important consideration is the potential role of accumulated sleep debt on testing performance. The participants reported sleeping on average 6.8 hours the night before the assessment, which is slightly less than the recommended 7±8 hours per night for most healthy individuals. Other than self-reported sleep for the night before testing, there was no extensive assessment of pre-study sleep, so it is not possible to establish the extent of sleep debt or whether participants were in fact fully rested when they took part in the study. However, participants were randomly assigned to the treatment conditions, so this should not have influenced the effects of light. It is also worth considering that the study began at 7:40 in the morning, at a time proximal to most participants' habitual wake up time, suggesting that many individuals may have truncated their sleep time the day of the study. Further, the two groups differed slightly in terms of habitual wake times, with amber normally awakening about 47 minutes earlier on average relative to the blue group. Conceivably, this could have placed the blue group in a particularly suboptimal positioning for cognitive performance relative to the amber group. However, we controlled for this statistically in our analyses and this did not appear to affect the outcomes. As such, it is possible that blue light may in fact lead to enhanced effects particularly when sleep pressure is high. It is therefore unclear whether our findings are generalizable to situations where individuals had the opportunity to be fully rested.

It should also be mentioned that the two light conditions were not equated for light intensity. The light emitted from the blue light devices emitted nearly three times greater irradiance as the light from the amber devices, although they appeared similar in overall visual brightness and averge lux. It is therefore possible that the improvements in memory consolidation seen in the blue light group could be attributed to light intensity rather than light color. However, studies have shown that 50 second bursts of blue light specifically, in comparison to violet light of the same intensity, led to increases in functional brain activation in the LC, supporting our proposed mechanism [4]. Replications of our findings while comparing the effects of different wavelengths of light of the same intensity on memory consolidation are nevertheless needed. In addition, it has been shown that 15 minutes of exposure to orange versus blue wavelength light 1 hour before a second exposure to blue light increased functional brain responses within the prefrontal cortex during a working memory task [26]. It is therefore possible that exposure to amber light during the ªwashoutº period in the present study, led to an enhanced effect of blue light exposure during memory consolidation. This intriguing possibility should be investigated further. Finally, this study was conducted with a relatively small sample of healthy adults; future research will therefore be necessary to replicate these findings across larger sample sizes and perhaps even in clinical populations with memory impairments.

Conclusion

In summary, exposure to a half hour of blue wavelength light during memory consolidation led to better subsequent delayed verbal memory recall, when compared to an amber (placebo) light condition. These findings may have important implications for clinical populations with memory impairments, as well as for healthy individuals who want to improve their ability to

retain newly learned material. Considering this is the first study to investigate whether 30 minutes of blue light exposure can influence memory performance, future research will be necessary to confirm this effect, and to investigate the precise mechanisms, optimal dose/timing of administration, and possible application to clinical samples.

Supporting information

S1 Dataset. Dataset for analyses.
(SAV)

Author Contributions

Conceptualization: William D. S. Killgore.

Data curation: Anna Alkozei.

Formal analysis: Anna Alkozei.

Funding acquisition: William D. S. Killgore.

Investigation: Anna Alkozei.

Methodology: Anna Alkozei, William D. S. Killgore.

Project administration: William D. S. Killgore.

Resources: William D. S. Killgore.

Supervision: William D. S. Killgore.

Writing ± original draft: Anna Alkozei.

Writing ± review & editing: Ryan Smith, Natalie S. Dailey, Sahil Bajaj, William D. S. Killgore.

References

1. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 2002; 295(5557):1070±3. https://doi.org/10.1126/science.1067262 PMID: 11834835
2. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. PLoS Biol. 2009; 7(6): e1000145. https://doi.org/10.1371/journal.pbio.1000145 PMID: 19547745
3. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nature neuroscience. 2001; 4(7):732±8. https://doi.org/10.1038/89522 PMID: 11426230
4. Vandewalle G, Schmidt C, Albouy G, Sterpenich V, Darsaud A, Rauchs G, et al. Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. PloS one. 2007; 2(11):e1247. https://doi.org/10.1371/journal.pone.0001247 PMID: 18043754
5. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. Brain research. 1996; 742(1):89±97.
6. Foote S, Berridge C, Adams L, Pineda J. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Progress in brain research. 1991; 88:521±32. PMID: 1813932
7. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? PloS one. 2011; 6 (1):e16429. https://doi.org/10.1371/journal.pone.0016429 PMID: 21298068
8. Cajochen C, Munch M, Kobialka S, Krauchi K, Steiner R, Oelhafen P, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. The Journal of Clinical Endocrinology & Metabolism. 2005; 90(3):1311±6.
9. Lockley SW, Evans EE, Scheer F, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 2006; 29(2):161. PMID: 16494083

10. Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, et al. Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. Sleep. 2016; 39(9):1671±80. https://doi.org/10.5665/sleep.6090 PMID: 27253770

11. Rüger M, Gordijn MC, Beersma DG, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. American Journal of Physiology-regulatory, integrative and comparative physiology. 2006; 290(5):R1413±R20. https://doi.org/10.1152/ajpregu.00121.2005 PMID: 16373441

12. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scandinavian journal of work, environment & health. 2008:297±306.

13. Vandewalle G, Collignon O, Hull JT, Daneault V, Albouy G, Lepore F, et al. Blue light stimulates cognitive brain activity in visually blind individuals. Journal of cognitive neuroscience. 2013; 25(12):2072±85. https://doi.org/10.1162/jocn_a_00450 PMID: 23859643

14. McGaugh JL, Roozendaal B. Drug enhancement of memory consolidation: historical perspective and neurobiological implications. Psychopharmacology. 2009; 202(1±3):3±14. https://doi.org/10.1007/s00213-008-1285-6 PMID: 18704369

15. Tully K, Bolshakov VY. Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. Molecular brain. 2010; 3(1):15.

16. Tronel S, Feenstra MG, Sara SJ. Noradrenergic action in prefrontal cortex in the late stage of memory consolidation. Learning & Memory. 2004; 11(4):453±8.

17. Sara SJ, Roullet P, Przybyslawski J. Consolidation of memory for odor±reward association: β-adrenergic receptor involvement in the late phase. Learning & memory. 1999; 6(2):88±96.

18. Delis DC, Kramer J, Kaplan E, Ober BA. CVLT-II: California verbal learning test: adult version: Psychological Corporation; 2000.

19. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996; 78(2):490±8.

20. Lasa L, Ayuso-Mateos J, Vazquez-Barquero J, Dõez-Manriqıe F, Dowrick C. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. Journal of affective disorders. 2000; 57(1):261±5.

21. Wechsler D. WASI II: Wechsler Abbreviated Scale of Intelligence. 2nd. Psychological Corporation. 2011.

22. Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nature reviews neuroscience. 2009; 10(3):211±23. https://doi.org/10.1038/nrn2573 PMID: 19190638

23. Riemersma-Van Der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. Jama. 2008; 299(22):2642±55. https://doi.org/10.1001/jama.299.22.2642 PMID: 18544724

24. Protopopescu X, Butler T, Pan H, Root J, Altemus M, Polanecsky M, et al. Hippocampal structural changes across the menstrual cycle. Hippocampus. 2008; 18(10):985±8. https://doi.org/10.1002/hipo.20468 PMID: 18767068

25. Vandewalle G, Maquet P, Dijk D-J. Light as a modulator of cognitive brain function. Trends in cognitive sciences. 2009; 13(10):429±38. https://doi.org/10.1016/j.tics.2009.07.004 PMID: 19748817

26. Chellappa SL, Ly JQ, Meyer C, Balteau E, Degueldre C, Luxen A, et al. Photic memory for executive brain responses. Proceedings of the National Academy of Sciences. 2014; 111(16):6087±91.

pii: sp-00684-15 http://dx.doi.org/10.5665/sleep.6090

SLEEP COGNITION AND BEHAVIOR

Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task

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Study Objectives: Prolonged exposure to blue wavelength light has been shown to have an alerting effect, and enhances performance on cognitive tasks. A small number of studies have also shown that relatively short exposure to blue light leads to changes in functional brain responses *during* the period of exposure. The extent to which blue light continues to affect brain functioning during a cognitively challenging task *after* cessation of longer periods of exposure (i.e., roughly 30 minutes or longer), however, has not been fully investigated.

Methods: A total of 35 healthy participants (18 female) were exposed to either blue (469 nm) (n = 17) or amber (578 nm) (n = 18) wavelength light for 30 minutes in a darkened room, followed immediately by functional magnetic resonance imaging (fMRI) while undergoing a working memory task (*N*-back task).

Results: Participants in the blue light condition were faster in their responses on the *N*-back task and showed increased activation in the dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex compared to those in the amber control light condition. Furthermore, greater activation within the VLPFC was correlated with faster *N*-back response times.

Conclusions: This is the first study to suggest that a relatively brief, single exposure to blue light has a subsequent beneficial effect on working memory performance, even after cessation of exposure, and leads to temporarily persisting functional brain changes within prefrontal brain regions associated with executive functions. These findings may have broader implication for using blue-enriched light in a variety of work settings where alertness and quick decision-making are important.

Keywords: blue light, amber light, working memory, functional magnetic resonance imaging, fMRI, prefrontal cortex, PFC, N-back task

Citation: Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, Shane BR, Knight SA, Killgore WD. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *SLEEP* 2016;39(9):1671–1680.

Significance

This study shows that exposure to thirty minutes of blue wavelength light in the morning subsequently leads to faster response times on a cognitive working memory task and greater functional brain responses within the prefrontal cortex than comparable exposure to amber light. This is the first study to show that a short, single exposure to blue light during the daytime can lead to enduring measurable changes in brain activation and speed of performance during subsequent completion of a cognitively challenging task. While these findings may have important implications for using blue light in occupational settings, future research will be necessary to establish whether these findings generalize to naturalistic settings.

INTRODUCTION

Exposure to light has important effects on human physiology that are independent of visual perception. These non-image forming effects of light include the regulation of circadian rhythms, melatonin production, changes in core body temperature, sleep propensity, and alertness.[1,2] Many of these effects of light are due to activation of retinal ganglion cells, which are maximally sensitive to light within the short wavelength (~480 nm; blue light). These cells transmit irradiance signals to hypothalamic nuclei (e.g., the suprachiasmatic nucleus [SCN]), which are responsible for regulating circadian rhythms and melatonin production.[1,2] Exposure to blue light in the evening or at night has been shown to increase alertness and improve performance on reaction time tasks, most likely as a result of the suppression of the evening onset of melatonin, which leads to a phase delay of the circadian rhythm.[3–6] In a similar vein, morning blue light exposure suppresses melatonin in the early part of the day and leads to a phase advance of the circadian rhythm by inducing the onset of plasma melatonin earlier in the evening.[7] In addition, blue light, and bright white light exposure more generally, during the day, has also been shown to have beneficial effects on alertness in a number of studies. One study compared the effects of bright (5,000 lux) versus dim light (< 10 lux) exposure during the day (between 12:00 and 16:00) and at night (between 00:00 and 04:00), and found that participants reported lower levels of sleepiness and fatigue, and greater energy during bright versus dim light exposure, regardless of time of day.[8] In addition, the effects of daytime blue light exposure appear to have beneficial effects over longer periods of exposure. In a work place office setting, participants who were exposed to blue-enriched white light during the work day for 4 weeks reported increased subjective alertness, performance, positive mood, and concentration, in comparison to 4 weeks of white light exposure.[9] Further evidence suggests that blue light can also be superior to caffeine for sustaining performance on tasks requiring psychomotor functioning.[10]

While the alerting effects of nighttime exposure to blue light appear to be produced predominantly by the suppression of melatonin, the increases in daytime alertness after blue light exposure are thought to be largely due to effects other than melatonin regulation.[11] In particular, the daytime alerting effect of blue light may come from the indirect effects of melanopsin photosensitive retinal ganglion cells, which also project to brain regions other than the hypothalamus. For example, these cells can also indirectly influence activation of the locus coeruleus (LC),[12] which in turn releases norepinephrine broadly throughout the cerebral cortex,[13] leading to increases in alertness.[14] Such downstream influences may explain some of the effects of blue light on alertness during the daytime, independent of the effects of melatonin. In fact, a functional magnetic resonance imaging (fMRI) study of in-scanner acute light exposure demonstrated that short 50-second bursts of

blue light increased activation within the middle frontal gyrus and the brainstem, in comparison to violet light, while participants completed an auditory working memory task.[15] While precise identification of brainstem nuclei is difficult using fMRI techniques, the location of the activation was consistent with the general stereotaxic coordinates of the LC.[15] Thus, it appears plausible that blue light exposure may result in increased noradrenergic influence over cortical regions involved in controlled cognitive processing.

The aforementioned research suggests that blue light exposure activates brain networks that underlie many aspects of cognitive performance. One especially important cognitive function that may benefit from blue light exposure is working memory. Working memory comprises a set of cognitive processes that allow information to be actively held in mind in order to guide decision-making.[16] Studies of healthy populations as well as patients with brain lesions have shown that working memory performance is associated with increased activation within the prefrontal cortex (PFC), and especially the dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC).[16,17] Since blue light exposure appears to influence the LC, which can increase the release of norepinephrine and lead to subsequent neural activation within the PFC, this may plausibly influence neural processes associated with working memory.

Neurocomputational models suggest that decision-making processes, such as those supported by working memory, require a trade-off between speed and accuracy. In this case, either a lot of time is spent to accumulate evidence for "safe and slow" decision-making, or less time is spent for "fast but risky" decision-making.[18] These models also suggest that changes in baseline activation levels, as opposed to changes in the decision-threshold itself, may control this trade-off. For example, increases in baseline activation levels would decrease the distance from threshold, leading to faster but less reliable choices.[18] One might therefore predict that blue light exposure would lead to faster response times within this type of task by increasing baseline activation levels. However, the few studies that have actually examined the effects of blue wavelength light during working memory performance (e.g., an auditory *N*-back task and an oddball task) have not found significant effects in terms of response time or accuracy when compared to non-blue wavelengths, despite significant increases in the activation of arousal and working memory systems of the brain.[15,19,20] It should be noted that the duration of blue light exposure was considerably longer in those behavioral studies[9] mentioned above (where a significant effect on performance was observed) compared to those fMRI studies finding no effect[15,19,20] (one to several hours of blue light exposure in behavioral studies in comparison to 50 seconds up to 21 minutes in fMRI studies). Importantly, a recent review has suggested that the performance-enhancing effects of blue light at night as well as during the day usually occur with an exposure duration of roughly 30 minutes or longer.[21] It is therefore possible that the shorter durations (e.g., 18 minutes) of blue light exposure applied in prior fMRI studies may not have been long enough to induce measurable behavioral changes. Furthermore, it has not been investigated in detail whether blue light exposure has the ability to affect functional brain responses and working memory performance *after* cessation of a single dose of daytime blue light exposure. While it has been shown that self-reported sleepiness is reduced after blue light exposure at nighttime,[3] it is unclear whether a single dose of daytime blue light exposure can lead to enduring effects in terms of cognitive performance and functional brain responses. It is also possible that the lack of findings in previous fMRI studies may have been the result of participants completing the working memory task *during* light exposure, and not afterwards.

The goal of the present study was therefore to examine how 30 minutes of continuous blue wavelength light exposure would affect subsequent working memory performance and associated functional brain responses after cessation of the light exposure. We hypothesized that the enduring effects of blue wavelength light exposure would be associated with greater activation during a working memory task (*N*-back task) within areas usually recruited by such tasks, specifically the DLPFC and VLPFC, and that this increased activation would be associated with faster response times during the task, in comparison to a control exposure of amber light under the same conditions.

METHODS

Participants

Thirty-five healthy 18- to 32-year olds (18 female; 17 male) took part in the study. Participants completed an average of 12.5 years of education, were all right handed, primary English speaking, free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 22:00 and 01:00 and waking between 06:00 and 09:00.

Materials

Light Exposure

Participants underwent the controlled light exposure while sitting in an otherwise completely darkened room. All participants began with a blue light *Washout Period* (described in more detail under Procedure) that involved sitting in a dark room while only exposed to two amber light devices (described below) mounted on a desk at a distance of approximately 80 cm from the participant's nasion, with each light centered at a 45-degree angle from midline (see Figure 1A). Actual distance and angle of the light devices were adjusted manually until the pair of amber devices used during the initial washout period resulted in a 20-lux reading as measured by a light meter (Digital Lux Meter LX1330B) on each side of the participant's nose. During the *Exposure Period,* light was administered by a similar configuration of 4 light devices, also centered at 45 degrees to each side of the participant with a distance of approximately 80 cm from the participant's nasion (see Figure 1B). During the *Exposure Period*, the light devices were either blue or amber depending on random assignment. Blue light exposure utilized an array of commercially available Philips goLITE BLU Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). Each device consisted of a plastic table-mounted chassis with

a 10 × 6 array of light emitting diodes (LEDs), encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU Energy Light is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 lux, and panel irradiance [mW/cm^2] = 1.23 at 20 cm). The amber devices were provided by the manufacturer for research purposes and were essentially identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 lux, and total irradiance [mW/cm^2] = 0.35).

N-back Task

This task was used during functional neuroimaging. The *N*-back task is a widely used task for assessing working memory[22] and is typically applied in either auditory or visual modalities. In the present study, we employed a widely used visual variant of the task whereby participants viewed and responded to a series of letters appearing in serial order on the screen.[16] Participants were presented with white letters appearing one letter at a time centered on a black screen. The *N*-back task included 3 conditions of varying cognitive load. During the control condition (i.e., "zero-back"), participants were asked to identify by button press whether each letter on the screen matched a predetermined letter (e.g., "P") by pressing "yes" with their middle finger or "no" with the index finger of their right hand. In the "one-back" condition, participants responded with a button press using their right hand to indicate whether the letter presented in the current trial was identical to the letter presented in the immediately preceding trial. In the same way, during the "two-back" condition, participants indicated whether the letter shown in the current trial was identical to the letter presented 2 letter trials previously. Each cognitive load condition was presented as a block lasting 42 seconds. These blocks each consisted of a 6-s instruction screen followed by 16 trials (trial = stimulus displayed for 500 ms + 1,750 ms blank screen, ISI = 2,250 ms). Each cognitive load block was presented 3 times in pseudo-random order for a total of 9 blocks (3 "zero-back"; 3 "one-back"; 3 "two-back") throughout the task. The task began and ended with a 10-s crosshair image requiring only visual fixation, and each block was also separated by a 10-s crosshair fixation image, for a total task run of 478 seconds (7 min 58 sec). Prior to neuroimaging, participants underwent a practice version of the task outside of the scanner. This involved completing each cognitive load condition once (i.e., 16 trials each) with immediate visual feedback on each trial to ensure that they understood the task before completing it in the scanner. Verbal instructions were given to participants while in the scanner and they were encouraged to ask any questions before beginning the task.

Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale (SSS)[23] is a one-item measure to assess participants' current level of sleepiness on a 1–7 point scale, ranging from "feeling active, vital, alert, or wide awake" to "no longer fighting sleep, sleep onset soon, having dream-like thoughts." Higher scores on the SSS indicate higher levels of sleepiness.

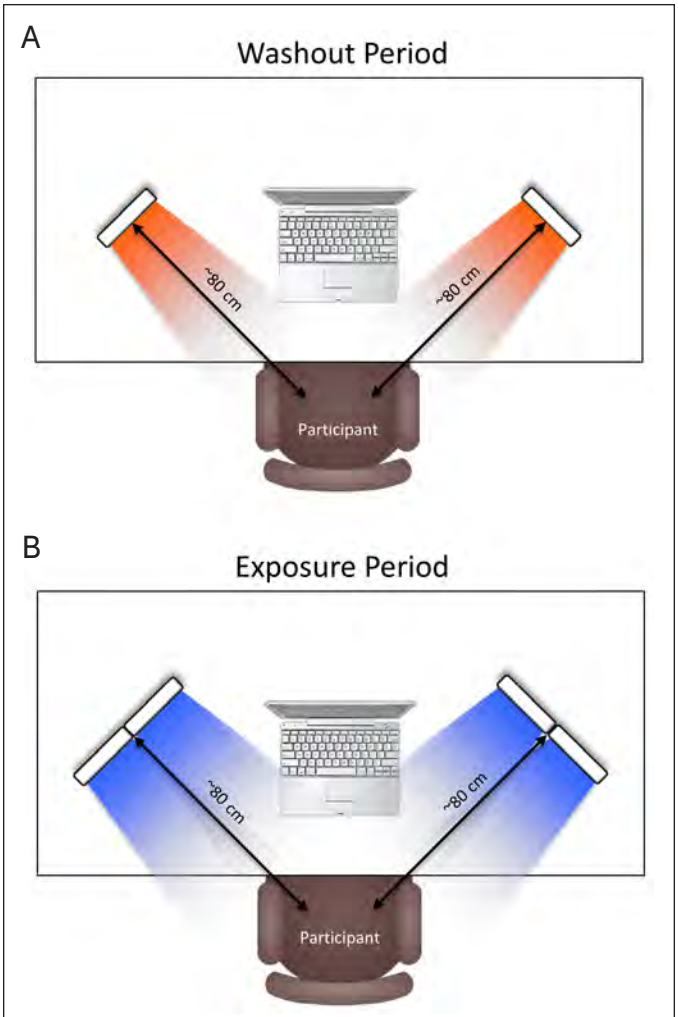


Figure 1—Diagram of light device placements. Participants were seated at a desk in a darkened room with light devices placed at a 45-degree angle to the right and left of center at a distance of approximately 80 cm. (A) During the 30-minute blue light Washout Period, 2 devices (one on the left and one on the right) fitted with amber light emitting diodes (LEDs; λ = 578 nm) were directed toward the participant, with each device centered at a 45-degree angle). (B) During the 30-minute *Exposure Period*, 4 devices (2 on the left and 2 on the right) were directed toward the participant, with each pair centered at a 45-degree angle. Devices were fitted with either blue (λ = 469 nm) or amber (λ = 578 nm) LEDs, according to random assignment.

Procedure

Participants completed the study on an individual basis, but all participants were run at the same time each day to control for circadian time of day effects. To ensure that participants were not in caffeine withdrawal during the procedure, they were asked to consume their normal levels of morning caffeine before arrival for the study. Participants arrived for the study at 07:45 and were escorted to the laboratory. For the first portion of the day, participants completed the informed consent process, and completed some basic information questionnaires and cognitive tasks. Participants were randomized to receive either 30 min of blue (n = 17) or amber (n = 18) light exposure. At approximately 09:15, participants were then fitted with wrap around polycarbonate blue light-blocking

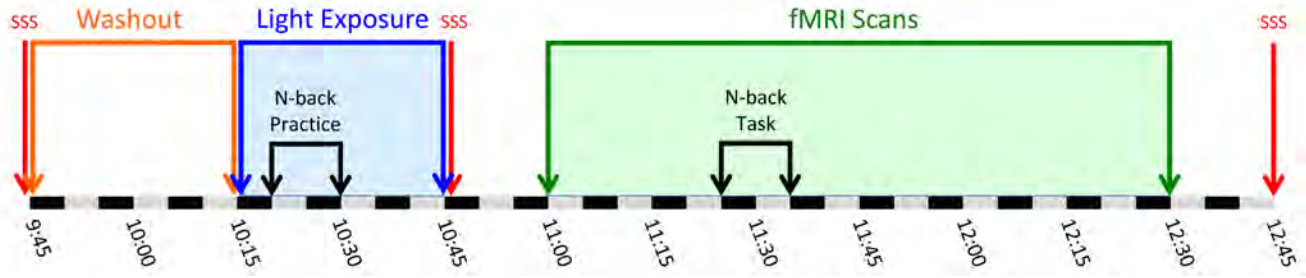


Figure 2—Timeline detailing the study procedure. Between 09:45 and 10:15, participants underwent 30 minutes of "washout" amber light exposure. Immediately following the washout period, participants either received 30 minutes of amber placebo light or blue light exposure (i.e., between 10:15 and 10:45). During this time, at 10:20, participants received instructions on the *N*-back task and completed one practice run, lasting 10 minutes in total. At 11:00, participants began the fMRI scan, and the *N*-back task was initiated at 11:25 and ended at 11:33. The scan ended at 12:30. Participants completed the Stanford Sleepiness Scale (SSS) 3 times during the procedure, including just before the start of the washout period, immediately after the light exposure, and at 12:45 after exiting the fMRI scanner.

glasses (to minimize extraneous blue light exposure) and were escorted to the neuroimaging center at the University of Arizona Department of Medical Imaging. At 09:45, participants then completed the SSS and immediately underwent a "blue light washout" period for 30 min to ensure that residual effects of outdoor and ambient lighting had dissipated before the beginning of the light exposure period. During this washout period, participants were seated comfortably in a darkened room and then removed the light-blocking glasses. Ambient lighting was provided by 2 amber light devices (see Materials), which were activated on the desk in front of the participant and located 45° to the left and right of center, approximately 80 cm from the participant's nasion (see Figure 1A). The amount of light exposure was measured and the lights were adjusted for each participant to ensure that 20 lux of amber light was registered on each side of the nose. Participants were instructed not to look directly at the light devices, and to relax with their eyes open and maintain a generally forward gaze. At 10:15, the 2 Washout Period light devices were replaced with the 4 Exposure Period devices (see Figure 1B). Then the 30-min Exposure Period was initiated by engaging the 2 pairs of light devices (either blue or amber, depending on condition), with each pair mounted side by side on the desk in front of the participant, centered at the same location as the Washout Period amber lights. During the 30-min Exposure and Washout Periods, participants maintained a forward gaze and completed several computerized practice tasks to prepare them for their time in the scanner. The laptop monitors were shielded by an amber colored Plexiglas panel, which was acquired from www.lowbluelights.com, to block blue wavelength light. These computerized practice tasks ranged from 5 to 10 min each and were interspersed with 5-min rest breaks that involved sitting silently and maintaining a forward gaze at a crosshair on the wall facing the participant. At the completion of the Exposure Period (10:45), participants again donned their blue light-blocking glasses, were escorted to the MRI scanner, and again completed the SSS. Once in the scanner, the scanner room lights were dimmed and the glasses were removed. While we have no measurement of the lux levels in the scanner due to the incompatibility of lux meters within the magnetic field of the scanner, the light conditions were held constant across participants. The scanning sequence was initiated at 11:00, and the *N*-back task was started at approximately 11:25, and the scan was completed by 12:30. At the conclusion of the scan, participants exited the scanner and completed one last SSS (10:45) and were released. Figure 2 details the timeline of the study procedure.

Ethical Considerations

The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office.

Neuroimaging Methods

Participants underwent fMRI immediately after completion of the 30-min exposure to either blue or amber light. Neuroimaging scans were collected on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR / TE / flip angle = 2.1 s / 2.33 ms / 12 degree) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR / TE / flip angle = 2.0 s / 25.0 ms / 90 degree) with 239 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

Image Processing

Processing and analysis of neuroimaging scans was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Raw functional images were first preprocessed by realigning and unwarping the functional images, and then co-registering the newly created mean functional image to each subject's structural T1 scan. Forward deformation fields were used to normalize the images from subject native space to Montreal Neurological Institute (MNI) coordinate space. Finally, the images were spatially smoothed (6 mm full-width at half maximum), and resliced to 2 × 2 × 2 mm voxels. A high pass

Table 1—Sample characteristics.

	Blue group (n = 17) Mean (SD)	Amber group (n = 18) Mean (SD)	Statistic
Age	21.71 (2.58)	22.22 (4.06)	$t_{33} = 0.63$, P = 0.53
Gender	47% female	55% female	$\chi^2 = 0.25$, P = 0.62
Years of Education	12.71 (3.58)	12.44 (3.34)	$t_{33} = 0.22$, P = 0.26
Mean hours of sleep on a weeknight	7.25 (0.97)	7.22 (0.94)	$t_{33} = 0.09$, P = 0.93
Hours of sleep the night before the assessment	6.88 (0.54)	6.86 (0.87)	$t_{33} = -0.09$, P = 0.93
Mean number of caffeinated products per day	0.78 (0.81)	1.08 (0.97)	$t_{33} = -0.97$, P = 0.34
Typical wake time on weeknights	07:52 (0:56)	07:24 (1:05)	$t_{33} = -0.13$, P = 0.19
Typical bed time on weeknights	23:40 (1:12)	23:25 (0:56)	$t_{33} = -0.70$, P = 0.48
SSS pre-washout	1.69 (0.87)	1.89 (0.58)	$F_{2, 32} = 0.63$, P = 0.43
SSS post-exposure	2.38 (1.25)	2.78 (1.14)	$F_{2, 32} = 0.98$, P = 0.33
SSS post-fMRI scan	1.94 (1.12)	2.11 (1.27)	$F_{2, 32} = 0.17$, P = 0.67

SSS, Stanford Sleepiness Scale.

filter with a 128-s cutoff period was used to remove low frequency confounds. The standard canonical hemodynamic response function in SPM was employed, and serial autocorrelation was corrected with an autoregressive model of 1 (+white noise). Motion artifacts exceeding 3 SD in mean global intensity and scan-to-scan motion that exceed 1.0 mm were regressed out using the Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect/).

Statistical Analysis

On an individual basis, a general linear model (GLM) was specified to contrast activation between the two-back > zero-back condition. These contrast images were entered into a second-level independent samples t-test analysis with light group (blue versus amber) as the independent variable. Based on our *a priori* hypotheses and previous findings from a large meta-analysis of normative functional neuroimaging studies using the *N*-back task,[16] spheres of a 10 mm radius centered on stereotaxic coordinates derived from the previous meta-analysis were placed in areas of the DLPFC and VLPFC. The Talairach coordinates reported in Owen et al.[16] were transformed to MNI coordinates using the MNI2TAL online program from Lacadie et al.[24] (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). The following MNI coordinates were used: DLPFC (x = 41, y = 31, z = 30; x = −37, y = 45, z = 21; x = −46, y = 19, z = 22), and VLPFC (x = −31, y = 21, z = 4; x = 34, y = 23, z = 1). Analyses were thresholded at P < 0.001 (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, family wise error (FWE) corrected at P < 0.05, and *k* (extent) ≥ 10 contiguous voxels.

In addition to the primary analysis of our hypothesized effects, we also conducted an exploratory whole brain analysis to provide complete data for future hypothesis generation. Here, we used a slightly more liberal height threshold of P < 0.005, while protecting against type I error through a cluster-corrected extent threshold of 201 voxels, which represents an FWE correction of P < 0.05.[25] Because this analysis was exploratory, we had no *a priori* hypothesis and merely present these supplemental findings for completeness and to obviate bias in reporting.

RESULTS

Descriptive Statistics

According to self-report, participants slept on average 7.2 h (SD 0.94) per night, and obtained 6.8 h (SD 0.72) of sleep the night before the assessment. Participants reported going to bed on average at 23:32 (SD 1 h 4 min) and waking at 07:37 (SD 1 h 2 min) on weekdays. Participants reported drinking an average of 0.93 (SD 0.89) caffeinated products per day, and 8 participants (4 in each group) reported having had one caffeinated product prior to the assessment, which was consistent with their normal morning consumption patterns. Groups did not differ on age, gender, years of education, mean number of hours slept on weeknights, number of hours slept the previous night, mean number of caffeinated products per day, and waking and bed times (see Table 1).

Behavioral Results

A repeated-measures ANOVA of the SSS scores showed no interaction between light color and session (pre-washout, post light exposure, and post-fMRI) ($F_{2, 31} = 0.12$, P = 0.88). An analysis of simple effects showed no difference between light color groups at each of the 3 sessions (see Table 1).

There was no difference in accuracy and response time between the blue and amber groups for the zero-back condition, but participants in the blue group responded faster during the one- ($t_{33} = -2.26$, P = 0.03) and two-back conditions ($t_{33} = -1.98$, P = 0.05) than participants in the control group (see Table 2).

Neuroimaging Results

Hypothesis Testing

For the two-back > zero-back contrast, individuals in the blue light group showed significantly greater activation in a cluster within the left DLPFC ($k = 29$; $P_{FWE} = 0.03$; $t = 4.12$; x = −50, y = 14, z = 22, small volume corrected) and a cluster within the right VLPFC ($k = 17$, $P_{FWE} = 0.006$, $t = 4.83$; x = 34, y = 20, z = −6, small volume corrected) than individuals who were exposed to the amber control light (see Figure 3). There were no regions within the brain where amber light exposure was

Table 2—Mean accuracy and reaction times for the *N*-back task.

	Accuracy (SD) in %	Total Reaction Time (SD) in milliseconds	Reaction Time for Correct Responses (SD) in milliseconds
Zero-back			
Blue	96.05 (0.39)	410.72 (97.04)	407.81 (91.55)
Amber	97.43 (0.25)	457.05 (94.07)	458.64 (93.03)
One-back			
Blue	87.31 (0.71)	485.09 (133.81)[a]	485.09 (133.81)[c]
Amber	88.49 (0.82)	601.97 (168.77)[a]	601.97 (168.77)[c]
Two-back			
Blue	88.60 (0.91)	556.00 (196.87)[b]	553.00 (192.05)[†]
Amber	88.74 (1.03)	691.01 (205.59)[b]	682.62 (204.16)[†]

[a], [b], and [c], denote groups that significantly differ at P < 0.05; [†] marginal difference (P = 0.06).

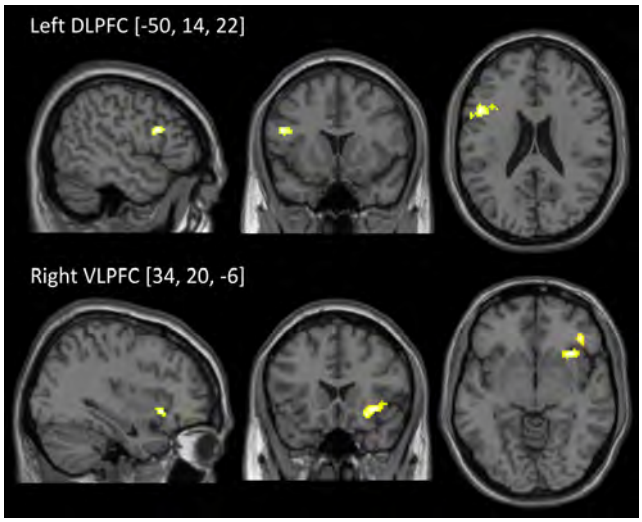


Figure 3—SPM images showing the clusters of significant activation where Blue > Amber for the *N*-Back task (two-back > zero-back). Based on the a priori regions of interest, this comparison revealed that the blue light condition was associated with significantly greater activation within the left dorsolateral prefrontal cortex (DLPFC) and the right ventrolateral prefrontal cortex (VLPFC) when compared to the amber light condition during complex working memory. Clusters are significant at P < 0.05, FWE corrected, but are displayed at P < 0.005 for ease of visualization.

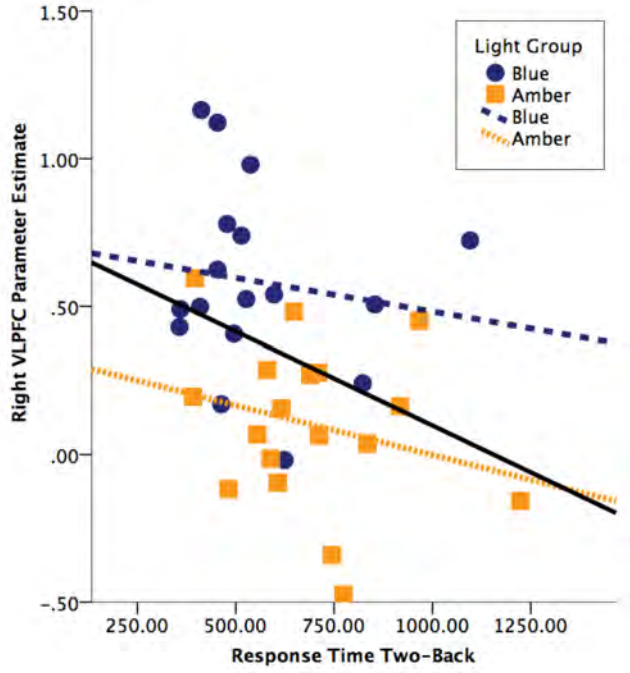


Figure 4—The scatterplots illustrate the association between the activation within the right ventrolateral prefrontal cortex (VLPFC) and reaction time during the two-back condition for the blue and amber light groups, and the sample as a whole.

associated with greater functional brain responses than blue light exposure.

In order to investigate the association between regional activation and behavioral responses, we extracted the activation for the unadjusted cluster eigenvariate for both brain regions and conducted Pearson correlations between the eigenvariate and response time and performance metrics during the two-back condition. There was a negative correlation between VLPFC activation and response time ($r = -0.35$, P = 0.04). This correlation was present among the sample as a whole and was not driven by one group in particular (Figure 4). No significant associations with accuracy were found. In addition, no significant associations were found between activation within the DLPFC and performance on the working memory task.

To investigate whether participants were more "efficient" with increases in working memory (i.e., the number of correct responses per second), a measure of cognitive throughput was calculated ([Accuracy × (1 / RT) * 1,000]).[26] Throughput provides a quantitative metric of the speed versus accuracy tradeoff. While there was no difference in throughput between the 2 groups in the zero-back condition ($t_{33} = -1.60$, P = 0.19), participants in the blue group showed enhanced throughput in the one-back ($t_{33} = -2.57$, P = 0.01), and marginally higher throughput in the two-back condition ($t_{33} = -1.92$, P = 0.06). In other words, participants in the blue light group provided a greater number of correct responses per unit of time than participants in the amber control group (Figure 5). Given that the groups were essentially equivalent with regard to accuracy, this difference suggests that exposure to blue light led to faster response times with no loss in accuracy.

Exploratory Analysis

Finally, exploratory whole brain analysis was undertaken for the purpose of facilitating future hypothesis generation, with a peak height threshold of $P < 0.005$, and cluster-corrected extent threshold of $P < 0.05$ (FWE corrected). Again comparing the two-back > zero-back contrast, we found that the blue-wavelength light exposure group showed significantly greater activation than the amber control group within several distributed regions including left and right VLPFC (i.e., inferior frontal gyrus/insula), left and right middle temporal gyrus, right posterior cingulate gyrus, left middle occipital cortex, brainstem, and thalamus (Figure 6). Table 3 lists the cluster maxima for these exploratory analyses. There were no regions in the brain showing greater activation for the amber control light group compared to blue light group during the working memory task.

DISCUSSION

The goal of the present study was to examine the effects of 30 minutes of controlled blue wavelength (469 nm) light exposure compared to amber placebo light (578 nm) exposure on subsequent functional brain responses and performance during an *N*-back working memory task among healthy non-sleep deprived individuals. We found that exposure to 30 minutes of blue wavelength light produced greater activation within regions of the DLPFC and VLPFC and faster response times during a subsequent working memory task than exposure to amber wavelength light under otherwise identical conditions. Moreover, greater activation in the VLPFC for both groups combined was significantly correlated with faster response times during the working memory task, consistent with this region's role in executive functioning. Finally, while blue light effects were observed for brain activation and response time, there were no group differences in accuracy on the working memory task. Together, these findings suggest that a relatively brief exposure to blue light has an enhancing effect on speeded cognition and brain function that may persist for at least 40 minutes after cessation of the light.

It is well established that both the DLPFC and VLPFC are critically involved in the encoding, retention, and retrieval of information during working memory tasks.[16,27,28] Our findings suggest that a single, relatively short exposure to blue wavelength light of only 30 minutes can increase neural activation over the subsequent 40-minute period within those prefrontal areas most critical for successful working memory performance. Prior work has shown that even short bursts of blue light for periods lasting from 50 seconds to 20 minutes are effective at activating similar regions of the DLPFC and VLPFC during auditory working memory tasks.[15,19,29] While previous studies have found increases within the prefrontal regions *during* exposure,[15,19] this study shows that brain activation and improved working memory task performance as a result of light exposure can substantially endure well beyond the exposure period and adds to emerging work suggesting that prolonged blue light exposure (30 minutes or more) may continue to affect brain function even after termination of the light.[30] Although previous studies suggest that light-induced changes in functional brain responses may decline within 10 minutes after the end of the exposure period,[20] it is important to consider that the duration of the light exposure was considerably shorter, roughly 10 to 29 minutes less time than in the present study.[15,19,20] It is therefore possible that the longer light exposure may have contributed to these differences in findings. However, it should be also pointed out that some of these previous studies may have employed shorter periods of light exposure (e.g., 50 second bursts of exposure[15]) in order to prevent the confounding effects of variations in alertness and performance on the *N*-back task. Future studies comparing varying durations of light exposure, and employing different tasks, will therefore be necessary to determine the

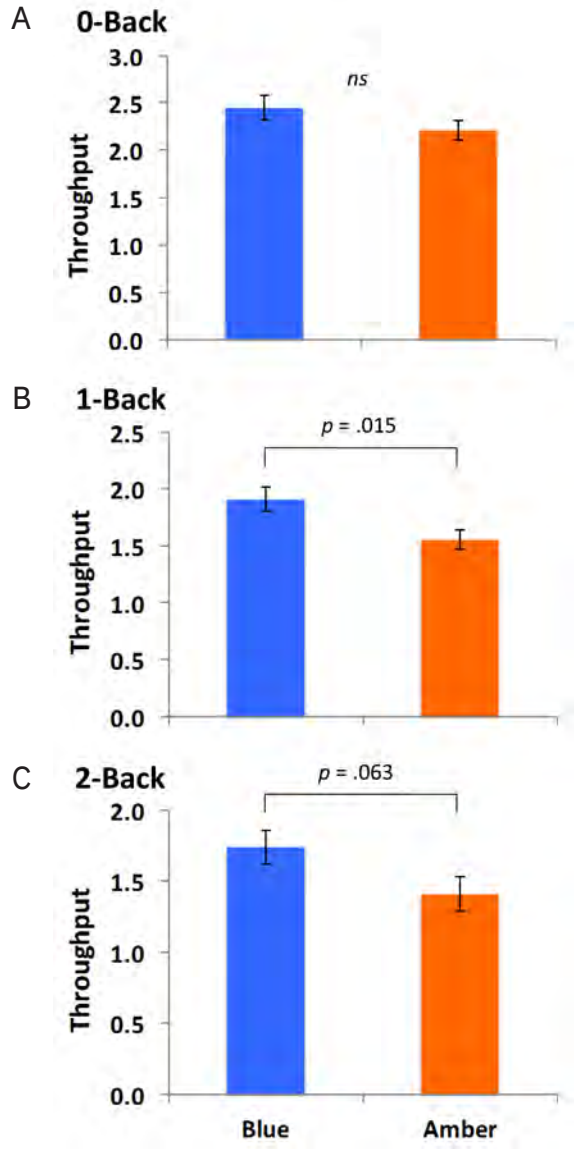


Figure 5—The figure shows group differences in working memory cognitive throughput (Accuracy × [1 / RT] * 1,000), which is a measure of the speed × accuracy trade-off. (A) There was no difference between the blue and amber groups with regard to throughput performance on the zero-back task. (B) On the one-back task, the blue light group showed significantly enhanced throughput performance compared to the amber control group. (C) On the two-back task, there was a marginally significant trend toward greater throughput for the blue compared to the amber control group.

Table 3—Cluster maxima for whole brain exploratory analysis of blue > amber light conditions.

Region	Cluster Size	x	y	z	T	Cluster P (FWE corrected)
Right Middle Temporal Gyrus	262	60	−24	−6	5.41	0.007
Right Posterior Cingulate Gyrus	611	12	−46	26	5.00	< 0.001
Left Middle Occipital Gyrus	306	−36	−74	4	4.90	0.002
Right Inferior Frontal Gyrus/Insula	210	34	20	−6	4.83	0.009
Left Inferior Parietal Cortex	201	−44	−46	60	4.76	0.010
Left Inferior Frontal Gyrus	277	−44	34	−10	4.37	0.002
Brainstem/Thalamus	553	−4	−28	−8	4.13	< 0.001
Left Middle Temporal Gyrus	284	−54	−32	8	3.90	0.002

Exploratory whole brain analyses were conducted using a height threshold of P < 0.005 (uncorrected) and a cluster-extent correction of P < 0.05, family-wise error (FWE) corrected.

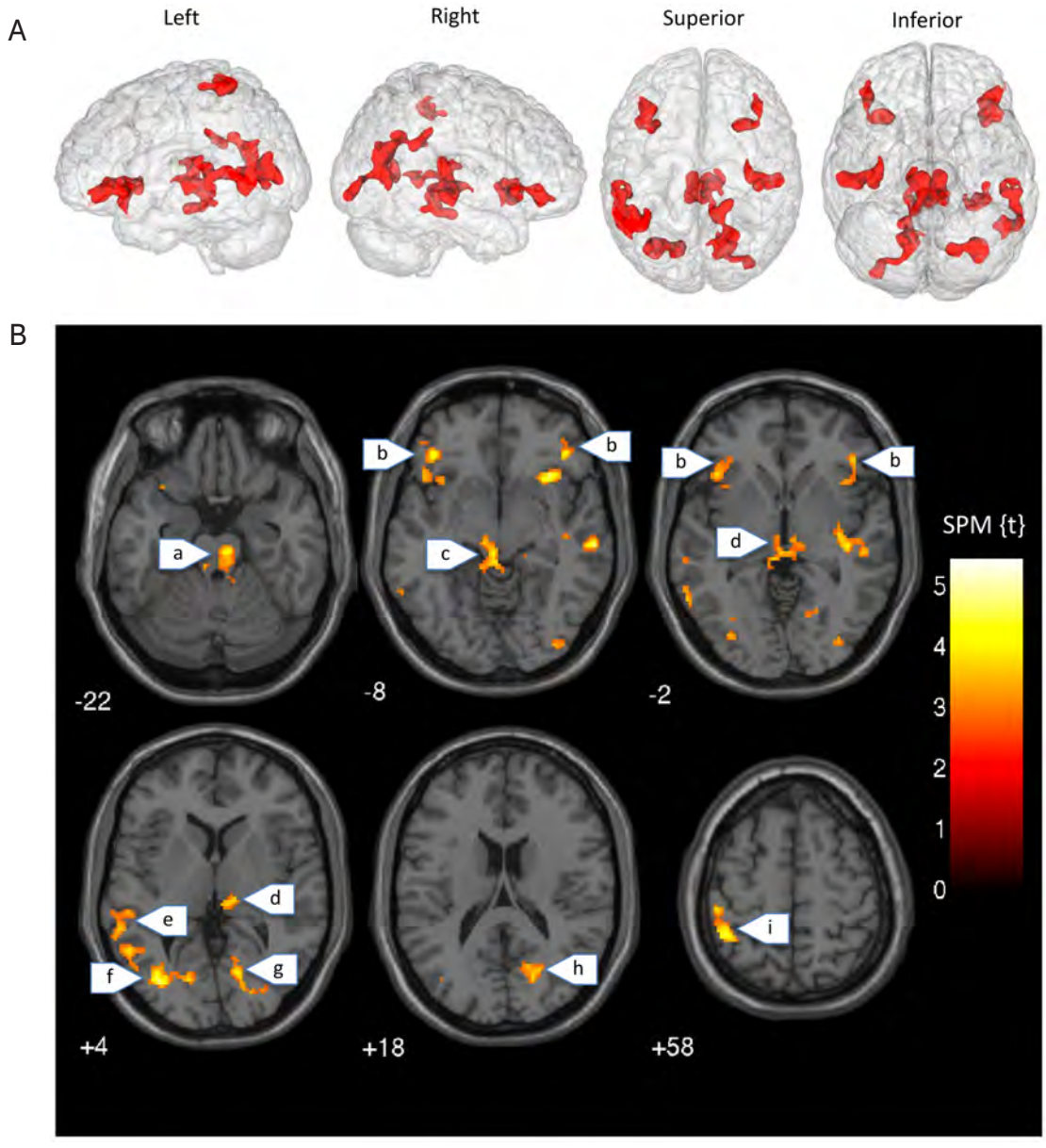


Figure 6—Whole brain exploratory analysis (height P < 0.005, cluster corrected P < 0.05, FWE). (A) The "glass brain" figures show the location of significant clusters of brain activation where Blue > Amber for the *N*-Back Task (two-back > zero-back). (B) The axial slices show the aforementioned clusters in greater anatomical detail. Blue light was associated with greater activation than amber control within: (a) pons, (b) inferior frontal gyrus, (c) superior brainstem, (d) thalamus, (e) middle temporal gyrus, (f) middle occipital gyrus, (g) lingual gyrus, (h) calcarine cortex, (i) inferior parietal lobule.

extent of the persisting effects of light on subsequent performance. It is conceivable that this prolonged effect may be a result of sustained noradrenergic activation. Prior research has shown that blue light exposure leads to greater activation within the LC, which in turn releases norepinephrine throughout the cortex.[13] If blue light exposure in our study promoted increased noradrenergic influence within the PFC (leading to an increase in baseline regional activation), this could plausibly explain the increased prefrontal BOLD responses and improved response times that we observed.

It is important to note that performance on the *N*-back task, in terms of faster response times, correlated positively with activation within the mid VLPFC. This finding is consistent with previous studies suggesting that an increase in baseline lateral prefrontal activation leads to faster decision-making.[31] Neurocomputational models suggest that the higher the baseline activity within a cortical area, the lower the activation needed to reach a response threshold, which can lead to faster response times.[18] This increase in baseline activation may in turn be explained by increased release of norepinephrine throughout the frontal cortex, due to stimulation of the LC[14] as a result of blue light exposure. It is also notable that blue light improved the speed of responses to the working memory task relative to amber control, but did not lead to an overall improvement in accuracy. Consideration of these data in light of the throughput metric, which quantifies the speed-accuracy tradeoff, suggests that while blue light was associated with an increase in the speed of responding to the working memory items, there was no corresponding loss of accuracy. Thus, blue light exposure was associated with the ability to make a greater number of correct responses per unit of time compared to the amber control light.

While previous studies that investigated the alerting effects of blue light have often employed study designs during nighttime,[5] or during prolonged (i.e., 4 hours) daytime exposure to blue light,[8] the present findings may have a broader application. Together with findings from previous studies, the results suggest that a relatively short duration (i.e., 30 minutes) of blue light exposure during the day can have a measurable effect on brain functioning and cognitive performance, not only acutely during the period of exposure, but that the effects may also endure for some time after termination of the light. This may have implications for the kind of light that is being used in office spaces, cockpits, and hospitals, in particular for individuals who have to perform their duties during sleep-deprived conditions. While the present study only examined the effects of light exposure under normally rested conditions, it is likely that these effects on brain activation and performance might be even more robust during periods of insufficient sleep. Prior work has suggested that blue wavelength light may be effective at improving some aspects of alertness and cognitive performance during nocturnal sleep loss,[32] but this has not been explored using neuroimaging techniques. It should also be pointed out that participants did not report any subjective differences in sleepiness/alertness depending on light condition. It is possible that longer light exposure is necessary to produce subjectively alerting effects of blue light exposure.

While the present findings suggest that blue wavelength light has meaningful effects on brain function and performance that persist beyond the exposure period, there are a number of limitations to be borne in mind. First, we present data on only a single cognitive task in a relatively artificial neuroimaging environment. Light exposure in the "real world" rarely follows these constraints. Further work with more ecologically valid tasks and environments will be necessary to establish the effectiveness of blue or blue-enriched white light in a variety of occupational settings. Some work has demonstrated increases in subjective alertness and performance after four weeks of blue-enriched white light exposure in offices,[9] but additional research will be necessary to determine the most effective parameters for administering light for the purpose of enhancing or sustaining performance in occupational settings. In addition, previous neuroimaging studies have employed an auditory, and not a visually presented letter variant of the *N*-back task as in the present study. It is unclear the extent to which the different variants of the *N*-back task might have contributed to some of the differences in findings across studies. It has been shown that an auditory *N*-back task may be more difficult than a visual variant of the *N*-back task. However, these differences in task type were only apparent at the three-back level.[33] The present study and previous fMRI studies investigating the effects of blue light on functional brain responses[15,19] have thus far been restricted to the two-back level. Nevertheless, future work that includes both visual and auditory *N*-back tasks that are more cognitively demanding will be necessary to establish whether blue wavelength light has a differential effect on these separate working memory systems. Furthermore, our sample sizes, while consistent with current practice in much of the neuroimaging literature, remain modest and limited in power, necessitating further replication to establish the reliability of the findings. Our sample was also relatively young and homogeneous in terms of background and health. Some evidence suggests that the effects of blue light on alertness may be attenuated among older individuals.[34] It has also been suggested that the effects of light on performance and brain responses may differ depending on genotype and circadian phase of testing.[35] Although participants were included if habitual bed and wake times fit within the pre-determined range to reduce variability due to circadian differences, the laboratory experiment started relatively early at 07:45 which may have led to elevated melatonin levels in some participants with later waking times. In addition, we did not collect genetic material in this sample, so examination of the role of genetics on the observed effects will require further study. Lastly, it should be pointed out that participants practiced the *N*-back task during either the blue light or amber light exposure (depending on condition). During the practice session participants received detailed instructions, were able to ask questions, and completed one trial of each condition (zero-back, one-back, and two-back) with feedback while undergoing light exposure. It is therefore possible that blue light exposure during the practice session influenced participants' ability to learn the task in such a way that they were able to perform better during the actual task. This potential role of light in learning is indeed an intriguing possibility. While the effects of blue light on immediate learning versus its persistent effects on subsequent performance cannot be disentangled here, this will likely be a fruitful question for further research.

CONCLUSIONS

The present findings suggest that daytime exposure to 30 minutes of blue wavelength light in non-sleep-deprived individuals has a beneficial impact on working memory performance and elicits measurable functional brain responses within prefrontal regions associated with executive functions. These results extend previous work by showing that exposure to blue light leads to persistent changes within the brain and performance during the post-exposure period (40 minutes). Additional research is necessary to identify the duration and breadth of these effects and how they may interact with individual difference factors such as gender, age, genotype, and other factors such as sleep debt and circadian influences.

REFERENCES

1. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002;295:1070–3.
2. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. PLoS Biol 2009;7:1221.
3. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert. PloS One 2011;6:e16429.
4. Cajochen C, Munch M, Kobialka S, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab 2005;90:1311–6.
5. Phipps-Nelson J, Redman JR, Schlangen LJ, Rajaratnam SM. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. Chronobiol Int 2009;26:891–912.
6. Lockley SW, Evans EE, Scheer F, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep 2006;29:161–8.
7. Wright HR, Lack LC, Kennaway DJ. Differential effects of light wavelength in phase advancing the melatonin rhythm. J Pineal Res 2004;36:140–4.
8. Rüger M, Gordijn MC, Beersma DG, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. Am J Physiol Regul Integr Comp Physiol 2006;290:R1413–20.
9. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J Work Environ Health 2008:297–306.
10. Beaven CM, Ekström J. A comparison of blue light and caffeine effects on cognitive function and alertness in humans. PloS One 2013;8:e76707.
11. Rautkyä E, Puolakka M, Halonen L. Alerting effects of daytime light exposure-a proposed link between light exposure and brain mechanisms. Light Res Technol 2012;44:238–52.
12. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nat Neurosci 2001;4:732–8.
13. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. Brain Res 1996;742:89–97.
14. Foote S, Berridge C, Adams L, Pineda J. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Progr Brain Res 1991;88:521–32.
15. Vandewalle G, Schmidt C, Albouy G, et al. Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. PLoS One 2007;2:e1247.
16. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005;25:46–59.
17. Kane MJ, Engle RW. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. J Exp Psychol Gen 2003;132:47.
18. Bogacz R, Wagenmakers E-J, Forstmann BU, Nieuwenhuis S. The neural basis of the speed–accuracy tradeoff. Trend Neurosci 2010;33:10–6.
19. Vandewalle G, Gais S, Schabus M, et al. Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. Cereb Cortex 2007;17:2788–95.
20. Vandewalle G, Balteau E, Phillips C, et al. Daytime light exposure dynamically enhances brain responses. Curr Biol 2006;16:1616–21.
21. Vandewalle G, Maquet P, Dijk D-J. Light as a modulator of cognitive brain function. Trend Cogn Sci 2009;13:429–38.
22. Gevins A, Cutillo B. Neuroelectric evidence for distributed processing in human working memory. Electroencephalogr Clin Neurophysiol 1993;87:128–43.
23. Hoddes E, Zarcone V, Dement W. Development and use of Stanford Sleepiness scale (SSS). In: Psychophysiology. New York, NY: Cambridge University Press, 1972.
24. Lacadie CM, Fulbright RK, Rajeevan N, Constable RT, Papademetris X. More accurate Talairach coordinates for neuroimaging using non-linear registration. Neuroimage 2008;42:717–25.
25. Woo CW, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. Neuroimage 2014;91:412–9.
26. Thorne DR. Throughput: a simple performance index with desirable characteristics. Behav Res Methods 2006;38:569–73.
27. D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res 2000;133:3–11.
28. Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 2003;7:415–23.
29. Vandewalle G, Archer SN, Wuillaume C, et al. Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. J Biol Rhythms 2011;26:249–59.
30. Alkozei A, Smith R, Killgore WD. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. Neurosci Lett 2016;616:5–10.
31. van Veen V, Krug MK, Carter CS. The neural and computational basis of controlled speed-accuracy tradeoff during task performance. J Cogn Neurosci 2008;20:1952–65.
32. Taillard J, Capelli A, Sagaspe P, Anund A, Akerstedt T, Philip P. In-car nocturnal blue light exposure improves motorway driving: a randomized controlled trial. PLoS One 2012;7:e46750.
33. Jaeggi SM, Buschkuehl M, Perrig WJ, Meier B. The concurrent validity of the N-back task as a working memory measure. Memory 2010;18:394–412.
34. Daneault V, Hebert M, Albouy G, et al. Aging reduces the stimulating effect of blue light on cognitive brain functions. Sleep 2014;37:85–96.
35. Gaggioni G, Maquet P, Schmidt C, Dijk DJ, Vandewalle G. Neuroimaging, cognition, light and circadian rhythms. Front Syst Neurosci 2014;8:126.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2015
Submitted in final revised form April, 2016
Accepted for publication April, 2016

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DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by a U.S. Army US Army MOMRP Grant as well as by an Arizona Health Education Centers (AHEC) Research Grant. The authors have no other conflict of interest. The authors have indicated no financial conflicts of interest.

Neuroscience Letters 616 (2016) 5–10

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli

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HIGHLIGHTS

- We compared the effects of thirty minutes of blue versus amber light exposure.
- Participants completed an emotional anticipation task after the light exposure.
- 'Uncertain event' > 'certain reward' led to lower activation for blue vs. amber.
- Blue light may improve adaptive learning-related synaptic processing within the ACC.

ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form 13 January 2016
Accepted 19 January 2016
Available online 22 January 2016

Keywords:
Blue light
fMRI
Emotional anticipation
Anterior cingulate cortex

ABSTRACT

Blue wavelength light has been used as an effective treatment for some types of mood disorders and circadian rhythm related sleep problems. We hypothesized that acute exposure to blue wavelength light would directly affect the functioning of neurocircuity implicated in emotion regulation (i.e., ventromedial prefrontal cortex, amygdala, insula, and anterior cingulate cortex [ACC]) during 'certain' and 'uncertain' anticipation of negative and positive stimuli. Thirty-five healthy adults were randomized to receive a thirty-minute exposure to either blue (active) or amber (placebo) light, immediately followed by an emotional anticipation task during functional magnetic resonance imaging (fMRI). In contrast to placebo, participants in the blue light group showed significantly reduced activation within the rostral ACC during 'uncertain' anticipation (i.e., uncertainty regarding whether a positive or negative stimulus would be shown) in comparison to 'certain' anticipation of a positive stimulus. These findings may be explicable in terms of interactions between blue light exposure and the influence of specific neuromodulators on ACC-mediated decision-making mechanisms.

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1. Introduction

Daily exposure to bright blue wavelength (≈480 nm) light has been used as a successful treatment for individuals with depression and seasonal affective disorder (SAD) [1]. The mechanisms underlying this effect of blue light on cognition/emotion remain poorly understood but likely include the well known indirect effects of light on the regulation of sleep and circadian rhythms, as well as more direct effects on neurological and neuroendocrine systems [2]. Considerable evidence suggests that the retina contains unique melanopsin photosensitive receptors that respond specifically to the blue wavelengths of light and that these neurons project predominantly to the suprachiasmatic nucleus of the hypothalamus, the primary regulator of circadian rhythms in the brain [3]. However, in addition to the circadian effects of light, some preliminary evidence suggests that light exposure may produce direct and immediate changes in the functioning of neural systems implicated in emotion-related functions. For example, it has been shown that direct exposure to a single dose of blue wavelength light for two hours not only led to improvements in alertness and cognitive performance, but also to increases in subjective wellbeing [4]. This may be explained by the fact that the melanopsin photosensitive ganglion cells also project to brain regions other than the hypothalamus. For example, blue light exposure has been shown to activate

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http://dx.doi.org/10.1016/j.neulet.2016.01.034
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the locus coeruleus (LC), which in turn releases norephinephrine throughout the cerebral cortex and influences a variety of brain functions as a result [5,6]. Several functional MRI studies have also suggested that blue light has an effect on emotion-related brain regions. For example, a 3-week daily white light intervention with peaks in the blue spectrum was associated with brain activation changes during perception of angry and fearful faces, including decreased activation within the amygdala and medial prefrontal cortex (mPFC), brain areas critical for the regulation of emotional responses [7]. Another study instead showed that short alternating periods of exposure (i.e., forty seconds) of blue versus green wavelength light were associated with increased activation within the temporal cortex and hippocampus during exposure to threatening versus neutral auditory stimuli [8], and such alternating light exposure produced greater activation within the hypothalamus in patients with SAD in comparison to healthy controls [9]. The inconsistencies in prior research require further exploration but may be due to differences in exposure time, the specific wavelengths used, the visual versus auditory nature of the tasks, differences in the populations or spatial location of the brain regions under investigation. Specifically, it is possible that prolonged daily exposure to blue light has distinct effects on functional brain responses when compared to short bursts of blue light exposure acutely during fMRI scanning, and that blue light has a differential effect in different regions of the brain, as well as in healthy versus clinical populations. However, the limited data on the effects of blue light on functional brain responses currently makes it impossible to draw firm conclusions and further research is necessary to clarify the effects of acute blue light exposure on emotional task responses.

The goal of the present study was to examine the effects of acute exposure to blue wavelength light on immediate post-exposure responses within neural systems implicated in affective regulation. Such systems, which include the amygdala, insula, anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC), among others, have been shown to be dysregulated in individuals with depression and anxiety, particularly when perceiving threatening stimuli [10,11] and when anticipating aversive stimuli [12–14]. For most people, uncertainty and unpredictability about the affective nature of future events is aversive, and has been shown to lead to hyperactivation of the insula, amygdala, and ACC relative to expectations about events with high certainty or predictability [15,16]. The ACC in particular appears to play an important regulatory role in decision-making within affective situations; recent models suggest that it does so by integrating information about uncertainty and reward expectations (in part, via dopaminergic reward prediction-error signals it receives from the ventral tegmental area [VTA]), and predicted cost/effort associated with perceptual cues and potential actions [17,18]. These decision-making functions also appear to be optimized via reward prediction-error based learning mechanisms. For example, it has been shown that in anticipation of reward, firing of neurons within the ACC increases as reward approaches [19]; interestingly, depressed individuals show reduced activation of the ACC during reward anticipation [20], and this resolves with successful treatment [21]. Further, synaptic plasticity within the ACC (which may underlie the learning rate within the aforementioned decision-making functions) appears to be facilitated by greater norepinephrine release under conditions of 'certain reward' anticipation [18,22,23]; as blue light is known to increase norepinephrine release from the LC (which itself has extensive projections to the ACC), this suggests that, under such conditions, blue light should increase the synaptic activation within the ACC associated with the integration of reward prediction-error and related learning mechanisms [5,6].

Considering that abnormalities in the processing of reward and uncertainty are implicated in multiple emotion-related psychiatric disorders, and that one major source of unpleasant emotion is uncertainty with respect to affectively significant future outcomes, the aim of this study was to investigate whether the effects of blue wavelength light discussed above might have a modulatory influence on brain responses during the anticipation of 'uncertain events' (i.e., a positive or a negative stimulus) versus 'certain threat' or 'certain reward' events. Specifically, we measured functional brain responses during three conditions of anticipation ('certain threat' cues, 'certain reward' cues, or 'uncertain event' cues) in healthy adults following a single dose of thirty minutes of blue wavelength versus an equal exposure to an amber wavelength light condition. We aimed to explore how exposure to thirty minutes of blue wavelength light would lead to functional brain changes within the amygdala, insula, ACC and mPFC during anticipation of 'certain threat', 'certain reward' and 'uncertain event' stimuli, in comparison to an equal dose of placebo (amber) light.

2. Methods

2.1. Participants

Thirty-five healthy adults who were free from psychiatric, neurological or substance use disorders, and reported a regular sleep schedule of going to bed between 10pm and 1am and waking between 6am and 9am participated in the study. Participants reported sleeping on average 7.2 h (SD = 0.93) per night, and obtained 6.8 (SD = 0.89) h of sleep the night before the assessment. Seventeen participants were randomized to receive thirty minutes of blue wavelength light exposure and eighteen participants were randomized to receive thirty minutes of placebo light exposure (see below). Groups did not differ regarding age, sex, BDI-II scores, number of hours slept on weeknights, and number of hours slept the night prior to assessment (see Table 1). All participants provided written informed consent. The research protocol was reviewed and approved by the Institutional Review Board of the University of Arizona and the U.S. Army Human Research Protections Office.

2.2. Materials

2.2.1. Light exposure

Participants were randomized to receive either thirty minutes of blue wavelength light or placebo amber wavelength light while sitting a darkened room. Blue light was administered by four commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT), mounted on a desk at a distance of 80 cm, with each light centered at a 45° angle from midline. Each device consisted of a plastic table-mounted device with a 10 × 6 array of light emitting diodes (LEDs), encased in 1 × 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU is commercially available and has a narrow bandwidth (peaking at λ = 469 nm, at 214 Lux, and panel irradiance (mW/cm^2) = 1.23 at 20 cm). The amber placebo devices were provided by the manufacturer for research purposes and were essentially identical to the goLite BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and total irradiance (mW/cm^2) = 0.35).

2.2.2. Emotional anticipation task

The Emotional Anticipation Task (EAT) was designed to evaluate the brain activation associated with anticipating a positive, negative, or uncertain stimulus. The task was adapted from Aupperle et al.'s [24] study design and lasted a total of 460 s. Participants completed the task in the MRI scanner by viewing images on a translucent projection screen and viewed through the mirror mounted on the head coil. For each trial, participants were presented with a grey background with a black arrow that alternated

Table 1
Participant Characteristics.

	Blue group (n = 17) Mean (SD)	Amber group (n = 18) Mean (SD)	Statistic
Age	21.59 (2.59)	21.78 (3.54)	t (33) = 0.17 p = 0.86
Sex	47% female	55% female	χ^2 = 0.25, p = 0.61
BDI-II	2.82 (3.45)	3.39 (4.04)	t (33) = 0.44, p = 0.66
Number of hours slept on weeknights	7.13 (0.86)	7.27 (1.01)	t (33) = 0.45, p = 0.65
Number of hours slept the night prior to the assessment	6.92 (0.91)	6.71 (0.88)	t (33) = 0.69, p = 0.49

randomly pointing either left or right (baseline condition). For each image, participants were instructed to indicate via button press the direction the arrow was pointing. Participants were told that occasionally the screen color would change to signify that another type of image was to follow. Specifically, when the screen turned yellow, a negative picture would soon appear ('certain threat' anticipation). If the screen turned blue, a positive picture would soon appear ('certain reward' anticipation), and if the screen turned green, either a positive *or* a negative picture would soon appear ('uncertain event' anticipation). The anticipation period always lasted 6 s, and the baseline period varied in duration from 4 s to 8 s. Each anticipation condition was presented 9 times in pseudorandom order and each anticipation period was preceded by a baseline condition. The picture stimuli were presented for 2 s each and consisted of positive and negative pictures from the International Affective Picture System (IAPS). The most unpleasant (e.g., mutilated bodies) (mean valence = 1.62, SD = 1.09, mean arousal = 6.87, SD = 2.14) as well as the most pleasant (e.g., animals) pictures (mean valence ratings = 7.48, SD = 1.53 mean arousal = 5.42, SD = 2.29) were chosen from the picture set.

2.2.3. Beck depression inventory (BDI-II)

The Beck Depression Inventory (BDI-II; [25]) is a 21-item self-report questionnaire to assess depressive symptoms within the last 2 weeks.

2.3. Procedure

Participants completed the study on an individual basis, but each participant was run at the same time each day to minimize circadian effects. Participants arrived for the study at 0745 and were escorted to the laboratory. For the next 1.5 h, participants completed the informed consent process, filled out some basic information questionnaires, and completed the BDI-II. At approximately 0915, participants were then fitted with blue light blocking glasses (to minimize extraneous blue light exposure) and escorted to the neuroimaging center at the University of Arizona Department of Medical Imaging. To ensure that residual effects of outdoor and ambient lighting had dissipated before the beginning of the light exposure period, all participants underwent a "blue-light washout" period for thirty minutes, beginning at 0945. During this period, participants were seated comfortably in a darkened room, without the light blocking glasses, with two amber lights activated on the desk in front of them at 45° to the left and right of center. Participants were instructed not to look directly at the lights, but to relax with their eyes open. At 1015, the thirty-minute active light condition was initiated by engaging four light devices (either blue or amber, depending on condition), which were mounted on the desk in front of the participant. At the completion of the active light condition, participants again donned their blue blocking glasses and were escorted to the MRI scanner. Once in the scanner, the glasses were removed. The scanning sequence, including the EAT was initiated at 1100 and completed by 1200. At the conclusion of the scan, participants completed a few more questionnaires and were released.

2.4. Neuroimaging methods

Participants underwent neuroimaging on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. Structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/2.33 ms/12°) over 176 sagittal slices (256 × 256) and a slice thickness of 1.00 mm (voxel size = 1 × 1 × 1). T2*-weighted functional MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm using an interleaved sequence (TR/TE/flip angle = 2.0 s/25.0 ms/90°) with 230 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 × 64 acquisition matrix.

2.5. Image processing

Processing and analysis of neuroimaging scans was conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Raw functional images were first realigned and unwarped. The mean functional images was then coregistered to each subject's MRPAGE image in accordance with standard algorithms. Images were then normalized from native space to Montreal Neurological Institute (MNI) coordinate space using forward deformation fields. Finally, images were spatially smoothed (6 mm full-width at half maximum), and resliced to 2 × 2 × 2 mm voxels. The standard canonical hemodynamic response function in SPM was employed, serial autocorrelation was corrected with the AR(1) function, and low-frequency confounds were minimized with a 128-second high-pass filter. The Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect/) was used to regress out scans exceeding 3 SD in mean global intensity and scan-to-scan motion that exceeded 1.0 mm.

2.6. Statistical analysis

On an individual basis, a general linear model was specified to contrast activation between all anticipation periods and baseline periods, as well as between the anticipation periods themselves. These contrast images were entered into a second-level independent samples t-test analysis with light group as the independent variable. Based on our a priori hypotheses, bilateral search territories were created using the Wake Forest University PickAtlas Utility [26] and the boundaries defined by the Automated Anatomical Labeling Atlas [27], focusing on the vmPFC, amygdala, insula, and ACC bilaterally. Analyses were thresholded at $p < 0.001$ (uncorrected) and subjected to small volume correction for multiple comparisons within each search territory, false discovery rate (FDR) corrected at the cluster level at $p < 0.05$, and k (extent) ≥ 10 contiguous voxels. In order to ensure that the results were not explained by participant's depression scores, which may have an impact on functional brain responses within these areas, analyses were re-run controlling for BDI-II scores.

3. Results

3.1. Anticipation > baseline

There were no significant differences in activation within the a priori ROIs between the two light groups for the following contrasts: 'certain threat' > baseline, 'certain reward' > baseline or 'uncertain event' > baseline.

3.2. Anticipation condition contrasts

There were no significant differences in activation within the ROIs between the two groups for the following contrasts: 'certain threat' > 'certain reward', and 'certain threat' > 'uncertain event'.

3.2.1. 'Uncertain event' > 'certain reward'

For the 'uncertain event' > 'certain reward' contrast, an independent samples *t*-test between the placebo (amber) > blue light group focusing on the a priori ROIs showed a significant difference in activation comprising two large clusters within the left rostral ACC (238 voxels, $p < 0.001$, $t = 4.72$, $x = -6$, $y = 42$, $z = 10$; and 108 voxels, $t = 4.35$, $x = -4$, $y = 42$, $z = -4$). Participants in the blue light condition showed reduced activation within those areas in comparison to participants in the placebo light condition (see Fig. 1).

When controlling for BDI-II scores in the analysis, the difference between the amber versus the blue light group was particularly pronounced for a large cluster within the rostral ACC (560 voxels, $p < 0.001$, cluster-level FDR corrected, and peak-level FWE-corrected at $p = 0.03$; $t = 5.10$, $x = -6$, $y = 42$, $z = 10$).

4. Discussion

In this study we found that a single dose of thirty minutes of blue light exposure immediately preceding the scanning session was associated with a reduced activation difference (relative to amber light exposure) within the left rostral ACC between 'uncertain' anticipation of negative or positive stimuli ('uncertain event' anticipation) and 'certain' anticipation of positive stimuli ('certain reward' anticipation). That is to say, the degree to which left rostral ACC activation was stronger during 'uncertain' than 'certain' anticipation was significantly greater in the amber light condition than the blue light condition. We suggest that this result may be explicable in terms of the known role of the ACC in the integration of uncertainty and valence-related information in decision-making and reinforcement learning.

In particular, we suggest these findings might be explained by the effects of blue light exposure on norepinephrine-mediated increases in learning-related synaptic plasticity within the ACC. The ACC has direct connections with the brainstem, including dopaminergic afferents from the VTA, as well as reciprocal connections with the LC [for a review see Ref. [18]], which releases norepinephrine in response to blue light exposure [5,6]. When exposed to a cue that predicts 'certain reward', dopaminergic neurons will increase their firing rate (i.e., positive reward prediction-error signaling), plausibly leading to an increase in BOLD response within the ACC regions that receive these signals [18]. In the case of the 'certain reward' condition in the present study, participants were told, and would learn quickly, that a blue screen predicts 'reward' in terms of a positive picture. This means that when the reward-predicting blue screen unexpectedly appeared, dopaminergic neuron firing rates in the VTA (signaling positive prediction-error) would increase, leading to a downstream influence on the ACC regions that receive these signals. However, synaptic plasticity (and associated learning rates) in response to such prediction-error signals have also been shown to be facilitated by norephinephrine, which has in turn been shown to be released by the LC in response to blue light exposure [5,22,23]. Thus, blue light, by increasing norepinephrine release in the ACC, may cause an increased 'learning rate' in response to dopaminergic positive reward prediction-error signals (reflected in greater synaptic activation/plasticity), leading to a greater BOLD response within the ACC. This would not be true of the uncertain condition, in which no reward prediction-error signal would be generated (and hence no learning signal would be present for norepinephrine to modulate). In summary, these considerations jointly suggest that individuals in the blue light condition should have exhibited greater synaptic activation (associated with a faster learning rate) when anticipating 'certain reward', due to the increase in norepinephrine, leading to greater BOLD response within the ACC, in comparison to the amber light group. As this increased activation in the certain condition would reduce the difference between the uncertain and certain condition in the blue light group, this would explain why ACC activation in the 'uncertain' > 'certain' contrast is greater in the amber light condition than in the blue light condition. The upshot of this interpretation is that it suggests that blue light may improve adaptive learning-related synaptic processing within the ACC during conditions of expected reward, which could in turn lead to more adaptive decision-making. In contrast, blue light would not be expected to have an effect of this kind in the uncertain condition, as the 'uncertain' cues do not generate prediction-error signal capable of driving learning (i.e., because they do not predict anything reliably about future positive or negative outcomes). However, future research will be necessary to establish whether these findings can be explained by differences in noradrenergic influence, for example, with the use of PET scans.

If blue light does, via its effects on norepinephrine release in the ACC, increase the adaptive use of reward prediction-error signals during learning and decision-making, this could help explain why depression is reduced after continued daily exposure to blue light over time. In particular, it would suggest that blue light exposure could help depressed individuals to become better able to learn from unexpected rewards (and reward-related cues). This may be particularly important in relation to the findings we report here, as the ACC has been identified as an important cortical region that predicts treatment response in mood disorders. For instance, greater ACC activation in anticipation of reward has been shown as a result of successful treatment of depression [21], and greater ACC activation at baseline has been shown to be a predictor of successful treatment response [28]. In the present study, our sample consisted of a healthy, nonclinical population. How these findings might apply to individuals with clinical symptoms of depression remains to be determined. In addition, our study lacks pre- and post-light exposure mood ratings or behavioral responses, it is therefore unclear how the functional brain changes correspond to differences in behavior. However, our findings complement those of previous studies in highlighting the potential of light treatment to improve depressive mood, possibly by changing individuals' internal responses to, and ability to learn from, reward-related processing.

Our results are also consistent with previous findings that showed that a 3-week daily bright light intervention led to reductions in activation within an overlapping medial prefrontal area in response to aversive stimuli [7]. However, as our study included only 30 min of light exposure on a single occasion, this suggests that the effect of blue light may be more immediate than previously thought, and the fact that our study design included positive as well as aversive conditions extends those findings further. This previous study suggested that these findings may reflect increases in emotion regulation abilities, possibly due to differences in neuromodulatory signaling, but proposed that other processes, in particular those involving reward, might also be involved. Our results may therefore compliment those of previous studies, and it should also be noted that the explanation we propose for our

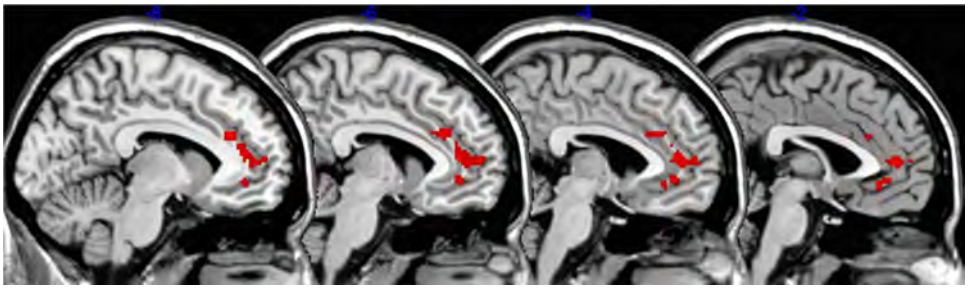


Fig. 1. There was a significantly greater activation difference between 'uncertain event' anticipation > 'certain reward' anticipation in the amber versus the blue light group after 30 min of light exposure within two clusters in the left ACC (MNI: x = −6, y = 42, z = 10, and x = −4, y = 42, z = −4).

results could also relate to emotion regulation. That is, if blue light improves the influence of reward cues on learning and decision-making within the ACC, then it is plausible that this would lead to better emotion regulation-related cognitive/behavior responses. However, as we did not gather behavioral data relevant to decision-making, these ideas will need to be tested in future work. It is also important to highlight that alternative explanations of our results cannot be ruled out. For example, considering the ACC has been shown to be recruited during conditions of unpredictable aversive stimuli [16,29], our results could also reflect a suppression of ACC activation during the 'uncertain event' condition, perhaps suggesting decreased emotional reactivity. Therefore, future research will be necessary to investigate the effects of blue light on ACC activation during emotional tasks in greater detail.

Contrary to our hypotheses, we did not find differences in activation between the two groups within the amygdala or insula during emotional anticipation, although some of these regions have been implicated in previous studies [7,30]. It is possible that the ACC is particularly responsive to the effects of blue wavelength light, because of the immediate increases in norepinephrine due to activation of the LC, whereas other structures require more prolonged daily exposure before functional changes become apparent. Future studies will therefore also need to establish whether this can explain the differences between the present findings and those of previous studies.

5. Conclusion

A single thirty-minute exposure to blue wavelength light versus exposure to a placebo amber wavelength light was associated with a reduced activation difference within the ACC during conditions of 'uncertain event' versus 'certain reward' anticipation. The findings suggest that blue wavelength light has the potential to enhance activation within the ACC during 'certain reward' anticipation, possibly due to an increase in norepinephrine, leading to an increase in the effectiveness of dopaminergic reward prediction-error signals. This increase in the learning rate during reward anticipation may partly explain the beneficial effect of blue light as a treatment for individuals with depression. Future neuroimaging studies including different brain imaging methods (e.g., PET), different functional tasks, and the inclusion of clinical populations will be necessary to illuminate these issues further.

Acknowledgment

This research was funded by a USAMRMC/CDMRP grant to WDSK (W81XWH-14-1-0571).

References

[1] R.N. Golden, et al., The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence, Am. J. Psychiatry 162 (4) (2005) 656–662.
[2] T.A. LeGates, D.C. Fernandez, S. Hattar, Light as a central modulator of circadian rhythms, sleep and affect, Nat. Rev. Neurosci. 15 (2014) 443–454.
[3] G.C. Brainard, et al., Sensitivity of the human circadian system to short-wavelength (420-nm) light, J. Biol. Rhythms 23 (5) (2008) 379–386.
[4] S.L. Chellappa, et al., Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? PLoS One 6 (1) (2011) pe16429.
[5] S.M. Florin-Lechner, et al., Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus, Brain Res. 742 (1) (1996) 89–97.
[6] G. Aston-Jones, et al., A neural circuit for circadian regulation of arousal, Nat. Neurosci. 4 (7) (2001) 732–738.
[7] P.M. Fisher, et al., Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling, Biol. Psychiatry 76 (4) (2014) 332–339.
[8] G. Vandewalle, et al., Spectral quality of light modulates emotional brain responses in humans, Proc. Natl. Acad. Sci. U. S. A. 107 (45) (2010) 19549–19554.
[9] G. Vandewalle, et al., Abnormal hypothalamic response to light in seasonal affective disorder, Biol. Psychiatry 70 (10) (2011) 954–961.
[10] B.-T. Lee, et al., The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (7) (2007) 1487–1492.
[11] M.B. Stein, et al., Increased amygdala and insula activation during emotion processing in anxiety-prone subjects, Am. J. Psychiatry 164 (2) (2007) 318–327.
[12] I.A. Strigo, et al., Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain, Arch. Gen. Psychiatry 65 (11) (2008) 1275–1284.
[13] T. Straube, H.-J. Mentzel, W.H. Miltner, Waiting for spiders: brain activation during anticipatory anxiety in spider phobics, Neuroimage 37 (4) (2007) 1427–1436.
[14] J.B. Nitschke, et al., Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response, Am. J. Psychiatry 166 (3) (2009) 302–310.
[15] C. Herry, et al., Processing of temporal unpredictability in human and animal amygdala, J. Neurosci. 27 (22) (2007) 5958–5966.
[16] I. Sarinopoulos, et al., Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala, Cereb. Cortex (2009) pbhp155.
[17] G. Bush, et al., Dorsal anterior cingulate cortex: a role in reward-based decision making, Proc. Natl. Acad. Sci. U. S. A. 99 (1) (2002) 523–528.
[18] M. Silvetti, et al., From conflict management to reward-based decision making: actors and critics in primate medial frontal cortex, Neurosci. Biobehav. Rev. 46 (2014) 44–57.
[19] M. Shidara, B.J. Richmond, Anterior cingulate: single neuronal signals related to degree of reward expectancy, Science 296 (5573) (2002) 1709–1711.
[20] M.J. Smoski, et al., fMRI of alterations in reward selection: anticipation, and feedback in major depressive disorder, J. Affect. Disord. 118 (1) (2009) 69–78.
[21] G.S. Dichter, et al., The effects of psychotherapy on neural responses to rewards in major depression, Biol. Psychiatry 66 (9) (2009) 886–897.
[22] Y. Izumi, C.F. Zorumski, Norepinephrine promotes long-term potentiation in the adult rat hippocampus in vitro, Synapse 31 (3) (1999) 196–202.
[23] H. Katsuki, Y. Izumi, C.F. Zorumski, Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region, J. Neurophysiol. 77 (6) (1997) 3013–3020.
[24] R.L. Aupperle, et al., Neural responses during emotional processing before and after cognitive trauma therapy for battered women, Psychiatry Res.: Neuroimaging 214 (1) (2013) 48–55.

[25] A.T. Beck, R.A. Steer, G.K. Brown, BDI-II: Beck Depression Inventory Manual, 2nd ed., Psychologial Corporation, San Antonio, TX, 1996.
[26] J.A. Maldjian, et al., An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets, Neuroimage 19 (3) (2003) 1233–1239.
[27] N. Tzourio-Mazoyer, et al., Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain, Neuroimage 15 (1) (2002) 273–289.
[28] R.J. Davidson, et al., The neural substrates of affective processing in depressed patients treated with venlafaxine, Am. J. Psychiatry 160 (1) (2014) 64–75.
[29] C. Grillon, et al., Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder, Am. J. Psychiatry 165 (7) (2008) 898–904.
[30] G. Vandewalle, et al., Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem, PLoS One 2 (11) (2007) 1247.

INDIVIDUAL ABSTRACT SUBMISSION DETAILS:

Date Submitted (still in DRAFT if blank): August 15, 2016, 5:26 PM
Control ID: 2592438
Abstract Title: Blue Wavelength Light Therapy Increases Thalamic Grey Matter Volume Following Mild Traumatic Brain Injury
Preferred Presentation Type: Poster Only
Selected Category: Acquired Brain Injury (TBI/Cerebrovascular Injury & Disease - Adult)
Selected Keyword(s): traumatic brain injury, sleep, neuroimaging, structural.
Contact / Submitting Author: Jenna Franco
Presenter (underlined in list below): William D. "Scott" Killgore

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ABSTRACT PROOF--PLEASE REVIEW CAREFULLY:

TITLE: Blue Wavelength Light Therapy Increases Thalamic Grey Matter Volume Following Mild Traumatic Brain Injury
AUTHOR(S): J. Franco, M. Millan, B. R. Shane, A. Castellanos, W. Killgore
ABSTRACT BODY:

Objective : Approximately 50% of patients with traumatic brain injury (TBI) complain of sleep disturbances. Current research shows that bright light therapy (BLT), which has been used in the past to treat depression, is also effective in reducing fatigue in patients with TBI. However, the underlying mechanisms are still unknown. We hypothesized that six weeks of blue BLT would lead to improved sleep and induce structural changes in the brains of individuals with mild TBI.
Participants and Methods: In a double blind design, 28 subjects (18-45 years of age) with mild TBI were randomly assigned to either the blue BLT treatment group or the amber BLT placebo group. Actigraphy watches were used for at-home monitoring of sleep and wake patterns, and the Epworth Sleepiness Scale (ESS) was administered to measure daytime sleepiness. MRI scans of each subject's brain were collected and voxel based morphometry (VBM) was utilized to measure changes in grey matter (GM) volume following treatment.
Results : Six weeks of blue BLT significantly shifted subjects' circadian rhythms towards earlier bedtimes ($p < 0.05$), and reduced daytime sleepiness by 30% when compared to pre-treatment values ($p < 0.01$). Blue BLT also caused a significant increase in thalamic GM after controlling for age, gender, and total intracranial volume. Specifically, the thalamic pulvinar nucleus had a significantly larger GM volume after treatment when compared to that of TBI subjects who had undergone the placebo therapy ($p < 0.01$ for difference in amber to blue post; $p < 0.0001$ for difference in blue pre to post).
Conclusions : Blue BLT improved timing of sleep by causing subjects to go to bed an hour earlier than their pre-treatment bedtime. It also reduced daytime sleepiness and significantly increased thalamic GM volume. These findings represent a first step to understanding how BLT works on a neurological level. In the future, light therapy may prove to be a novel and effective way to treat sleep disturbance and improve neurocognitive recovery following a mild TBI.

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Received: 5 September 2017 | Revised: 20 December 2017 | Accepted: 1 January 2018

DOI: 10.1002/hbm.23951

RESEARCH ARTICLE

WILEY

Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury

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Funding information
U.S. Army Medical Research and Materiel Command, Grant/Award Numbers: W81XWH-11-1-0056, W81XWH-12-1-0109, W81XWH-12-1-0386

Abstract

There is currently a critical need to establish an improved understanding of time-dependent differences in brain structure following mild traumatic brain injury (mTBI). We compared differences in brain structure, specifically cortical thickness (CT), cortical volume (CV), and cortical surface area (CSA) in 54 individuals who sustained a recent mTBI and 33 healthy controls (HCs). Individuals with mTBI were split into three groups, depending on their time since injury. By comparing structural measures between mTBI and HC groups, differences in CT reflected cortical thickening within several areas following 0–3 (time-point, TP1) and 3–6 months (TP2) post-mTBI. Compared with the HC group, the mTBI group at TP2 showed lower CSA within several areas. Compared with the mTBI group at TP2, the mTBI group during the most chronic stage (TP3: 6–18 months post-mTBI) showed significantly higher CSA in several areas. All the above reported differences in CT and CSA were significant at a cluster-forming $p < .01$ (corrected for multiple comparisons). We also found that in the mTBI group at TP2, CT within two clusters (i.e., the left rostral middle frontal gyrus (L. RMFG) and the right postcentral gyrus (R. PostCG)) was negatively correlated with basic attention abilities (L. RMFG: $r = -.41$, $p = .05$ and R. PostCG: $r = -.44$, $p = .03$). Our findings suggest that alterations in CT and associated neuropsychological assessments may be more prominent during the early stages of mTBI. However, alterations in CSA may reflect compensatory structural recovery during the chronic stages of mTBI.

KEYWORDS
concussion, cortical plasticity, cortical structure, cortical surface area, cortical thickness, cortical volume, sleep

1 | INTRODUCTION

Traumatic brain injury (TBI) is a highly prevalent condition, affecting an estimated 1.7 million annually in the United States (Faul, Xu, Wald, & Coronado, 2010). Of these, it is estimated that ~75% of injuries can be classified as mild traumatic brain injury (mTBI) (Centers for Disease Control and Prevention (CDC), 2003), often described as "concussion." Most mTBIs resolve quickly and without complications (McCrea et al., 2003). However, a significant proportion of individuals who sustain an mTBI continue to experience chronic postconcussive symptoms, which may include deficits in attention, concentration, and memory, and chronic complaints of fatigue, headaches, mood lability, and sleep difficulties (Bigler, 2008; Haboubi, Long, Koshy, & Ward, 2001; Packard, 2008; Pare, Rabin, Fogel, & Pepin, 2009). Notably, ~50% of patients with an mTBI will experience chronic sleep disruption in the months and years after their injury (Orff, Ayalon, & Drummond, 2009), including poor sleep quality, delayed sleep phase, daytime hypersomnia, and/or impaired daytime vigilance (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Castriotta et al., 2007; Makley et al., 2008; Parcell,

Abbreviations: CSA, cortical surface area; CT, cortical thickness; CV, cortical volume; ESS, Epworth Sleepiness Scale; HCs, healthy controls; MTBI, mild traumatic brain injury; TBI, traumatic brain injury; TP, time-point; TPs, time-points.

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Ponsford, Redman, & Rajaratnam, 2008; Rao et al., 2008; Verma, Anand, & Verma, 2007; Williams, Lazic, & Ogilvie, 2008). Moreover, the presence of a sleep problem following an mTBI is problematic, as it is typically associated with poorer recovery and exacerbation of neuropsychiatric complications (Gilbert, Kark, Gehrman, & Bogdanova, 2015). Finally, recent evidence suggests that sleep may play a critical role in brain repair and recovery processes by enhancing neurotoxin clearance (Xie et al., 2013) and increasing the proliferation of oligodendrocyte precursor cells, which are necessary for myelin repair and regrowth (Bellesi et al., 2013). *Sleep is essential to recovery* but patients with mTBI often obtain insufficient quantity and quality of sleep to optimize recovery.

Although the effects of mTBI on specific brain areas and its long-term effect on brain and behavior have been previously investigated (Dean et al., 2013; Dean and Sterr, 2013; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017), the natural progression of recovery from mTBI has not been clearly documented using multiple structural imaging techniques. For instance, it would be useful to know how cerebral gray and white matter volumes or their morphology differ over the natural course of recovery so that departures from normal can be identified and appropriate interventions initiated as soon as possible. At present, our understanding of the recovery process has been hindered by the inconsistency of injury time frames studied across various investigations. For example, previous studies have explored functional, structural, and symptomatic complaints within 1 month post-mTBI (Ling, Klimaj, Toulouse, & Mayer, 2013; Paniak et al., 2002), 3 months post-mTBI (Laborey et al., 2014; Ling et al., 2013; Wang et al., 2015), and 6 months or more post-mTBI (De Kruijk et al., 2002; Novack, Alderson, Bush, Meythaler, & Canupp, 2000; Zhou et al., 2013). Studies on mTBI, conducted at a given time-point postinjury, provide valuable information about postconcussive symptoms and functional and structural recovery. However, when injury groups are studied in isolation, it is difficult to visualize the larger picture of brain recovery. Therefore, a better understanding of the complex brain mechanisms that unfold in the months following mTBI is needed, which might lead to more reliable and cost-effective rehabilitation techniques for those suffering from mTBI. Keeping that in mind, in our study, we subcategorized mTBI individuals into three groups depending on their time since injury (0–3 months, 3–6 months, and 6–18 months).

In recent years, a number of structural brain measures, such as cortical thickness (CT), cortical volume (CV), and cortical surface area (CSA) have been proposed to be of importance in evaluating changes in brain structure following mTBI (Dall'Acqua et al., 2016; Govindarajan et al., 2016; Zhou et al., 2013). Although these cortical metrics of brain structure tend to covary together to some extent, following an mTBI, they each reflect different facets of morphology that contribute uniquely to overall brain function. Cortical measures also play a potentially important role in evaluating attention abilities and sleep quality (Altena, Vrenken, Van Der Werf, van den Heuvel, & Van Someren, 2010; Spira et al., 2016; Stoffers et al., 2012; Westlye, Grydeland, Walhovd, & Fjell, 2011). For instance, in mTBI patients, significant cortical thinning in the right precuneus and anterior cingulate gyrus was associated with poor performance on memory and attention tasks (Zhou et al., 2013). In patients with persistent insomnia, cortical thinning was reported in the anterior cingulate cortex, precentral cortex, and the lateral prefrontal cortex (Suh, Kim, Dang-Vu, Joo, & Shin, 2016). Reduced CV within the superior frontal cortex was also reported to be associated with poor sleep quality (Chao, Mohlenhoff, Weiner, & Neylan, 2014; Sexton, Storsve, Walhovd, Johansen-Berg, & Fjell, 2014). Reduced gray matter volume within the bilateral lateral orbitofrontal cortices and bilateral inferior frontal gyri pars orbitalis was also associated with sleep interruptions due to repeated awakenings (Lim et al., 2016). Nonetheless, it is unclear the extent to which different structural measures of the brain and their associated capacities pertaining to better attention abilities and sleep vary independently of one another or whether the dynamics of one structural measure depends on the dynamics of another following mTBI. Previously, Mota and Herculano-Houzel (2015) showed the interdependent nature of structural measures, such as cortical folding, CSA, and CT, reporting that the changes in cortical folding depended not only on CSA but also on CT. Taken together, such studies interpret the dependence of brain performance on the integrated impact of surface area and cortical thickness in a healthy brain, but this possibility has not been extended to TBI. While prior structural neuroimaging has not been able to reliably identify consistent morphological changes associated with mTBI, it is conceivable that these metrics, when applied in conjunction with one another, may prove more sensitive to subtle changes during the recovery process.

In this study, our primary goal was to explore differences in multiple brain structural measures, such as CT, CV, and CSA at different stages post-mTBI. Our second goal was to examine the association between the three brain morphology metrics, attentional processes, and sleep-related outcomes for all the *regions of interest* which showed differences in structural measures at the various time points in the year following injury. We hypothesized that the differences in each of the three brain morphological measures would (i) display unique and significant structural differences across different stages post-mTBI and (ii) show that differences in CT, CV, and CSA would correlate with differences in attention and sleep measures.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 87 adults, recruited from the general population within the greater metropolitan area of Boston, MA and New England, participated in this study. Thirty-three participants were included as healthy controls (HCs, mean age = 24.52 ± 3.0 years, 19 female) and 54 participants with a recent mTBI were included in the mTBI group (mean age = 22.40 ± 4.6 years, 33 female, time since injury between 0 and 18 months, mean = 5.73 ± 3.9 months). Any participant from the HC group or mTBI group with any history of drug or alcohol abuse or current use of illicit substances was excluded. Current alcohol use was required to be lower than the Center for Disease Control criteria for excessive alcohol use (www.cic.gov/alcohol). All HCs were recruited as part of a separate study (although no data from these subjects regarding cortical thickness, volume, or surface area

TABLE 1 Demographic characteristics of healthy controls and mTBI participants

Demographics	Healthy controls ($N = 33$)	MTBI overall ($N = 54$)	MTBI (TP1) ($N = 18$)	MTBI (TP2) ($N = 22$)	MTBI (TP3) ($N = 14$)	Statistical significance
Mean age (S.D.)	24.52 (3.0)[a]	22.40 (4.6)	24.56 (6.1)[b]	21.77 (3.5)	20.61 (2.6)[a,b]	$F(3,86) = 4.98^*$
(in years)						
Gender	58	61	61	64	57	$\chi^2(3) = 0.26$
(% female)						
Time-since-injury (TSI) in months	-	$0 < TSI \leq 18$	$0 < TSI \leq 3$	$3 < TSI \leq 6$	$6 < TSI \leq 18$	-
ATT	-	105.02 (13.4)	104.05 (9.1)	108.45 (12.9)	100.86 (17.8)	$F(2,53) = 1.47$
ESS	-	8.89 (3.6)	8.39 (3.6)	8.86 (4.0)	9.57 (3.1)	$F(2,53) = 0.41$
PSQI	-	6.25 (2.7)	5.67 (2.4)	6.59 (2.9)	6.50 (2.6)	$F(2,53) = 0.66$

Note. Abbreviation: TP = time-point.
Superscripts "a" and "b" denote the groups that significantly differ at $^*p < .05$.

have been published previously) but with the same scanning parameters and on the same scanner as the mTBI group. Neuropsychological testing was completed at the Social Cognitive and Affective Neuroscience laboratory located at McLean Hospital. All participants underwent high-resolution anatomical brain imaging using a Siemens Tim Trio 3T scanner (Erlangen, Germany) located at the McLean Hospital Imaging Center.

2.1.1 | Inclusion/exclusion criteria for HCs

All the HCs were screened via a comprehensive telephone interview and were excluded if there was any history of psychiatric or neurological disorder, significant medical problems—including head injury, sleep disorders—or current use of psychotropic medications that could affect neuroimaging. Additionally, the inclusion eligibility of all the HCs was determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV Axis I Disorders) (SCID) (First, Spitzer, Gibbon, & Williams, 2002). All the HCs met inclusion criteria and none of them met diagnostic criteria for any current/lifetime Axis I disorder.

2.1.2 | Inclusion/exclusion criteria for mTBI individuals

An mTBI was defined based on the criteria established by the American Congress on Rehabilitation Medicine (Head, 1993) and later adopted by the Department of Veterans Affairs and the Department of Defense (Management of Concussion/mTBI Working Group, 2009) as a traumatically induced event that was associated with an alteration in mental state (e.g., confusion, disorientation), consciousness (i.e., loss of consciousness <30 min; alteration of consciousness up to 24 h) and post-traumatic amnesia up to 24 h. Individuals with any history of neurological, mood, or psychotic disorder with an onset prior to the mTBI, or who suffered a loss of consciousness exceeding 30 min following an injury were excluded. Although the study was funded by the U.S. Army Medical Research and Materiel Command, none of the participants were active duty military and none of the head injuries were caused by exposure to combat.

2.1.3 | Grouping of mTBI individuals

In this study, eligible individuals with mTBI were grouped into one of three subcategories based on time-since injury: <3 months, between 3 and 6 months, and between 6 and 18 months. Eighteen individuals experienced an mTBI (mean age = 24.56 ± 6.09 years, 11 female) within the preceding 3 months (TP1), 22 experienced an mTBI (mean age = 21.77 ± 3.53 years, 14 female) between 3 and 6 months prior to evaluation (TP2), and 14 experienced an mTBI (mean age = 20.61 ± 2.56 years, 8 female) between 6 and 18 months prior to the evaluation (TP3). Groups were different in "age" ($F(3,86) = 4.98$, $p < .05$, one-way ANOVA), but not "gender" ($\chi^2(3) = 0.26$, $p > .05$, Pearson's Chi-square). Demographic information of all the groups (HCs and three mTBI groups) is summarized in Table 1.

2.1.4 | Consent, compensation, and IRB approval

Written consent was obtained from each participant before the experiment. Additionally, each participant was thoroughly briefed on the potential risks and benefits of the study and participants were financially compensated for their time. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Office (HRPO). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2 | Data acquisition

2.2.1 | Magnetic resonance imaging

All participants were instructed to rest, relax, and try their best to stay motionless during scanning. Neuroanatomical data were acquired using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence which consisted of 176 sagittal slices (voxel resolution = 1 × 1 mm, field of view (FOV) = 256 mm) with TR/TE/FA/inversion time of 2100 ms/2.30 ms/12°/1100 ms encompassing the whole brain.

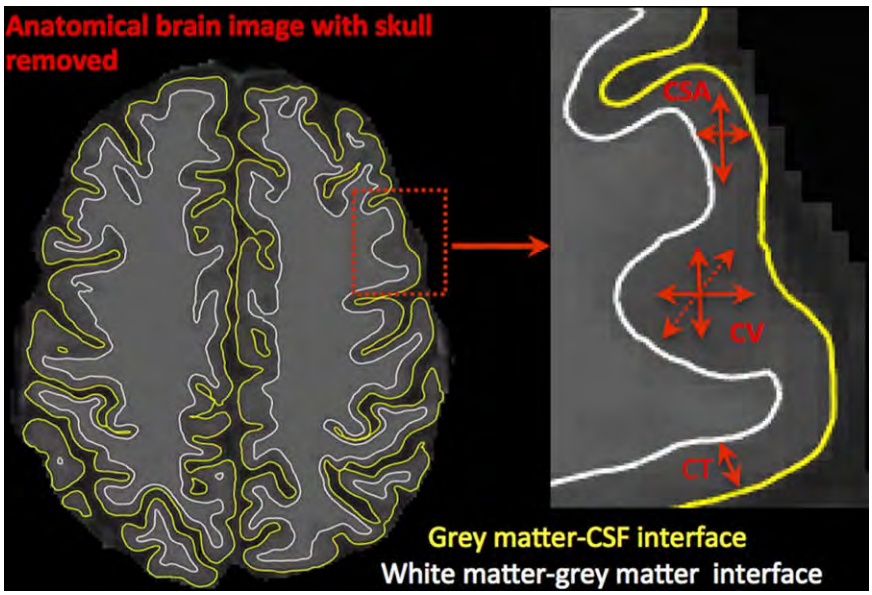


FIGURE 1 Cortical thickness (CT), cortical volume (CV), and cortical surface area (CSA). Representation of cortical measures (CT, CV, and CSA) within original anatomical brain image [Color figure can be viewed at wileyonlinelibrary.com]

2.2.2 | Attention and sleep measures

The mTBI participants completed three well-validated assessments: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998) for attention (ATT), a combination of digit span and coding subtests, the Epworth Sleepiness Scale (ESS) (Johns, 1991) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). No such data were recorded from HCs. The RBANS ATT index is a measure of speed and accuracy of information processing, with a mean of 100 and standard deviation of 15. Here a lower RBANS ATT index score represents difficulty in basic attention processing. The use of the RBANS has been shown to be a clinically valid and reliable screening tool for patients with traumatic brain injury (McKay, Casey, Wertheimer, & Fichtenberg, 2007). ESS measures the severity of daytime sleepiness and PSQI is a measure of sleep problems, which takes into account several facets of sleep, including sleep latency, sleep duration, and sleep disturbances. ESS scores range from 0 to 24, where higher scores represent severe excessive daytime sleepiness and PSQI scores range from 0 to 21, where higher scores represent poor sleep quality. A subset of other, unrelated behavioral data from this mTBI sample have been reported elsewhere (Killgore et al., 2016).

2.3 | Data analysis

2.3.1 | Identification of affected brain areas following mTBI

The "recon-all" pipeline in FreeSurfer (version 6.0) (https://surfer.nmr.mgh.harvard.edu/fswiki) was used to process anatomical images for all the participants (HCs and individuals with mTBI). Processing involved motion-correction, brain extraction (i.e., removal of skull, skin, neck, and eye-balls), automated transformation to the Talairach co-ordinate system, intensity correction, volumetric segmentation, and smoothing using a 15 mm full-width at half-maximum (FWHM) Gaussian kernel. For each HC and mTBI participant, we visually inspected raw T1-weighted image data to determine any possible imaging artifacts, which could affect FreeSurfer's segmentation accuracy. Accuracy of the FreeSurfer generated skull-stripped brain masks and brain surfaces (pial and white) were visually inspected for all the participants from the HC and mTBI groups. The measures of CT, CV, and CSA were calculated separately for the left and the right hemispheres for each participant. CT is defined as the mean distance from the white–grey matter interface to the nearest point on the pial surface (grey matter–CSF interface) and from that point on the pial surface back to grey/white matter interface (Fischl and Dale, 2000), CV is defined as the amount of grey matter that lies between the white–grey matter interface and pial matter (Winkler et al., 2010), and CSA is the sum of the areas of the triangles making up the surface model and is defined as the extent of the two-dimensional surface enclosed by the outer layer of the cerebral cortex (http://cna.hanyang.ac.kr/research/research02.htm) (Fischl, Sereno, & Dale, 1999) (Figure 1). For vertex-by-vertex general linear model (GLM) estimation across the left and the right cortical surface, CT, CV, and CSA were used as individual dependent variables. This method was used to generate statistical parametric maps to identify the brain areas, which showed significantly different CT, CV, or CSA in those with a mTBI (TP1, TP2, or TP3) compared to HCs and within three TPs (TP1 versus TP2, TP1 versus TP3, and TP2 versus TP3). These statistical maps display the distribution of p values. Effects of "age" (demeaned) and "gender" were regressed out when performing group analyses. As the group-wise sample size in our study is small and the differences in brain structure between HCs and mTBI groups and within the mTBI groups are not expected to be localized finely, we selected a moderately larger smoothing kernel size of 15 mm. Moreover, unlike volume-based analysis, larger smoothing kernel size in surface-based analysis never extends into bone/air/white matter. Furthermore, we used a cluster forming threshold (CFT) of $p < 0.01$. Multiple comparisons were

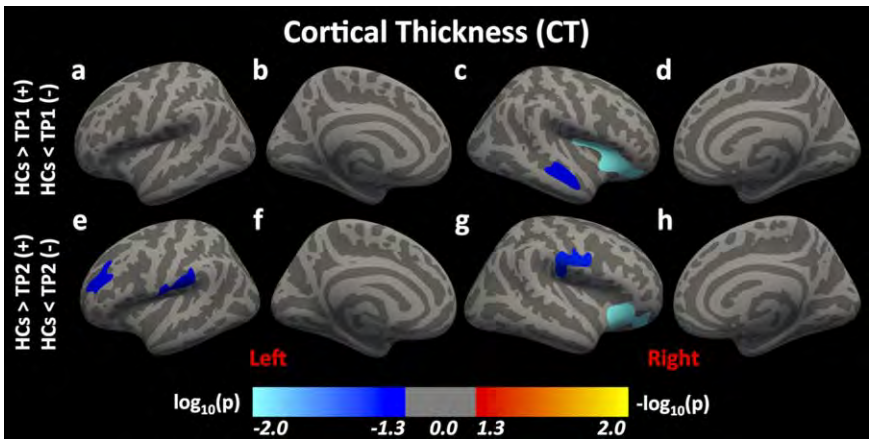


FIGURE 2 Differences in cortical thickness (CT) following mTBI. Here, we report significant differences in CT between HCs and individuals with mTBI at time-points (TPs) 1 and 2 [Color figure can be viewed at wileyonlinelibrary.com]

corrected at a clusterwise statistical threshold (CWP) of $p < 0.05$ using Monte-Carlo simulations.

2.3.2 | Association between structural measures, ATT, and sleep measures

The method described above was used to generate statistical parametric maps to identify the brain areas, which showed significant differences in CT, CV, or CSA when compared across each of the three time-points and when compared to HC group. Multiple brain regions identified over the whole brain, which showed significant differences in CT, CV, or CSA between mTBI groups and HC group or across time-points (i.e., from TP1 to TP2, and/or from TP1 to TP3 and/or from TP2 to TP3), were selected as *regions of interest* (ROIs). Subject-wise CT, CV, and CSA of corresponding ROIs were calculated by performing a whole brain parcellation into 34 brain areas using the "Desikan–Killiany" atlas (Desikan et al., 2006). In this atlas, the automated method used to subdivide the human cerebral cortex into 34 cortical ROIs is both anatomically valid and reliable with average intraclass correlation coefficients of 0.835 across all of the ROIs (Desikan et al., 2006). Partial correlation analyses were performed between structural measures (CT, CV, and CSA), attention (RBANS ATT), and sleep measures (ESS and PSQI) for all ROIs identified during the initial analysis, after considering the effects of "age" (demeaned), "gender," and corresponding whole-brain structural measures. The correlation analysis was performed only for the ROIs; therefore, partial correlations were not corrected for multiple comparisons.

3 | RESULTS

3.1 | Structural measures for HCs versus three mTBI groups

CT: Compared to HCs, 2 clusters—the right insula and the right superior temporal gyrus (STG)—in the mTBI group at TP1 showed significantly greater CT (Figure 2a–d). Compared to HCs, 4 clusters—the left rostral middle frontal gyrus (RMFG), the left supramarginal gyrus (SMG), the right lateral orbitofrontal cortex (LOFC), and the right postcentral gyrus (PostCG)—in the mTBI group at TP2 showed significantly greater CT (Figure 2e–h). These findings are summarized in Table 2. There were no significant difference in CT between HCs and mTBI group at TP3. Within the three TPs also, we did not find significant differences in CT, that is, for TP1 versus TP2, for TP2 versus TP3, or for TP1 versus TP3.

CV: We did not find significant differences in CV when compared between HCs and any of the three mTBI groups and within three mTBI groups.

CSA: Compared to HCs, 3 clusters—the right PostCG, the right inferior temporal cortex, and the right superior frontal cortex—in the mTBI group at TP2 showed significantly lower CSA (Figure 3a–d). There were no significant difference in CSA between HCs and mTBI groups at TP1 or TP3. These findings are summarized in Table 3. Within the three-mTBI groups, 3 clusters—the left STC, the left PostCG, and the right isthmus of cingulate gyrus—in the mTBI group at TP3 showed significantly higher CSA compared to TP2 (Figure 3e–h). These findings are summarized in Table 4.

3.2 | Correlation analysis between structural measures, RBANS ATT, and sleep measures

For two ROIs—the right postcentral gyrus (R. PostCG) and the left rostral middle frontal gyrus (L. RMFG)—there were negative correlations between CT and the RBANS ATT index within TP2 (R. PostCG: $r = -.44$, $p = .03$ and L. RMFG: $r = -.41$, $p = .05$) (Figure 4a,b). However, the mTBI groups were not significantly different on RBANS ATT ($F(2,53) = 1.47$, $p = .24$, one-way ANOVA), ESS ($F(2,53) = 0.41$, $= 0.66$, one-way ANOVA) or PSQI ($F(2,53) = 0.66$, $p = .52$, one-way ANOVA) (Table 1).

3.2.1 | Impressions

Bilateral cortical thickening was observed during the acute stages of mTBI (i.e., within 0–3 and 3–6 months post-mTBI) compared to HCs. During the less acute stage of mTBI (i.e., 3–6 months post-mTBI), CSA was lower as compared to HCs. During the chronic stage of mTBI (i.e., 6–18 months post-mTBI), CSA was higher in comparison to acute stages of mTBI (i.e., 3–6 months post-mTBI). Moreover, in mTBI

TABLE 2 Comparison of cortical thickness (CT) between healthy controls (HCs) and individuals with an mTBI at time-points 1, 2, and 3

Cluster number	MNIX, MNIY, MNIZ (Peak)	Annotation (Peak)	Cluster size (Voxels)	(+) HCs > TP 1/2/3 (−) HCs < TP 1/2/3
Cortical thickness (CT): HCs versus mTBI (TP1)				
Left hemisphere (LH)				
None				
Right hemisphere (RH)				
1	31.5, 21.2, −0.1	Insula	3901	(−)
2	48.8, −19.8, −6.3	Superior temporal gyrus	1297	(−)
Cortical thickness (CT): HCs versus mTBI (TP2)				
Left hemisphere (LH)				
1	−32.6, 41.1, 19.3	Rostral middle frontal gyrus	1453	(−)
2	−56.5, −23.9, 21.4	Supramarginal gyrus	1859	(−)
Right hemisphere (RH)				
1	29.5, 24.9, −8.4	Lateral orbitofrontal cortex	2387	(−)
2	62.9, −12.1, 23.7	Postcentral gyrus	2280	(−)
Cortical thickness (CT): HCs versus mTBI (TP3)				
Left hemisphere (LH)/right hemisphere (RH)				
None				

Note. Abbreviations: HCs = healthy controls; mTBI = mild traumatic brain injury; TP = time-point.

individuals, higher CT of the left PostCG and the right RMFG within TP2 was associated with lower attention scores.

4 | DISCUSSION

In this study, we document time-dependent differences across several measures of brain structure following an mTBI. Our findings suggest that cortical alterations in thickness and their associated behavioral outcomes may occur at early stage of mTBI. However, cortical alterations in surface area are suggestive of trends of potential partial physical recovery with greater time since injury.

4.1 | Time-dependent cortical differences following mTBI

CT: In general, previous studies on CT following an mTBI reported thinning and thickening of the cortex (Govindarajan et al., 2016; Wang et al., 2015). It has been suggested that cortical differences might depend on several factors, including the time since injury, symptom severity, regional microedema, localized microhemorrhages, and cytotoxic edema (Lewen, Fredriksson, Li, Olsson, & Hillered, 1999; Wang et al., 2015). It was also suggested that due to subsequent cortical thinning after several weeks, differences in cortical thickness were

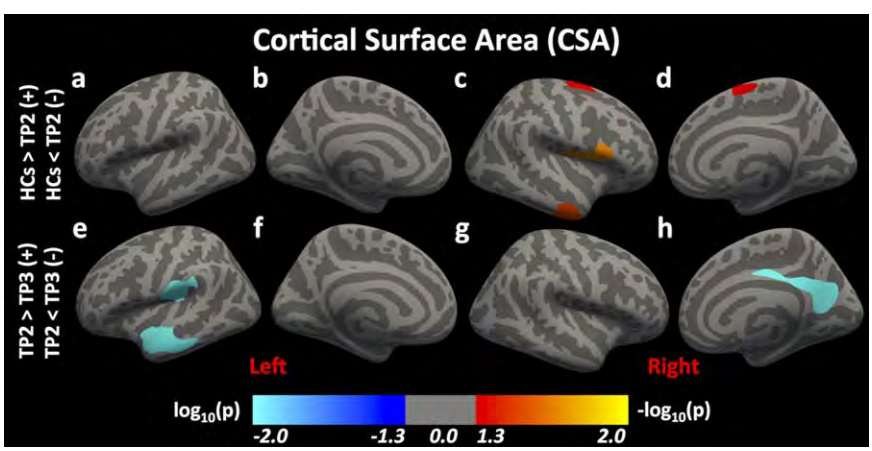


FIGURE 3 Differences in cortical surface area (CSA) following mTBI. Here, we report significant differences in CSA between HCs and individuals with mTBI at time-point (TP) 2 and between mTBI groups at TPs 2 and 3 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Comparison of cortical surface area (CSA) between healthy controls (HCs) and individuals with an mTBI at time-points 1, 2, and 3

Cluster number	MNIX, MNIY, MNIZ (Peak)	Annotation (Peak)	Cluster size (Voxels)	(+) HCs > TP 1/2/3 (−) HCs < TP 1/2/3
Cortical surface area (CSA): HCs versus MTBI (TP1)				
Left hemisphere (LH)/right hemisphere (RH)				
None				
Cortical surface area (CSA): HCs versus MTBI (TP2)				
Left hemisphere (LH)				
None				
Right hemisphere (RH)				
1	40.9, −3.3, 18.0	Postcentral gyrus	2488	(+)
2	46.4, −5.7, −38.7	Inferior temporal cortex	1835	(+)
3	23.1, 2.2, 60.9	Superior frontal cortex	2047	(+)
Cortical surface area (CSA): HCs versus MTBI (TP3)				
Left hemisphere (LH)/right hemisphere (RH)				
None				

Note. Abbreviations: HCs = healthy controls; TP = time-point.

undetectable at later time points (Govindarajan et al., 2016; Lewen et al., 1999; Tate et al., 2014). However, in this study, compared to HCs, we reported thickening within the right insula and the right STG among mTBI individuals who were between 0 and 3 months of injury and within the left RMFG, left SMG, right LOFC, and right PostCG among mTBI individuals who were between 3 and 6 months of injury.

Recently, brain regions including the insula, STC, and PostCG have been shown to display greater neural activation among individuals with mTBI relative to controls (Dretsch et al., 2017). In that study, it was proposed that several psychological health symptoms such as depression and attentional bias toward negatively valenced stimuli could be responsible for the neural hyperacivation within several regions of interest in the mTBI group. However, the validity of similar mechanisms resulting in cortical thickening within these regions following an mTBI still needs to be confirmed. In a separate study, higher numbers of mTBIs were also associated with reduced CT within the bilateral insula and right middle temporal gyrus (List, Ott, Bukowski, Lindenberg, & Floel, 2015). In that study, it was hypothesized that recurrent mTBIs may induce distinct alterations, especially thinning of the cortex. Consistent with our findings, it was proposed that cortical alterations from the acute phase following an mTBI may normalize in the chronic phase. Moreover, cortical thickening within the right RMFG was reported immediately following an mTBI (Wang et al., 2015). At 3 months post-mTBI, no more cortical thinning was observed in the supramarginal gyrus (Govindarajan et al., 2016). However, we observed thickening of the supramarginal gyrus at 3 months post-mTBI. During the first year after mTBI, changes in CT indicated thickening of the prefrontal cortex, including orbitofrontal cortex in mTBI patients (Dall'Acqua et al., 2017; Wilde et al., 2012). Cortical thickening during initial scans following an mTBI and cortical thinning in later scans may reflect progressive normalization of CT, that is, physical recovery from brain lesions (Lewen et al., 1999; Wang et al., 2015). In addition, the brain areas, such as RMFG, which are more susceptible to direct impacts following a frontal–rear axis head injury, may result in the release of excitotoxins from damaged tissues causing inflammatory reactions, including microedema (Barkhoudarian, Hovda, & Giza, 2011; Lillie, Urban, Lynch, Whitlow, &

TABLE 4 Comparison of cortical surface area (CSA) between mTBI time-point (TP) 2 and TP3

mTBI: time-point 2 (TP2) versus time-point 3 (TP3)				
Cluster number	**MNIX, MNIY, MNIZ (Peak)**	**Annotation (Peak)**	**Cluster Size (Voxels)**	**(+) TP 2 > TP 3 (−) TP 2 < TP 3**
Cortical surface area (CSA)				
Left hemisphere (LH)				
1	−52.2, 7.4, −14.6	Superior temporal cortex	3587	(−)
2	−56.0, −17.5, 16.2	Postcentral gyrus	2892	(−)
Right hemisphere (RH)				
1	5.4, −47.2, 30.1	Isthmus cingulate	3480	(−)

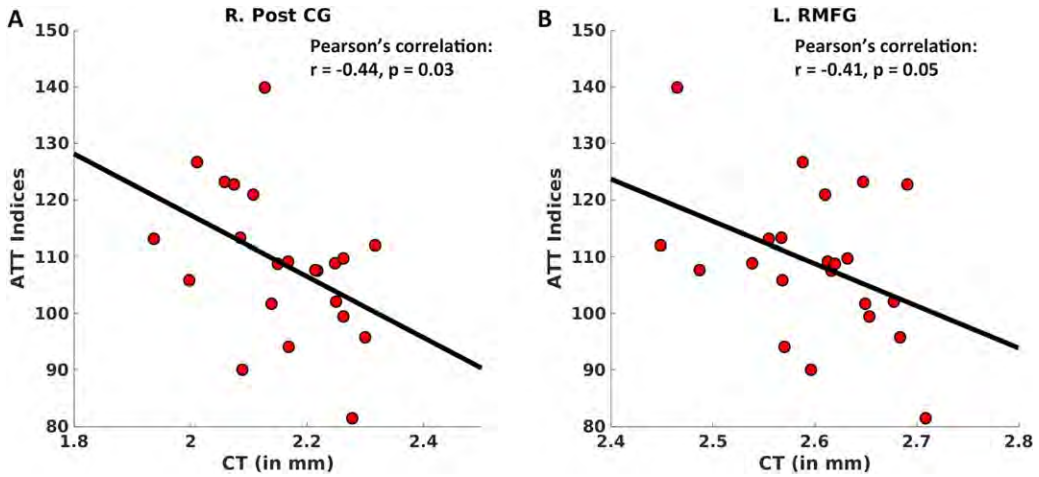


FIGURE 4 Significant partial correlations between RBANS ATT and cortical thickness (CT). After regressing out the effects of age, gender, and whole-brain CT, here we plot significant correlations found between RBANS ATT and CT for both the ROIs (a) the right postcentral gyrus (R. PostCG) ($r = -.44$, $p = .03$) and (b) the left rostral middle frontal gyrus (R. RMFG) ($r = -.41$, $p = .05$) [Color figure can be viewed at wileyonlinelibrary.com]

Stitzel, 2013; Patterson and Holahan, 2012; Urban et al., 2012). These inflammatory reactions have been reported to elevate fractional anisotropy, thicken the cortical regions initially but cause cortical thinning over time with the reduction of microedema (Lewen et al., 1999; Ling et al., 2013).

CV: CV is a composite of both CT and CSA, therefore, changes in CV could be due to changes in either CT or CSA, or both. Therefore, significant increase in CT and significant reduction in CSA or vice versa could be responsible for an unknown CV proportionality across the cortex or even the absence of differences in CV in the three mTBI groups, as observed in our study. Previously in a study on gene identification, it was reported that measures of grey matter volume are less sensitive than CT or CSA, where CT and CSA are also distinct from genetic origins (Winkler et al., 2010). In that study, there was no clear interpretation made from regional grey matter volume differences in terms of genetic influences. In the same study, it was also reported that since the variability in CSA was higher compared to CT, variability on CV might therefore be more associated with CSA as compared to CT. Our findings are partially consistent with these mechanisms as we also found more variability in CT measures as compared to CV and CSA. We acknowledge the fact that the preceding analogy is not ideal and is made between mTBI groups and a gene identification study but the geometrical relationships between these three cortical measures (CT, CV, and CSA) and relatively more dependence of CV on CSA compared to CT may partially explain the underlying mechanisms behind our findings.

CSA: We observed greater CSA at the later stages of mTBI (i.e., 6 and 18 months post-mTBI). Specifically, we found that there were many regions with significantly lower CSA at TP2 compared to HCs but greater CSA at TP3 compared to TP2. The observed differences in CSA contrast with prior findings, as decreases in CSA were previously reported to be one of the earlier existing and sensitive biomarkers for the quantification of brain damage following mTBI (Dall'Acqua et al., 2016). However, larger CSA was shown by others to be associated with complex brain interactions and better cognitive skills (Raznahan et al., 2011; Schnack et al., 2015). In humans, a larger proportion of CSA due to larger surface convolutions is attributed to an extended and dynamic network of brain projections (Hofman, 2014). This generation of an extended dynamic network may not be quick and immediate but might instead be a slow process, which could be the backbone for brain plasticity resulting in compensation of behavioral skills following an injury. Significant increases in CSA, regardless of increases in CT, have also been associated with an increase in radial column units during expansion of the neocortex in primate evolution (Rakic, 2009). Integration of these neocortical columns at higher levels of information processing sets the neural basis of multiple brain regions and their unique features to interact dynamically, which could result in greater synaptic plasticity (Budd and Kisvarday, 2012; Hofman, 2014). Moreover, at the chronic stage of mTBI (i.e., 6–18 months post-mTBI), increases in CV rather than CT and CSA individually, which can account for changes in both CT and CSA, could be an indication of an increase in the formation of dendrites resulting in modest remodeling of the cortex over time (Killgore et al., 2016). These improvements in functional and structural abnormalities could also be closely associated with beneficial neural reorganization of the affected brain hemisphere. Experience-based changes in brain structure over time, also known as experience-dependent neural plasticity, were also found to be beneficial for reducing behavioral and physical disorders (Kerr, Cheng, & Jones, 2011).

In sum, the differences in multiple structural measures following an mTBI might indicate that various brain systems change at different rates. Previous brain imaging studies on mild, moderate, and severe TBI showed that although TBI patients performed equally well as HCs, they recruited a larger number of brain areas, including the frontal and posterior cortices (da Costa et al., 2015; Turner and Levine, 2008). Larger recruitment of these areas during later stages of mTBI could be due to reduced involvement of damaged brain areas immediately after an mTBI or greater compensatory recruitment in more chronic stages.

Diffusion imaging studies on TBI have also reported microstructural white-matter alterations that differ at various stages following injury, such as axonal swelling and/or an increase in glial cells (Pasternak et al., 2014), causing variations in CT, CV, or CSA across the recovery period following mTBI.

4.2 | Attention and sleep measures following mTBI

We observed that between 3 and 6 months post-mTBI, abnormally higher cortical thickening within the left RMFG and right PostCG compared to HCs, was negatively associated with performance on measures of attention. Previous work has shown that both RMFG and PostCG are reliably associated with attention capacities. For instance, it was reported that the posterior region within the rostral middle frontal cortex is activated by various cognitive tasks, *including* the ones designed to engage in internal monitoring of action, error and attention (Amodio and Frith, 2006). A positive correlation between thickness within the left posterior middle frontal cortex and performance on a dichotic listening task (a measure of executive attention) further suggested that the left middle frontal cortex is part of an executive attention network (Andersson, Ystad, Lundervold, & Lundervold, 2009). Furthermore, the PostCG or somatosensory cortex, which is the most anterior portion of the parietal lobe, is also one of the three major major sites (intraparietal, postcentral, and precentral) of activation for attention (Corbetta, 1998). A study on a group of right hemisphere stroke patients also suggested a vital role of the PostCG/somatosensory cortex in visuospatial attention (Balslev, Odoj, & Karnath, 2013). Thus, it is clear that the RMFG and PostCG play an important role in attention.

Interestingly, in this study, we did not observe significant differences in attention or sleep measures between any of the three mTBI groups. There was no significant association observed between increased CSA and improved attention abilities or sleep quality. One possible explanation may involve the construct of "cognitive reserve," or the ability to maintain cognitive functioning in the presence of brain damage or degenerative process (Stern, 2009, 2012). Previously, it was found that increased cognitive reserve might play a protective role against obstructive sleep apnea syndrome (OSAS)-related cognitive decline, *including* intelligence and attention (Alchanatis et al., 2005). Given the fact that our data did not include specific cognitive measures relevant to a range of sleep disorders, it is beyond the scope of our study to directly confirm that cognitive reserve played a role in the nonsignificant differences in attention and sleep measures across the three time-points. Regarding the sleep measures we used, another possibility is that some of the specific features of sleep biology are not well captured by self-reported measures (Lim et al., 2016). Future research in these areas is therefore needed to investigate these intriguing possibilities further.

4.3 | What are the benefits of using multiple structural measures?

In this study, we report the time-line of differences in multiple cortical measures, especially CT and CSA, following mTBI. In particular, we report that when CT was significantly different following mTBI, there were no differences observed in CSA, whereas when CT did not differ across time-points, CSA appeared to be higher, which could be due to greater cortical folding. Human brain development is associated with increased cortical folding, which leads to a progressively more convoluted brain structure and gyrification along spatial and temporal scales (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Richman, Stewart, Hutchinson, & Caviness, 1975). Compared to other species, the folds in the human brain are unique and are associated with specific behavioral skills (Gautam, Anstey, Wen, Sachdev, & Cherbuin, 2015; Gregory et al., 2016). Approximately one-third of the brain's cortical surface is visible, whereas two-thirds of the surface is hidden from view among its folds, leading to overall greater CSA and extra space for the accommodation of additional neurons (Toro, 2012). Cortical folding also shortens the distance of cortical connections by reducing the fiber length necessary between neural regions, resulting in reduced conduction delays across axons (Buzsaki, Logothetis, & Singer, 2013; Chklovskii, Mel, & Svoboda, 2004). Mathematically, there is an interdependent relationship between cortical folding and structural cortical measures. More specifically, it is suggested that the amount of cortical folding increases as CSA increases, where CT becomes an important factor to consider (Mota and Herculano-Houzel, 2015). These relationships suggest that more brain folds lead to more CSA, and thicker cortex could be responsible for restricted brain folds, and both, that is, brain folds or CSA and CT might have unique contribution toward stronger behavioral responses. Therefore, it becomes crucial to consider multiple cortical measures to better understand the time-dependent differences in brain structure following an mTBI or in general.

5 | LIMITATIONS

The present findings should be interpreted with consideration of the following, noted, limitations. First, despite having a relatively large sample size for this type of neuroimaging study, we categorized mTBI individuals into only three subcategories based on previous literature. It was, therefore, not possible to examine more fine-grained differences in associations at the acute and subacute periods postinjury. We also suggest that future studies consider employing more precise ranges of time-since-injury onsets, with particular emphasis on explicating the various periods of recovery after 6 months, which would be important for identifying the later recovery mechanisms of mTBI. Second, we did not have attention and sleep data collected from HCs, making it difficult to ascertain the extent to which individuals with mTBI experienced weaker attention abilities, higher daytime sleepiness, and worse sleep quality than the average healthy adult. Finally, the research design of our study is cross-sectional in nature. Consequently, the identified brain clusters reflect significant differences across three discrete time-points and not longitudinal changes over time within a given individual. Future work would benefit from following mTBI patients longitudinally to determine whether the differences observed here are consistent when calculated in a longitudinal design.

6 | CONCLUSIONS

In summary, CT and CSA each show unique and specific patterns of differences in brain structure following mTBI. For CT, these patterns of differentiation from HCs and associated weaker attention abilities are most prominent in the first 6 months postinjury. With greater time since injury extending into the short-term and long-term chronic phases, we observe differences in CSA indicative of progressive but partial brain structural recovery, particularly characterized by increased CSA. These findings demonstrate the importance of analyzing multiple brain structural measures in order to more comprehensively understand the neural mechanisms involved following an mTBI, which may reflect brain damage during the early postacute period but compensatory physical recovery during the more chronic stages of mTBI.

ACKNOWLEDGMENTS

This research was supported by grants from the U.S. Army Medical Research and Materiel Command to WDSK (11-1-0056, and W81XWH-12-1-0386) and SLR (W81XWH-12-1-0109). The opinions, interpretations, conclusions, and recommendations in this article are solely those of the authors and are not necessarily endorsed by the Department of Defense or the U.S. Army Medical Research and Materiel Command.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare with regard to this work.

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REFERENCES

Alchanatis, M., Zias, N., Deligiorgis, N., Amfilochiou, A., Dionellis, G., & Orphanidou, D. (2005). Sleep apnea-related cognitive deficits and intelligence: An implication of cognitive reserve theory. *Journal of Sleep Research*, *14*, 69–75.

Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Van Someren, E. J. (2010). Reduced orbitofrontal and parietal gray matter in chronic insomnia: A voxel-based morphometric study. *Biological Psychiatry*, *67*, 182–185.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews. Neuroscience*, *7*, 268–277.

Andersson, M., Ystad, M., Lundervold, A., & Lundervold, A. J. (2009). Correlations between measures of executive attention and cortical thickness of left posterior middle frontal gyrus - a dichotic listening study. *Behavioral and Brain Functions*, *5*, 41.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., & Zilles, K. (1995). The ontogeny of human gyrification. *Cerebral Cortex (New York, N.Y.: 1991)*, *5*, 56–63.

Balslev, D., Odoj, B., & Karnath, H. O. (2013). Role of somatosensory cortex in visuospatial attention. *The Journal of Neuroscience*, *33*, 18311–18318.

Barkhoudarian, G., Hovda, D. A., & Giza, C. C. (2011). The molecular pathophysiology of concussive brain injury. *Clinics in Sports Medicine*, *30*, 33–48. vii-iii.

Baumann, C. R., Werth, E., Stocker, R., Ludwig, S., & Bassetti, C. L. (2007). Sleep-wake disturbances 6 months after traumatic brain injury: A prospective study. *Brain*, *130*, 1873–1883.

Bellesi, M., Pfister-Genskow, M., Maret, S., Keles, S., Tononi, G., & Cirelli, C. (2013). Effects of sleep and wake on oligodendrocytes and their precursors. *The Journal of Neuroscience*, *33*, 14288–14300.

Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society*, *14*, 1–22.

Budd, J. M., & Kisvarday, Z. F. (2012). Communication and wiring in the cortical connectome. *Frontiers in Neuroanatomy*, *6*, 42.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193–213.

Buzsaki, G., Logothetis, N., & Singer, W. (2013). Scaling brain size, keeping timing: Evolutionary preservation of brain rhythms. *Neuron*, *80*, 751–764.

Castriotta, R. J., Wilde, M. C., Lai, J. M., Atanasov, S., Masel, B. E., & Kuna, S. T. (2007). Prevalence and consequences of sleep disorders in traumatic brain injury. *Journal of Clinical Sleep Medicine*, *3*, 349–356.

Centers for Disease Control and Prevention (CDC). (2003). Report to Congress on Mild Traumatic Brain injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA, USA: National Center for Injury Prevention and Control.

Chao, L. L., Mohlenhoff, B. S., Weiner, M. W., & Neylan, T. C. (2014). Associations between subjective sleep quality and brain volume in Gulf War veterans. *Sleep*, *37*, 445–452.

Chklovskii, D. B., Mel, B. W., & Svoboda, K. (2004). Cortical rewiring and information storage. *Nature*, *431*, 782–788.

Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 831–838.

da Costa, L., Robertson, A., Bethune, A., MacDonald, M. J., Shek, P. N., Taylor, M. J., & Pang, E. W. (2015). Delayed and disorganised brain activation detected with magnetoencephalography after mild traumatic brain injury. *Journal of Neurology, Neurosurgery & Psychiatry*, *86*, 1008–1015.

Dall'Acqua, P., Johannes, S., Mica, L., Simmen, H. P., Glaab, R., Fandino, J., ... Hanggi, J. (2016). Connectomic and surface-based morphometric correlates of acute mild traumatic brain injury. *Frontiers in Human Neuroscience*, *10*, 127.

Dall'Acqua, P., Johannes, S., Mica, L., Simmen, H. P., Glaab, R., Fandino, J., ... Hanggi, J. (2017). Prefrontal cortical thickening after mild traumatic brain injury: A one-year magnetic resonance imaging study. *Journal of Neurotrauma*, *34*, 3270–3279.

De Kruijk, J. R., Leffers, P., Menheere, P. P., Meerhoff, S., Rutten, J., & Twijnstra, A. (2002). Prediction of post-traumatic complaints after mild traumatic brain injury: Early symptoms and biochemical markers. *Journal of Neurology, Neurosurgery & Psychiatry*, *73*, 727–732.

Dean, P. J., Otaduy, M. C., Harris, L. M., McNamara, A., Seiss, E., & Sterr, A. (2013). Monitoring long-term effects of mild traumatic brain injury with magnetic resonance spectroscopy: A pilot study. *Neuroreport*, *24*, 677–681.

Dean, P. J., & Sterr, A. (2013). Long-term effects of mild traumatic brain injury on cognitive performance. *Frontiers in Human Neuroscience*, *7*, 30.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*, 968–980.

Dretsch, M. N., Daniel, T. A., Goodman, A. M., Katz, J. S., Denney, T., Deshpande, G., & Robinson, J. L. (2017). Differential neural activation when voluntarily regulating emotions in service members with chronic mild traumatic brain injury. *Applied Neuropsychology: Adult*, 1–13.

Faul, M., Xu, L., Wald, M. M., & Coronado, V. (2010). Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006, 1–74.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders (SCID-I/P)*. New York, NY: New York State Psychiatric Institute.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 11050–11055.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage*, *9*, 195–207.

Gautam, P., Anstey, K. J., Wen, W., Sachdev, P. S., & Cherbuin, N. (2015). Cortical gyrification and its relationships with cortical volume, cortical thickness, and cognitive performance in healthy mid-life adults. *Behavioural Brain Research*, *287*, 331–339.

Gilbert, K. S., Kark, S. M., Gehrman, P., & Bogdanova, Y. (2015). Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clinical Psychology Review*, *40*, 195–212.

Govindarajan, K. A., Narayana, P. A., Hasan, K. M., Wilde, E. A., Levin, H. S., Hunter, J. V., ... McCarthy, J. J. (2016). Cortical thickness in mild traumatic brain injury. *Journal of Neurotrauma*, *33*, 1809–1817.

Gregory, M. D., Kippenhan, J. S., Dickinson, D., Carrasco, J., Mattay, V. S., Weinberger, D. R., & Berman, K. F. (2016). Regional variations in brain gyrification are associated with general cognitive ability in humans. *Current Biology*, *26*, 1301–1305.

Haboubi, N. H., Long, J., Koshy, M., & Ward, A. B. (2001). Short-term sequelae of minor head injury (6 years experience of minor head injury clinic). *Disability and Rehabilitation*, *23*, 635–638.

Head, J. (1993). Definition of mild traumatic brain. *The Journal of Head Trauma Rehabilitation*, *8*, 86–87.

Hofman, M. A. (2014). Evolution of the human brain: When bigger is better. *Frontiers in Neuroanatomy*, *8*, 15.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*, 540–545.

Kerr, A. L., Cheng, S. Y., & Jones, T. A. (2011). Experience-dependent neural plasticity in the adult damaged brain. *Journal of Communication Disorders*, *44*, 538–548.

Killgore, W. D., Singh, P., Kipman, M., Pisner, D., Fridman, A., & Weber, M. (2016). Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury. *Neuroscience Letters*, *612*, 238–244.

Laborey, M., Masson, F., Ribereau-Gayon, R., Zongo, D., Salmi, L. R., & Lagarde, E. (2014). Specificity of postconcussion symptoms at 3 months after mild traumatic brain injury: Results from a comparative Cohort study. *The Journal of Head Trauma Rehabilitation*, *29*, E28–E36.

Lewen, A., Fredriksson, A., Li, G. L., Olsson, Y., & Hillered, L. (1999). Behavioural and morphological outcome of mild cortical contusion trauma of the rat brain: Influence of NMDA-receptor blockade. *Acta Neurochirurgica (Wien)*, *141*, 193–202.

Lillie, E. M., Urban, J. E., Lynch, S. K., Whitlow, C. T., & Stitzel, J. D. (2013). Evaluation of the extent and distribution of diffuse axonal injury from real world motor vehicle crashes - BIOMED 2013. *Biomedical Sciences Instrumentation*, *49*, 297–304.

Lim, A. S., Fleischman, D. A., Dawe, R. J., Yu, L., Arfanakis, K., Buchman, A. S., & Bennett, D. A. (2016). Regional neocortical gray matter structure and sleep fragmentation in older adults. *Sleep*, *39*, 227–235.

Ling, J. M., Klimaj, S., Toulouse, T., & Mayer, A. R. (2013). A prospective study of gray matter abnormalities in mild traumatic brain injury. *Neurology*, *81*, 2121–2127.

List, J., Ott, S., Bukowski, M., Lindenberg, R., & Floel, A. (2015). Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults. *Frontiers in Human Neuroscience*, *9*, 228.

Makley, M. J., English, J. B., Drubach, D. A., Kreuz, A. J., Celnik, P. A., & Tarwater, P. M. (2008). Prevalence of sleep disturbance in closed head injury patients in a rehabilitation unit. *Neurorehabilitation and Neural Repair*, *22*, 341–347.

Management of Concussion/mTBI Working Group. (2009). VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury. *Journal of Rehabilitation Research and Development*, *46*, Cp1–C68.

McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., ... Kelly, J. P. (2003). Acute effects and recovery time following concussion in collegiate football players: The NCAA Concussion Study. *JAMA*, *290*, 2556–2563.

McInnes, K., Friesen, C. L., MacKenzie, D. E., Westwood, D. A., & Boe, S. G. (2017). Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. *PLoS One*, *12*, e0174847.

McKay, C., Casey, J. E., Wertheimer, J., & Fichtenberg, N. L. (2007). Reliability and validity of the RBANS in a traumatic brain injured sample. *Archives of Clinical Neuropsychology*, *22*, 91–98.

Mota, B., & Herculano-Houzel, S. (2015). Cortical folding scales universally with surface area and thickness, not number of neurons. *Science*, *349*, 74–77.

Novack, T. A., Alderson, A. L., Bush, B. A., Meythaler, J. M., & Canupp, K. (2000). Cognitive and functional recovery at 6 and 12 months post-TBI. *Brain Injury*, *14*, 987–996.

Orff, H. J., Ayalon, L., & Drummond, S. P. (2009). Traumatic brain injury and sleep disturbance: A review of current research. *The Journal of Head Trauma Rehabilitation*, *24*, 155–165.

Packard, R. C. (2008). Chronic post-traumatic headache: Associations with mild traumatic brain injury, concussion, and post-concussive disorder. *Current Pain and Headache Reports*, *12*, 67–73.

Paniak, C., Reynolds, S., Phillips, K., Toller-Lobe, G., Melnyk, A., & Nagy, J. (2002). Patient complaints within 1 month of mild traumatic brain injury: A controlled study. *Archives of Clinical Neuropsychology*, *17*, 319–334.

Parcell, D. L., Ponsford, J. L., Redman, J. R., & Rajaratnam, S. M. (2008). Poor sleep quality and changes in objectively recorded sleep after traumatic brain injury: A preliminary study. *Archives of Physical Medicine and Rehabilitation*, *89*, 843–850.

Pare, N., Rabin, L. A., Fogel, J., & Pepin, M. (2009). Mild traumatic brain injury and its sequelae: Characterisation of divided attention deficits. *Neuropsychological Rehabilitation*, *19*, 110–137.

Pasternak, O., Koerte, I. K., Bouix, S., Fredman, E., Sasaki, T., Mayinger, M., ... Echlin, P. S. (2014). Hockey Concussion Education Project, Part 2. Microstructural white matter alterations in acutely concussed ice hockey players: A longitudinal free-water MRI study. *Journal of Neurosurgery*, *120*, 873–881.

Patterson, Z. R., & Holahan, M. R. (2012). Understanding the neuroinflammatory response following concussion to develop treatment strategies. *Frontiers in Cellular Neuroscience*, *6*, 58.

Rakic, P. (2009). Evolution of the neocortex: A perspective from developmental biology. *Nature Reviews. Neuroscience*, *10*, 724–735.

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, *20*, 310–319.

Rao, V., Spiro, J., Vaishnavi, S., Rastogi, P., Mielke, M., Noll, K., … Makley, M. (2008). Prevalence and types of sleep disturbances acutely after traumatic brain injury. *Brain Injury*, *22*, 381–386.

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G. L., Greenstein, D., … Giedd, J. N. (2011). How does your cortex grow? *The Journal of Neuroscience*, *31*, 7174–7177.

Richman, D. P., Stewart, R. M., Hutchinson, J. W., & Caviness, V. S. Jr. (1975). Mechanical model of brain convolutional development. *Science*, *189*, 18–21.

Schnack, H. G., van Haren, N. E., Brouwer, R. M., Evans, A., Durston, S., Boomsma, D. I., … Hulshoff Pol, H. E. (2015). Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cerebral Cortex (New York, N.Y.: 1991)*, *25*, 1608–1617.

Sexton, C. E., Storsve, A. B., Walhovd, K. B., Johansen-Berg, H., & Fjell, A. M. (2014). Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology*, *83*, 967–973.

Spira, A. P., Gonzalez, C. E., Venkatraman, V. K., Wu, M. N., Pacheco, J., Simonsick, E. M., … Resnick, S. M. (2016). Sleep duration and subsequent cortical thinning in cognitively normal older adults. *Sleep*, *39*, 1121–1128.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*, 2015–2028.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet. Neurology*, *11*, 1006–1012.

Stoffers, D., Moens, S., Benjamins, J., van Tol, M. J., Penninx, B. W., Veltman, D. J., … Van Someren, E. J. (2012). Orbitofrontal gray matter relates to early morning awakening: A neural correlate of insomnia complaints? *Frontiers in Neurology*, *3*, 105.

Suh, S., Kim, H., Dang-Vu, T. T., Joo, E., & Shin, C. (2016). Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. *Sleep*, *39*, 161–171.

Tate, D. F., York, G. E., Reid, M. W., Cooper, D. B., Jones, L., Robin, D. A., … Lewis, J. (2014). Preliminary findings of cortical thickness abnormalities in blast injured service members and their relationship to clinical findings. *Brain Imaging and Behavior*, *8*, 102–109.

Toro, R. (2012). On the possible shapes of the brain. *Evolutionary Biology*, *39*, 600–612.

Turner, G. R., & Levine, B. (2008). Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology*, *71*, 812–818.

Urban, J. E., Whitlow, C. T., Edgerton, C. A., Powers, A. K., Maldjian, J. A., & Stitzel, J. D. (2012). Motor vehicle crash-related subdural hematoma from real-world head impact data. *Journal of Neurotrauma*, *29*, 2774–2781.

Verma, A., Anand, V., & Verma, N. P. (2007). Sleep disorders in chronic traumatic brain injury. *Journal of Clinical Sleep Medicine*, *3*, 357–362.

Wang, X., Xie, H., Cotton, A. S., Tamburrino, M. B., Brickman, K. R., Lewis, T. J., … Liberzon, I. (2015). Early cortical thickness change after mild traumatic brain injury following motor vehicle collision. *Journal of Neurotrauma*, *32*, 455–463.

Westlye, L. T., Grydeland, H., Walhovd, K. B., & Fjell, A. M. (2011). Associations between regional cortical thickness and attentional networks as measured by the attention network test. *Cerebral Cortex (New York, N.Y.: 1991)*, *21*, 345–356.

Wilde, E. A., Merkley, T. L., Bigler, E. D., Max, J. E., Schmidt, A. T., Ayoub, K. W., … Levin, H. S. (2012). Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. *International Journal of Developmental Neuroscience*, *30*, 267–276.

Williams, B. R., Lazic, S. E., & Ogilvie, R. D. (2008). Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury. *Clinical Neurophysiology*, *119*, 429–438.

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., … Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*, 1135–1146.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., … Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, *342*, 373–377.

Zhou, Y., Kierans, A., Kenul, D., Ge, Y., Rath, J., Reaume, J., … Lui, Y. W. (2013). Mild traumatic brain injury: Longitudinal regional brain volume changes. *Radiology*, *267*, 880–890.

How to cite this article: Bajaj S, Dailey NS, Rosso IM, Rauch SL, Killgore WDS. Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury. *Hum Brain Mapp*. 2018;00:1–12. https://doi.org/10.1002/hbm.23951

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 November 2017
doi: 10.3389/fneur.2017.00616

Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain

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Mild traumatic brain injury (mTBI) is a common and often inconspicuous wound that is frequently associated with chronic low-grade symptoms and cognitive dysfunction. Previous evidence suggests that daily blue wavelength light therapy may be effective at reducing fatigue and improving sleep in patients recovering from mTBI. However, the effects of light therapy on recovering brain structure remain unexplored. In this study, we analyzed white matter diffusion properties, including generalized fractional anisotropy, and the quantity of water diffusion in isotropic (i.e., isotropic diffusion) and anisotropic fashion (i.e., quantitative anisotropy, QA) for fibers crossing 11 brain areas known to be significantly affected following mTBI. Specifically, we investigated how 6 weeks of daily morning blue light exposure therapy (compared to an amber-light placebo condition) impacted changes in white matter diffusion in individuals with mTBI. We observed a significant impact of the blue light treatment (relative to the placebo) on the amount of water diffusion (QA) for multiple brain areas, including the corpus callosum, anterior corona radiata, and thalamus. Moreover, many of these changes were associated with improvements in sleep latency and delayed memory. These findings suggest that blue wavelength light exposure may serve as one of the potential non-pharmacological treatments for facilitating structural and functional recovery following mTBI; they also support the use of QA as a reliable neuro-biomarker for mTBI therapies.

Keywords: concussion, diffusion tensor imaging, fractional isotropy, isotropic diffusion, neuropsychological function, quantitative anisotropy, sleep, structural recovery

OPEN ACCESS

Edited by:
Stefania Mondello, University of Messina, Italy

Reviewed by:
Rao P. Gullapalli, University of Maryland Medical Center, United States
Shoji Yokobori, Nippon Medical School, Japan

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Specialty section:
This article was submitted to Neurotrauma, a section of the journal Frontiers in Neurology

Received: *03 September 2017*
Accepted: *06 November 2017*
Published: *22 November 2017*

Citation:
Bajaj S, Vanuk JR, Smith R, Dailey NS and Killgore WDS (2017) Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain. Front. Neurol. 8:616. doi: 10.3389/fneur.2017.00616

INTRODUCTION

Mild traumatic brain injury (mTBI) is a common and often unobtrusive wound that occurs when kinetic energy is transferred to the brain through some form of traumatic event, such as a fall, blow to the head, or blast wave. While there are typically no exceptionally conspicuous physical or neuroimaging signs of mTBI, the mechanical trauma to the brain leads to a mild temporary disruption of consciousness or other alteration of ongoing cognition. Also commonly known as "concussion," mTBI can further lead to persistent alterations in neuropsychological functions, including changes in mood (e.g., depression), poor attention and concentration, and memory problems (1, 2). Importantly, sleep deprivation is also known to produce many of these same symptoms (3, 4).

It is therefore possible that sleep disturbances following mTBI may cause, or at least exacerbate, ongoing post-concussion symptoms. However, the nature of these complaints and their contribution to the experience of daytime sleepiness is not well understood (5). An objective measure of daytime sleepiness is the multiple sleep latency test (MSLT), which is used to determine the time it takes an individual to fall asleep (sleep onset latency) when given the opportunity to take a nap. Following a head trauma, symptoms are believed to result from neuronal damage in the form of diffuse axonal injury (6, 7), leading to the release of specific proteins that in turn promote maladaptive functional and structural changes within the brain (8). Identifying neuro-markers of these changes remains an important challenge in ongoing attempts to understand and treat mTBI and post-concussive symptoms.

A very limited number of treatment options for mTBI have been proposed and experimentally validated. Available treatments include cognitive behavior therapy (9), neuropsychological rehabilitation (10), educational intervention (11), and pharmacological intervention (12). Although the effects are small, some intervention studies report reliable reductions in post-concussion symptoms, including sleep problems, following successful treatment (13). Considering a range of post-concussion symptoms can also occur as the result of sleep loss, it is likely that improving sleep quality in particular would also lead to improvements of other post-concussion symptoms, such as attention, concentration, memory, and mood disturbances. While improving sleep makes sense, this is often easier said than done. A natural and potentially powerful method for regulating the sleep–wake cycle is through targeted exposure to bright light in the morning hours. Exposure to short wavelength light (~430–475 nm; blue wavelength light) has been demonstrated as an alternative to pharmacological treatment methods that focus on improving alertness, concentration, daytime sleepiness, as well as sleep quality (14, 15). Intrinsically photosensitive retinal ganglion cells are particularly responsive to light within the short wavelengths. These cells transmit signals to hypothalamic nuclei, which in turn regulate the production of melatonin (16, 17). Morning exposure to blue wavelength light leads to a suppression of melatonin production, which contributes to a phase delay and stabilization of the circadian rhythm (18), increases daytime alertness and vigilance, and earlier onset of evening sleep (19, 20). Interestingly, a recent clinical trial showed that 4 weeks of 45 min of morning blue-light therapy (BLT) in comparison to longer wavelength placebo light was effective at reducing self-rated fatigue and daytime sleepiness among individuals recovering from TBI (21). However, the extent to which these behavioral changes correspond to structural changes within the brain has not been explored.

When considering the potential influences of BLT on mTBI, it is important to consider that mTBI is associated with microscopic changes in brain structure, particularly within the white matter axonal tracts. Abnormalities in fractional anisotropy (FA) in the brain following an mTBI have been studied extensively using diffusion tensor imaging (DTI), a method that allows high-resolution imaging of the directional movement of water molecules along axonal fiber tracts (i.e., how fast water molecules move along fiber tracts). Abnormalities in FA in individuals with an mTBI are reported in areas such as uncinate fasciculus (UF) (22), superior longitudinal fasciculus (SLF) (23), anterior corona radiata (ACR) (22), corpus callosum (CC) (24), and thalamus (25). Alterations in FA within (a) UF are reported to be associated with changes in Mini-Mental State Examination (MMSE) scores (cognitive function) and specifi ally, memory performance (22, 26); (b) SLF and CC are reported to be associated with executive function (attention and memory) (27); (c) ACR changes are correlated with changes in attention (22); and (d) anterior thalamic nucleus changes are also linked to changes in executive function, memory, and attention (25). In addition, studies have found that individuals with mTBI show alterations in white matter within the frontal lobe (frontal cortex/dorsolateral prefrontal cortex, DLPFC), and that these alterations are correlated with lower executive control and related cognitive functions (28). Also, compared to healthy controls (HCs), there are multiple studies that have reported abnormally high FA values in individuals with mTBI within several areas, including the genu and splenium of CC, ACR (bilaterally), lUF, and internal capsule (IC; bilaterally) (29, 30). Recently, new diffusion measures—quantitative anisotropy (QA), isotropic diffusion (ISO), and generalized fractional anisotropy (GFA)—were introduced to the fi ld of DTI for the analysis of diffusion properties of white matter (31). QA and ISO represent *how much* water diffuses (i.e., density) in a specific/restricted direction and in an isotropic fashion (i.e., total isotropic component), respectively. In contrast, GFA, which is calculated from an orientation distribution function, is a measure of *how fast* water diffuses (i.e., diffusivity) in an anisotropic fashion, i.e., it represents degree to which diffusion is anisotropic (31, 32). Highly signifi ant correlations between FA and GFA were reported in the past (33). In addition, the difference between QA and GFA pertains to the fact that QA is a measure of water diffusion along each fiber orientation, whereas GFA/FA is defi ed for each voxel. Compared to GFA/FA, QA is also reported to have lower susceptibility to partial volume effects of crossing-fibers, free-water diffusion in ventricles, and non-diffusive particles (31). Moreover, normalization of QA helps to stabilize the spin-density measurement across subjects. In this study, we investigated multiple diffusion measures (i.e., diffusivity as well as density measures) simultaneously to better characterize the white matter properties; therefore, in conjunction with GFA, we also estimated normalized QA (NQA) and ISO measures. To the best of our knowledge, no study to date has used these metrics simultaneously to examine the effect of light exposure treatment on the brain following mTBI.

In individuals with mTBI, how changes in post-concussion symptoms following an exposure to BLT may correspond to structural changes within the brain has not yet been explored. Recent evidence suggests that sleep is important for clearing the neurotoxins that build up throughout the day (34) and increases the production of oligodendrocyte progenitor cells that contribute to myelin formation (35), which could conceivably facilitate repair of axonal damage. Based on this, we hypothesized that 6 weeks of daily morning BLT, compared to a placebo condition with an amber-light therapy (ALT) device, would improve sleep and, consequently, lead to changes in white matter water diffusion, improvements in cognitive abilities such as attention and memory, and daytime sleepiness. To this end, we investigated

whether individuals in the BLT and ALT groups showed significant changes in diffusion (i.e., GFA, NQA, and ISO), cognitive, and sleep measures. Furthermore, we examined the correlations between changes in diffusion measures from pre- to post-treatment and changes in neuropsychological performance and sleep onset latency.

MATERIALS AND METHODS

Participants

Twenty-eight individuals meeting criteria for mTBI (mean age = 21.48 ± 3.76 years, 15F) underwent neuroimaging using a Siemens Tim Trio 3T scanner (Erlangen, Germany) at the McLean Hospital Imaging Center. The majority of the individuals (19 out of 28) sustained an mTBI while engaged in a physical activity (e.g., soccer, rugby, hiking, and karate); whereas 9 individuals sustained an mTBI during either a vehicular or household accident. All of the mTBI individuals had a documented mTBI within the preceding 12 months, but not sooner than 4 weeks before their screening. An mTBI was defi ed based on the criteria established by the VA/DoD practice guidelines (36) as a traumatically induced event (e.g., head impact, blast wave) that was associated with an alteration in mental status (e.g., confusion, disorientation, retrograde, or anterograde amnesia), consciousness (i.e., loss of consciousness less than 30 min; alteration of consciousness up to 24 h), post-traumatic amnesia up to 24 h, and a Glascow Coma Scale from 13 to 15. All participants were right-handed and primary English speakers. All study participants were required to have some level of self-reported sleep problem, e.g., if they were sleepier during the day, having difficulty in sleeping at night and staying alert during the day, etc. Therefore, all participants were screened using a set of sleep questionnaires where they indicated self-reported sleep problems and endorsed that the sleep problems either emerged or worsened following the injury. Participants with any history of neurological, mood, or psychotic disorder with an onset before the mTBI, or who suffered a loss of consciousness exceeding 30 min following an injury were excluded. Participants were thoroughly briefed on the potential risks and benefits of the study and all completed written informed consent before enrollment. Participants were fi ancially compensated for their time. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Offi . All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Protocol

All the participants underwent DTI, neuropsychological testing, and MSLT sessions on two occasions; separated by 6 weeks of daily morning light therapy with either blue light or a sham placebo amber light. Participants were instructed to rest and relax during scanning. All data were collected within a period of 3 years. All eligible participants completed daily sleep diaries and questionnaires and were fitted with a wrist actigraph for sleep monitoring throughout the period of the study. Participants were asked to use a commercially available light therapy device (GoLite Blu®, Philips Electronics) for 6 weeks (i.e., 30 min everyday within 2 h of awakening, but before 11:00 a.m.). Half of the individuals (N = 14, mean age = 21.75 ± 4.43 years, 8F) were randomly assigned to BLT and half (N = 14, mean age = 21.21 ± 3.09 years, 7F) were assigned to ALT. ALT and BLT groups did not differ signifi antly in age [$F(1,26) = 0.14$, $p > 0.05$, one-way ANOVA], gender [$\chi^2(1) = 0.14$, $p > 0.05$, Pearson's Chi-square], and body-mass index [$F(1,25) = 2.77$, $p > 0.05$, one-way ANOVA]. However, two important covariates were included in our analyses: (1) "light compliance" was calculated as the percentage of the total number of days that the participant acknowledged actually using the light *via* self-report divided by the total number of days in the study (i.e., number of days between baseline and post-treatment assessments), and (2) "time since injury," which was calculated as the number of days between the index mTBI and the baseline assessment.

DTI Data Acquisition and Image Processing

Diffusion-weighted imaging (DWI) data were acquired along 72 directions with a b-value = 1,000 s/mm^2, voxel size = 1.75 mm × 1.75 mm × 3.5 mm, fl p angle = 90°, repetition time (TR) = 6,340 ms, echo time (TE) = 99, slices thickness = 3.5 mm, and number of slices = 40 encompassing the whole brain. A set of eight images with no diffusion weighting (b0 images) was also acquired. Using dcm2nii toolbox [part of MRIcron (37)], we converted DWI data from DICOM into NIFTI format. A b-value and b-vector file was generated during this step. Next, we performed standard eddy current correction using FMRIB Software Library v6.0 processing software package[1] on DWI data for head motion correction.

Neuropsychological Assessments and Sleep Measures

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (38), which included scales assessing delayed memory (DM), immediate memory (IM), attention (ATT), visuospatial/constructional (VC), and language (LAN) abilities was administered pre- and post-light exposure.

The RBANS IM is a measure of initial encoding and learning of simple and complex verbal information and RBANS DM is a measure of delayed recall of visual and verbal stimuli and recognition of verbal stimuli. The RBANS ATT is a measure of speed and accuracy of information processing. The RBANS VC is a measure of visuospatial perception, and RBANS LAN is a measure of ability to express language. Lower RBANS IM and DM scores represent difficulty in the recognition and recall of long-term memories and verbal learning, respectively. Lower RBANS ATT scores represent difficulty in the basic attention processes. Lower RBANS VC and LAN scores represent difficulty with using visuospatial information and language (expressive and receptive), respectively. The use of the RBANS has been shown to

[1] http://www.fmrib.ox.ac.uk/fsl.

be clinically valid and reliable screening tool to assess cognitive deficits following traumatic brain injury (39).

The MSLT has been shown to better reflect the degree of daytime sleepiness when compared to self-report, and with high test–retest reliability (40–42). During each assessment session, participants underwent a modified MSLT protocol, using a standard electrode montage for polysomnographic (PSG) recording (ALICE LE®, Phillips Respironics). Signals were recorded from EEG (C3A2, C4A2, O1A1, and O2A2), electrooculogram, submental electromylogram, and electrocardiogram. On three occasions throughout the testing session (11:50 a.m., 1:50 p.m., 3:50 p.m.), participants were given a 20-min opportunity to take a nap in a sound attenuated bedroom. Increased sleep propensity and/or abnormal daytime sleepiness is inferred from decreased sleep onset latency during these MSLT trials. PSG recordings were monitored for the duration and then scored by certified sleep technicians using 30-s epochs and Somnologica software. Sleep onset latency was classified as the first epoch in which >50% was identified as any stage of sleep. Sleep onset latency was quantified for each trial, as well as the average onset latency across the three MSLT administrations.

Data Analysis

For each participant, we estimated water diffusion parameters such as mean GFA, mean NQA, and mean ISO, using the Q-space diffeormophic reconstruction (QSDR) approach (43) implemented in DSI Studio.[2] QSDR is a model-free approach, which calculates the density distribution of water diffusion using a high-resolution standard brain atlas constructed from 90-diffusion spectrum imaging datasets in the ICBM-152 space. Tractography was performed using 25,000 sub-voxel seeds in each region of interest for each participant. A turning angle threshold of 60°, QA threshold of 0.10, and length constrained between 30 and 200 mm was used to estimate diffusion parameters. To ensure consistency across subjects, we normalized the QA measure by scaling the subject-wise maximum QA value to 1. Normalization of QA assumes that all the subjects have identical compactness of white matter. In order to avoid any bias among participants, an identical set of tracking parameters was used for each participant before and after the light therapy. For each participant, GFA, NQA, and ISO were estimated for all the possible tracts crossing 11 brain areas, namely the DLPFC, the genu, body and splenium of the CC, the left and the right uncinate fasciculus (lUF and rUF), the left and the right superior longitudinal fasciculus (lSLF and rSLF), the left and the right anterior corona radiata (lACR and rACR), and the thalamus. DLPFC is attributed anatomically to Brodmann areas (BAs) 9 and 46 (44). To define DLPFC in this study, we integrated BAs 9 and 46 whereas we used the ICBM-DTI-81 white matter labels atlas (45) and the JHU white matter tractography atlas (45) (implemented in DSI Studio) to define all other regions of interest. Diffusion parameters (GFA, NQA, and ISO) from tracts crossing the 11 specified seed regions were used in the analyses. In order to estimate the diffusion measures across all the possible tracts crossing each of the 11 brain areas, no waypoint regions of interest were included in the analysis.

Metrics of GFA, NQA, and ISO were compared using mixed analysis of covariance (ANCOVA), with light group (BLT/ALT) as a between groups variable and session (pre- versus post-treatment) as a within-subjects variable, while "time since injury" and "light compliance" were included as nuisance covariates. To test the association between the changes in white matter integrity with changes in neuropsychological performance and sleep latency measures, change metrics for each variable were evaluated with partial correlations, controlling for time since injury and light compliance. For this analysis, we used residualized change scores derived by regressing post-treatment scores on pre-treatment scores and determining the residual value for each participant. This provides a metric of post-treatment status controlling for pre-treatment status (i.e., residualized change). We report false discovery rate (FDR) corrected *p*-values for the partial correlations.

RESULTS

In order to estimate different diffusion parameters, we first performed whole-brain tractography, followed by limiting the white matter tracts to those passing through 11 predefined seed regions, namely—R01: the DLPFC, R02: genu, R03: body, R04: splenium of the CC, R05: the lUF, R06: the rUF, R07: the lSLF, R08: the rSLF, R09: the left anterior corona radiata (ACR), R10: right anterior corona radiata (ACR), and R11: the thalamus. Selection of these 11 regions was purely based on previous literature showing abnormalities water diffusion in these regions following mTBI (22–28). In **Figure 1**, we show fiber tracts crossing through each region for a representative participant. Here, fibers are colored coded to represent their direction, where "red" indicates fibers along the *X*-axis (i.e., left–right), "green" indicates fibers along the *Y*-axis (i.e., anterior–posterior), and "blue" indicates fibers along the *Z*-axis (i.e., inferior–superior).

Effect of Light Therapy on Diffusion Properties of the Brain following an mTBI

A detailed comparison of diffusion parameters, GFA, NQA, and ISO, was performed on fiber pathways crossing through the 11 specified seed regions (R01 to R11). All the results were corrected for multiple comparisons using Bonferroni's method. In Figure S1 in Supplementary Material, for each area, we showed subject and fiber averaged GFA, NQA, and ISO measures before and following 6 weeks of either ALT or BLT, where error bars represent the SEM. The presented data in Figure S1 in Supplementary Material are raw data, which are uncorrected for confounds.

GFA

There was a significant time (pre- and post-treatment) × group (ALT/BLT) interaction [$F(1,24) = 6.151$, $p = 0.021$] such that following BLT, but not ALT, individuals showed a significant decrease in GFA for only the fibers crossing the splenium of the CC. Furthermore, within-subject pairwise comparison showed a significant decrease in GFA following BLT [$F(1,24) = 5.619$,

[2] http://dsi-studio.labsolver.org.

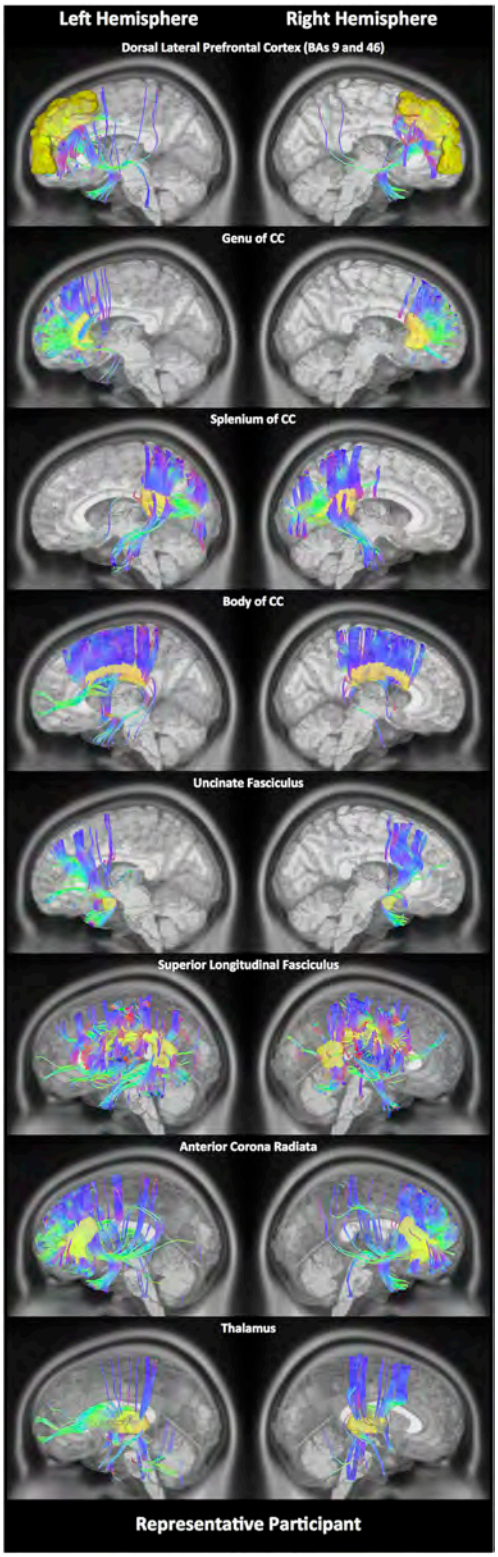


FIGURE 1 | White matter fiber tracking. Here, for a representative participant, we illustrate white matter fiber tracts for each of the 11 regions. Tracts shown in red indicate a fiber direction from left to right or *vice versa*. Blue indicates a fiber direction from anterior to posterior or *vice versa*. Green indicates a fiber direction from superior to inferior or *vice versa*.

$p = 0.026$], but not ALT [$F(1,24) = 1.511$, $p = 0.231$]. ANCOVA results for GFA of the fibers crossing the splenium of the CC are summarized in **Figure 2** and **Table 1**.

NQA

There was a signifi ant time (pre- and post-treatment) × group (ALT/BLT) interaction such that following BLT, but not ALT, individuals showed a signifi ant decrease in NQA for the fibers crossing three brain areas, i.e., body of CC [$F(1,24) = 4.932$, $p = 0.036$], the left ACR [$F(1,24) = 9.460$, $p = 0.005$], and thalamus [$F(1,24) = 5.688$, $p = 0.025$]. Furthermore, pairwise comparison showed that following BLT, there was signifi ant decrease in NQA for the fibers crossing these three areas, i.e., body of CC [$F(1,24) = 5.984$, $p = 0.022$], the left ACR [$F(1,24) = 12.347$, $p = 0.002$], and thalamus [$F(1,24) = 8.226$, $p = 0.008$], but not following ALT. ANCOVA results for NQA of the fibers crossing these three areas are summarized in **Figure 3** and **Table 2**.

ISO

There were no signifi ant changes in ISO for fibers crossing any of the 11 areas from pre- to post-treatment for either group.

Effect of Light Therapy on Neuropsychological Function and Sleep Onset Latency

Contrary to our expectations, we did not fi d signifi ant time (pre- versus post-treatment) × group (ALT/BLT) interaction for neuropsychological function and sleep onset latency. However, because we found signifi ant differences in GFA (for 1 out of 11 brain areas) as well as in NQA (for 3 out of 11 brain areas) following BLT, we then examined whether individual differences in white matter within these 4 brain regions were related to individual differences in our behavioral measures of neuropsychological function (attention and memory) and daytime sleep onset latency during the MSLT trials. Specifi ally, partial regression analyses were performed (corrected for "time since injury" and "light compliance") between diffusion measures (GFA and NQA) and neuropsychological function measures (i.e., RBANS scores) as well as sleep onset latency.

Neuropsychological Function

Following BLT or ALT, we did not fi d signifi ant association between residualized changes in any neuropsychological measures or MSLT scores and residualized changes in GFA for fibers crossing the splenium of the CC. But signifi ant negative partial correlations were observed between residualized changes in RBANS DM scores and residualized changes in NQA for fibers crossing two brain areas: the body of the CC ($r = -0.76$, $p = 0.00$; FDR corrected $p = 0.02$) (**Figure 4A**) and the thalamus ($r = -0.64$, $p = 0.02$; FDR corrected $p = 0.02$) (**Figure 4B**), i.e., greater changes in NQA were associated with better DM performance following BLT. After multiple comparisons correction, we did not fi d signifi ant association between residualized changes in any neuropsychological measure and residualized changes in NQA for fibers crossing any of the regions of interest following ALT (**Figures 4C,D**).

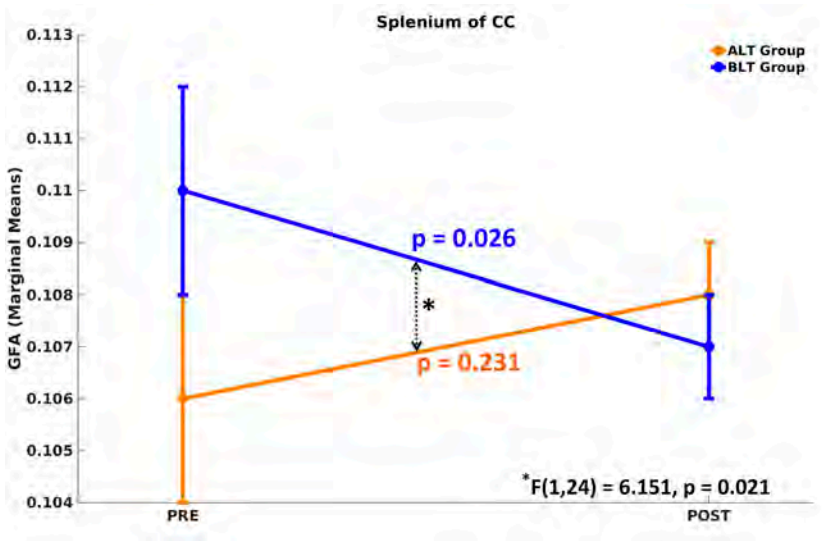


FIGURE 2 | Mixed analysis of covariance of generalized fractional anisotropy (GFA). Compared to baseline, only the fibers crossing the splenium of corpus callosum (CC) showed significant differences in GFA following blue-light therapy (BLT). No significant difference in GFA was found for fibers crossing any brain area, including the splenium of CC, following amber-light therapy (ALT).

TABLE 1 | Summary of analysis of variance (repeated measures ANOVA) for GFA.

Within-subjects effects					
Interaction					
Source	**Brain areas**	**Type III sum of squares**	**Mean square**	***F*(1, 24)**	**Significance (GFA)**
Time (pre and post) × group (ALT/BLT) (sphericity assumed)	Splenium of CC	0.000	0.000	6.151	0.021*
Pairwise comparisons (pre versus post)					
Effect of treatment	**Brain areas**	**Groups**	***F*(1, 24)**		**Significance (GFA)**
Pre versus post	Splenium of CC	ALT	1.511		0.231
		BLT	5.619		0.026**

GFA, generalized fractional anisotropy; BLT, blue-light therapy; ALT, amber-light therapy; CC, corpus callosum.
**Interaction is significant at $p < 0.05$.*
***Mean difference between post- and pre-treatment is significant at $p < 0.05$.*

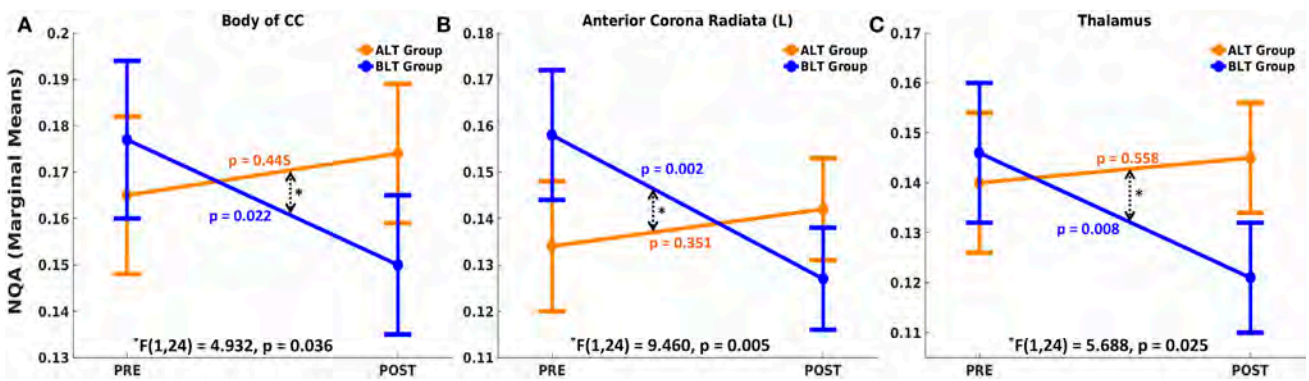


FIGURE 3 | Mixed analysis of covariance of normalized quantitative anisotropy (NQA). Fibers crossing three brain areas, the body of the corpus callosum (CC) **(A)**, left anterior corona radiata (ACR) **(B)**, and thalamus **(C)** showed significant time (pre and post) × group (ALT/BLT) interaction in normalized QA (NQA). Compared to baseline, pairwise comparison showed significant reduction in NQA for these three regions following BLT, but not following ALT. BLT, blue-light therapy; ALT, amber-light therapy.

TABLE 2 | Summary of analysis of variance (repeated measures ANOVA) for normalized quantitative anisotropy (NQA).

Within-subjects effects (ANCOVA)

Interaction					
Source	**Brain areas**	**Type III sum of squares**	**Mean square**	***F*(1, 24)**	**Significance[a] (NQA)**
Time (pre and post) × group (ALT/BLT) (sphericity assumed)	Body of CC	0.004	0.004	4.932	0.036*
	Left anterior corona radiata	0.005	0.005	9.460	0.005*
	Thalamus	0.003	0.003	5.688	0.025*
Pairwise comparisons (pre versus post)					
Effect of treatment	**Brain areas**	**Groups**	***F*(1, 24)**		**Significance[a] (NQA)**
Pre versus post	Body of CC	ALT	0.604		0.445
		BLT	5.984		0.022**
	Left anterior corona radiata	ALT	0.903		0.351
		BLT	12.347		0.002**
	Thalamus	ALT	0.352		0.558
		BLT	8.226		0.008**

NQA, normalized quantitative anisotropy; BLT, blue-light therapy; ALT, amber-light therapy; CC, corpus callosum; ANCOVA, analysis of covariance.

[a]*Adjustment for multiple comparisons using Bonferroni's method.*

**Interaction is significant at $p < 0.05$.*

***Mean difference between post- and pre-treatment is significant at $p < 0.05$.*

Daytime Sleep Onset Latency

Signifi ant negative partial correlations were observed between residualized changes in sleep onset latency during the fi st MSLT administration and residualized changes in NQA for fibers crossing ACR (L) ($r = -0.72$, $p = 0.01$; FDR corrected $p = 0.01$) (**Figure 4E**), i.e., greater changes in NQA were associated with delayed sleep onset latency during the day following BLT. However, after multiple comparisons correction, we did not fi d signifi ant association between residualized changes in sleep onset latency during any of the MSLT administrations and residualized changes in NQA for fibers crossing any of the regions of interest following ALT (**Figure 4F**). The fi dings above are summarized in **Table 3**.

DISCUSSION

In this study, we analyzed several white matter water diffusion properties including GFA, NQA, and ISO, for fibers crossing several brain areas in individuals with a recent mTBI. From a group of individuals with mTBI, half were randomly assigned to a placebo condition of ALT and the other half to an active condition of BLT. Consistent with our hypotheses, we observed signifi ant changes in some of these white matter properties (i.e., GFA and NQA) for multiple brain areas following BLT. Contrary to our hypotheses, we did not observe signifi ant changes in cognitive abilities such as attention and memory, or in the daytime sleep onset latency measures. However, an analysis of cognitive abilities and daytime sleep onset latency measures in relation to white matter properties revealed a signifi ant relationship between increased DM scores and decreased normalized quantitative anisotropy, as well as an association between increased daytime sleep onset latency and decreased normalized quantitative anisotropy after BLT. These fi dings suggest that BLT may provide an effective method for facilitating recovery from mTBI.

Previous DTI studies of mTBI have tended to focus on FA as a measure of the diffusion properties of white matter tracts. However, these studies have yielded somewhat inconsistent results, as some report abnormally high (30) and others report abnormally low FA (24) values following an mTBI (i.e., as compared to HCs). Such inconsistencies may be due to several factors, including type, severity and location of injury, time since injury, and variability across subject samples (30). In this study, we examined NQA and ISO, in addition to FA, in order to fully characterize potential treatment effects. In doing so, we found a signifi ant effect of BLT on white matter water diffusion properties (i.e., both GFA and NQA) for several brain areas, which were associated with signifi ant correlations between diffusion measures, behavioral measures of neuropsychological function, as well as daytime sleep onset latency. In contrast, none of the 11 brain areas showed signifi ant change in GFA, NQA, or ISO following the placebo ALT. More specifi ally, we found that, following BLT (but not ALT), there was signifi ant decrease in GFA for fibers passing through the splenium of the CC, and a signifi ant decrease in NQA for fibers passing through the body of CC, left ACR, and thalamus. These changes in NQA for fiber pathways going through the body of the CC and thalamus were also signifi antly negatively correlated with changes in RBANS DM scores, suggesting that decreases in NQA were associated with improvements in DM performance from pre- to post-treatment. In addition, changes in NQA for fiber pathways going through the left ACR were signifi antly negatively correlated with changes in MSLT scores, suggesting that decreases in NQA were associated with improvements in sleep onset latency during the day from pre- to post-treatment. The role of the CC during recovery following BLT might be due to the fact that CC

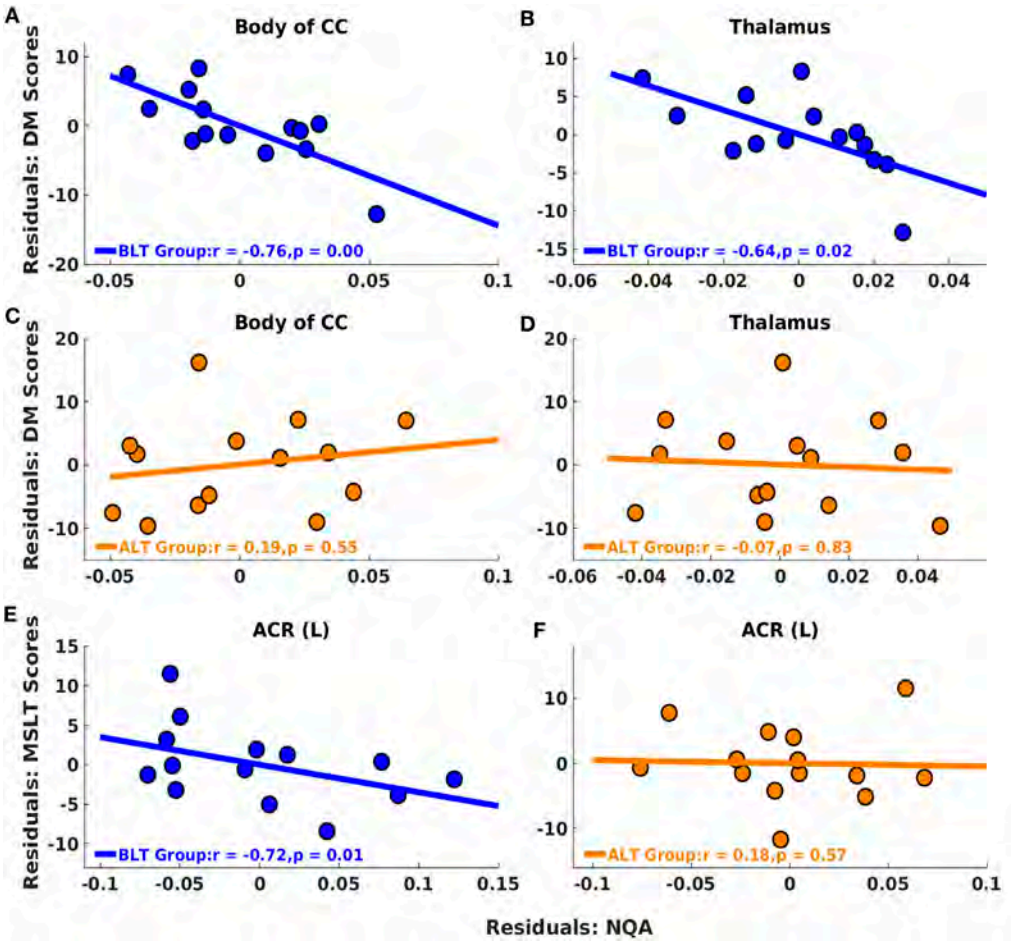


FIGURE 4 | Associations between residualized changes in white matter diffusion measures, neuropsychological measures, and multiple sleep latency test (MSLT) scores following BLT and ALT. For BLT and ALT groups, correlations found between residualized changes in NQA and neuropsychological function measures (DM) [BLT: **(A,B)**, ALT: **(C,D)**], and between residualized changes in NQA and MSLT scores [BLT: **(E)**, ALT: **(F)**] are reported. Significant negative correlations between residualized changes in Repeatable Battery for the Assessment of Neuropsychological Status DM scores and NQA measures were found for fibers crossing the body of the corpus callosum (CC) **(A)** and thalamus **(B)** for BLT group. No significant correlations were found for ALT group, including for fibers crossing the body of the CC **(C)** and thalamus **(D)**. Significant negative correlations between residualized changes in sleep onset latency during the first MSLT administration and NQA measures were also found for fibers crossing the left anterior corona radiata (ACR) **(E)** for BLT group but not for ALT group **(F)**. BLT, blue-light therapy; ALT, amber-light therapy, DM, delayed memory.

tracts facilitate communication of somatosensory information between parietal and occipital lobes (46) as well as communication between the two cortical hemispheres more generally (47). These tracts are known for their vital role in regulating several advanced brain skills such as memory, learning, and abstract thinking. Damage to these tracts could lead to loss of interhemispheric connections, causing multiple neuropsychological impairments (47). Moreover, the CC is also a common site affected following a brain injury. In the previous work, axons of the CC were reported to exhibit multiple stages of degeneration following a traumatic brain injury (48). In addition, generation of myelin sheaths within the CC could be responsible for its greater responsiveness to BLT. Furthermore, the connections between the anterior thalamus and hippocampal gyrus are believed to operate in parallel but with different organization and any damage to such network or any of the participating areas could contribute to impaired memory and discrimination skills (49, 50). The improvements in memory scores as a result of changes in NQA could be due to the effects of blue light exposure on sleep quality, which plausibly results in decreased daytime sleepiness and increases in alertness. Future work assessing PSG or actigraphic changes in sleep duration and quality will be necessary to test these hypotheses directly. In a diffusion kurtosis imaging study, several brain areas including the CC, thalamus, and IC showed correlations between changes in mean kurtosis or radial kurtosis between 1 and 6 months post mTBI and improvements in cognition between the 1- and 6-month visits (51). In that study, no signifi ant differences in other diffusion parameters (such as FA and mean diffusivity) were observed between mTBI patients and age-matched controls. The fi dings reported in our

TABLE 3 | Summary of correlations between residualized changes in neuropsychological function measures (DM) and GFA, and between residualized changes in MSLT scores and normalized quantitative anisotropy (NQA) measures.

#	ROIs	Partial correlations (*r*, *p*) between residualized changes in									
		GFA and					NQA and				
		DM	MSLT 1	MSLT 2	MSLT 3	Mean MSLT	DM	MSLT 1	MSLT 2	MSLT 3	Mean MSLT
BLT group											
1	Splenium of CC	0.35, 0.27	−0.33, 0.29	−0.17, 0.60	−0.48, 0.12	−0.37, 0.23			–		
2	Body of CC			–			−0.76, 0.00**	−0.18, 0.58	−0.43, 0.16	−0.17, 0.60	−0.37, 0.24
3	ACR (L)			–			−0.37, 0.23	−0.72, 0.01**	−0.45, 0.14	−0.45, 0.15	−0.58, 0.05
4	Thalamus			–			−0.64, 0.02**	−0.45, 0.14	−0.48, 0.11	−0.39, 0.21	−0.54, 0.07
ALT group											
1	Splenium of CC	−0.02, 0.96	−0.56, 0.06	−0.61, 0.04*	−0.38, 0.22	−0.61, 0.04*			–		
2	Body of CC			–			0.19, 0.55	−0.52, 0.08	−0.52, 0.08	−0.51, 0.09	0.60, 0.04*
3	ACR (L)			–			0.43, 0.16	0.18, 0.57	0.04, 0.91	−0.04, 0.92	0.07, 0.83
4	Thalamus			–			−0.07, 0.83	0.13, 0.70	−0.19, 0.56	0.42, 0.17	0.17, 0.60

ROIs, regions of interest; GFA, generalized fractional anisotropy; NQA, normalized quantitative anisotropy; DM, delayed memory; MSLT, multiple sleep latency test; BLT, blue-light therapy; CC, corpus callosum; ACR (L), anterior corona radiata (left); ALT, amber-light therapy; FDR, false discovery rate.

**p < 0.05 (uncorrected for multiple comparisons).*

***p < 0.05 (FDR corrected for multiple comparisons).*

study are also consistent with previous findings demonstrating microstructural white matter changes in the ACR for patients suffering from narcolepsy, a disorder characterized by rapid sleep onset latency during the daytime (52).

We observed a significant reduction in diffusion measures (GFA and NQA) following BLT. One of the potential explanations for changes in GFA and NQA measures could be attributed to the way axons are packed. Previously, changes in FA are reported to be dependent on axonal packing. It was reported that light axonal packing leaves more intercellular water as compared to dense packing causing less restriction to water molecules, which further results into lower FA values whereas higher degree of myelination results into higher FA values due to tight axonal packing (53). In addition, in a separate study, we recently demonstrated that acute exposure to 30 min of blue light subsequently led to increased functional brain responses within the prefrontal cortex and improved cognitive performance during a working memory task (54). Blue light exposure in the morning may therefore facilitate brain function later during the day, possibly when individuals are at work. If individuals are exposed to 30 min of morning blue light every day for 6 weeks and are able to sustain regular attentional focus, this may plausibly also be reflected in better white matter integrity and improved performance on neuropsychological tasks and decreased daytime sleepiness. Another possible reason for changes in diffusion measures (GFA and NQA) following BLT could be that before BLT, GFA, and NQA were higher and BLT helped to restore these diffusion levels back to normal. In fact, increased water diffusion after an mTBI has been associated with the stretching and deformations of axons following mTBI, which leads to an increase in intra- but decrease in extra-cellular water causing an increase in diffusion along the axons (55, 56). Modeling studies have shown that the inter-hemispheric fibers, especially of the CC, could be more sensitive to mechanical strain following brain deformation after a concussion (57). Diffusion of water molecules through strained axons could further be responsible for higher GFA or NQA. Abnormal disruption of water due to axonal swelling, compression of axons, and expansion of tissues may also lead to abnormal changes in water diffusion (30, 58). Myelin also plays a significant role in axon susceptibility following an mTBI. For instance, compared to myelinated axons, unmyelinated fibers within white matter are more adversely affected following traumatic axonal injury (59). BLT may improve myelination and help in regenerating new structural fibers, which could cause the observed improvements in neurobehavioral scores and possibly the observed changes in GFA and NQA values. However, the potential mechanism behind increased myelination or regeneration of structural fibers following light therapy is not completely understood. It may involve clearance of neurotoxins (34) and increases in oligodendrocyte precursor cells (35) due to shifts in circadian rhythms and improved sleep (18, 60, 61). Previously, it was reported that mean water diffusivity values were reduced within several brain regions including CC, corona radiata, and thalamic radiation in patients with obstructive sleep apnea compared to HCs (62). In a study of patients with bipolar disorder, reduced water diffusivity within the same regions identified here (CC, corona radiata, and thalamic radiation) indicated that sleep quantity could be associated with integrity of myelin sheaths (63). Therefore, BLT may enrich or stimulate the production of myelin-enriched brain debris, which may further stimulate microglial/macrophage activation in white matter tracts (64), especially within the CC, corona radiata, and thalamic radiation, which are associated with various sleep problems. Adaptive alterations in water diffusivity following BLT may also act to strengthen brain function. The association between sleep and variation in diffused water quantity could also be responsible for circadian changes in diffusion measures (65, 66), which may further lead to improvements in brain structure and function following BLT. Furthermore, it is known from other studies that acute exposure to blue light also has a positive impact on brain function and cognitive performance and it makes people faster at responding during working memory tasks without

loss of accuracy (54). Separate from the effects of blue light on melatonin suppression, it is possible that blue light may have more direct cognitive alerting effects *via* direct stimulation of the locus coeruleus, which in turn releases norepinephrine throughout the cerebral cortex (54, 67, 68). While speculative, it is conceivable that the effects could be even more robust during periods of insuffici t sleep that are extremely common following a traumatic brain injury (69). Th s is an important area for further research.

Finally, it is noteworthy that NQA appeared to yield a larger number of signifi ant fi dings than GFA or ISO. One possibility is that NQA is a more sensitive measure to detect microstructural changes of white matter integrity following an mTBI. By contrast, we predict that GFA could be a more sensitive measure to determine white matter differences between controls and mTBI patients. Th s is also consistent with the previous literature, which has suggested that density measures like NQA are more sensitive to individual physiological differences, whereas diffusivity measures like GFA are more sensitive to pathological conditions (70). NQA is also generally considered to be a more robust measure for deterministic tractography, due to its lower susceptibility to partial volume effects (31). It has also been found that NQA has the capability to filter out noisy fiber tracts, which further results in a higher spatial resolution in NQA-aided tractography. By contrast, voxel-based indices, such as GFA, are not capable of filtering out the noisy fibers since the same magnitude of anisotropy is shared by all the fiber orientations within a voxel (31). These considerations support the idea that NQA-aided tractography may be a better approach than GFA-based tractography for examining abnormal white matter content following an injury and injury-related therapies. It should be noted that the deterministic tractography methods implemented in DSI Studio has achieved the highest "valid connection" examined by an open competition among 96 methods submitted from 20 different research groups around the world.[3]

Th s study had several limitations. First, we acknowledge the fact that there is no way to assert the accuracy of tractography. Thus, further research will be needed to provide convergent validity to these fi dings. Second, our data sample was focused on participants with mTBI and did not include healthy controls. The goal was to compare the active versus a placebo condition on the recovery of a patient population, but future work would benefit from a sample of healthy individuals to determine the extent to which the outcomes represent full normalization of brain structure. Thi d, our mTBI sample also included individuals with different injury mechanisms. Mild injuries of this type are extremely heterogeneous and may vary signifi antly among samples. Finally, our data sample was relatively small. Low statistical power due to smaller sample size could account for the non-signifi ant fi dings observed in many neuropsychological function and sleep onset latency measures following BLT.

[3]http://www.tractometer.org/ismrm_2015_challenge/results.

In summary, these fi dings provide preliminary evidence that BLT can affect recovery of brain structure and function following mTBI. Following BLT, normalized values of water diffusion were associated with increases in memory and sleep latency scores. While more research is warranted, these preliminary fi dings raise the possibility that BLT might be useful as a means of facilitating brain and cognitive recovery among individuals with mTBI. Finally, our results also support the use of NQA as a sensitive measure to analyze the effect of treatment following a brain injury.

ETHICS STATEMENT

Participants were thoroughly briefed on the potential risks and benefits of the study and all completed written informed consent before enrollment. The experimental protocol was approved by the Institutional Review Board of McLean Hospital, Partners Health Care, and the U.S. Army Human Research Protections Offic (HRPO). All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

SB conducted the neuroimaging analyses and wrote the initial draft of the manuscript and organized the revisions. JV, RS, and ND each contributed to the writing of revisions of the manuscript and helped with data analysis. WK designed the study, oversaw data collection and analysis, and contributed to writing revisions of the manuscript.

ACKNOWLEDGMENTS

Th s research was supported by a U.S. Army Medical Research and Materiel Command Grant (W81XWH-11-1-0056) to WK. Opinions, interpretations, conclusions, and recommendations in this study are those of the author and are not necessarily endorsed by the Department of Defense. We would also like to thank Dr. Fang-Cheng Yeh for answering our enquires on numerous occasions during data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fneur.2017.00616/full#supplementary-material.

FIGURE S1 | Subject-averaged generalized fractional anisotropy (GFA), NQA, and isotropic diffusion (ISO) measure. Here, we plot the subject-averaged magnitude of raw diffusion measures before and after either amber-light therapy (ALT) **(A–C)** or blue-light therapy (BLT) **(D–F)** for GFA **(A,D)**, NQA **(B,E)**, and ISO **(C,F)**. Error bars represent the SEM.

REFERENCES

1. Levin HS, Mattis S, Ruff RM, Eisenberg HM, Marshall LF, Tabaddor K, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg* (1987) 66(2):234–43. doi:10.3171/jns.1987.66.2.0234
2. Silver JM, McAllister TW, Arciniegas DB. Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry* (2009) 166(6): 653–61. doi:10.1176/appi.ajp.2009.08111676
3. Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. Self-reported changes to nighttime sleep after traumatic brain injury. *Arch Phys Med Rehabil* (2006) 87(2):278–85. doi:10.1016/j.apmr.2005.10.024
4. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* (2007) 130(Pt 7):1873–83. doi:10.1093/brain/awm109
5. Sullivan KA, Edmed SL, Allan AC, Karlsson LJ, Smith SS. Characterizing self-reported sleep disturbance after mild traumatic brain injury. *J Neurotrauma* (2015) 32(7):474–86. doi:10.1089/neu.2013.3284
6. Inglese M, Makani S, Johnson G, Cohen BA, Silver JA, Gonen O, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* (2005) 103(2):298–303. doi:10.3171/jns.2005.103.2.0298
7. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol* (2013) 246:35–43. doi:10.1016/j.expneurol.2012.01.013
8. Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Clark RS, Ruppel RA, et al. Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatrics* (2002) 109(2):E31. doi:10.1542/peds.109.2.e31
9. Ruff R. Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil* (2005) 20(1):5–18. doi:10.1097/00001199-200501000-00003
10. Cicerone KD, Smith LC, Ellmo W, Mangel HR, Nelson P, Chase RF, et al. Neuropsychological rehabilitation of mild traumatic brain injury. *Brain Inj* (1996) 10(4):277–86. doi:10.1080/026990596124458
11. Paniak C, Toller-Lobe G, Reynolds S, Melnyk A, Nagy J. A randomized trial of two treatments for mild traumatic brain injury: 1 year follow-up. *Brain Inj* (2000) 14(3):219–26. doi:10.1080/026990500120691
12. Petraglia AL, Maroon JC, Bailes JE. From the fi ld of play to the fi ld of combat: a review of the pharmacological management of concussion. *Neurosurgery* (2012) 70(6):1520–33; discussion 1533. doi:10.1227/NEU.0b013e31824cebe8
13. Kurowski BG, Wade SL, Dexheimer JW, Dyas J, Zhang N, Babcock L. Feasibility and potential benefits of a web-based intervention delivered acutely after mild traumatic brain injury in adolescents: a pilot study. *J Head Trauma Rehabil* (2016) 31(6):369–78. doi:10.1097/HTR.0000000000000180
14. Viola AU, James LM, Schlangen LJ, Dijk DJ. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health* (2008) 34(4):297–306. doi:10.5271/sjweh.1268
15. Phipps-Nelson J, Redman JR, Schlangen LJ, Rajaratnam SM. Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiol Int* (2009) 26(5):891–912. doi:10.1080/07420520903044364
16. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* (2002) 295(5557):1070–3. doi:10.1126/science.1067262
17. Dijk D-J, Archer SN. Light, sleep, and circadian rhythms: together again. *PLoS Biol* (2009) 7(6):e1000145. doi:10.1371/journal.pbio.1000145
18. Wright HR, Lack LC, Kennaway DJ. Differential effects of light wavelength in phase advancing the melatonin rhythm. *J Pineal Res* (2004) 36(2):140–4. doi:10.1046/j.1600-079X.2003.00108.x
19. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Gotz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS One* (2011) 6(1):e16429. doi:10.1371/journal.pone.0016429
20. Correa A, Barba A, Padilla F. Light effects on behavioural performance depend on the individual state of vigilance. *PLoS One* (2016) 11(11):e0164945. doi:10.1371/journal.pone.0164945
21. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair* (2014) 28(4):303–13. doi:10.1177/1545968313508472
22. Niogi SN, Mukherjee P, Ghajar J, Johnson CE, Kolster R, Lee H, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain* (2008) 131(Pt 12):3209–21. doi:10.1093/brain/awn247
23. Geary EK, Kraus MF, Pliskin NH, Little DM. Verbal learning differences in chronic mild traumatic brain injury. *J Int Neuropsychol Soc* (2010) 16(3): 506–16. doi:10.1017/S135561771000010X
24. Matsushita M, Hosoda K, Naitoh Y, Yamashita H, Kohmura E. Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. *J Neurosurg* (2011) 115(1):130–9. doi:10.3171/2011.2.JNS101547
25. Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, et al. Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology* (2010) 74(7):558–64. doi:10.1212/WNL.0b013e3181cff5d5
26. Xiong K, Zhu Y, Zhang Y, Yin Z, Zhang J, Qiu M, et al. White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident. *Brain Res* (2014) 1591:86–92. doi:10.1016/j.brainres.2014.10.030
27. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* (2007) 130(Pt 10):2508–19. doi:10.1093/brain/awm216
28. Lipton ML, Gulko E, Zimmerman ME, Friedman BW, Kim M, Gellella E, et al. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology* (2009) 252(3):816–24. doi:10.1148/radiol.2523081584
29. Mayer AR, Ling J, Mannell MV, Gasparovic C, Phillips JP, Doezema D, et al. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology* (2010) 74(8):643–50. doi:10.1212/WNL.0b013e3181d0ccdd
30. Ling JM, Pena A, Yeo RA, Merideth FL, Klimaj S, Gasparovic C, et al. Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: a longitudinal perspective. *Brain* (2012) 135(Pt 4):1281–92. doi:10.1093/brain/aws073
31. Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY. Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS One* (2013) 8(11):e80713. doi:10.1371/journal.pone.0080713
32. Tuch DS. Q-ball imaging. *Magn Reson Med* (2004) 52(6):1358–72. doi:10.1002/mrm.20279
33. Fritzsche KH, Laun FB, Meinzer HP, Stieltjes B. Opportunities and pitfalls in the quantifi ation of fiber integrity: what can we gain from Q-ball imaging? *Neuroimage* (2010) 51(1):242–51. doi:10.1016/j.neuroimage.2010.02.007
34. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Th yagarajan M, et al. Sleep drives metabolite clearance from the adult brain. *Science* (2013) 342(6156):373–7. doi:10.1126/science.1241224
35. Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C. Effects of sleep and wake on oligodendrocytes and their precursors. *J Neurosci* (2013) 33(36):14288–300. doi:10.1523/jneurosci.5102-12.2013
36. Management of Concussion/mTBI Working Group. VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury. *J Rehabil Res Dev* (2009) 46(6):C1–68. doi:10.1682/JRRD.2008.03.0038
37. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci* (2007) 19(7):1081–8. doi:10.1162/jocn.2007.19.7.1081
38. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* (1998) 20(3):310–9. doi:10.1076/jcen.20.3.310.823
39. McKay C, Casey JE, Wertheimer J, Fichtenberg NL. Reliability and validity of the RBANS in a traumatic brain injured sample. *Arch Clin Neuropsychol* (2007) 22(1):91–8. doi:10.1016/j.acn.2006.11.003
40. Carskadon MA. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* (1986) 9(4):519–24. doi:10.1093/sleep/9.4.519
41. Fong SY, Ho CK, Wing YK. Comparing MSLT and ESS in the measurement of excessive daytime sleepiness in obstructive sleep apnoea syndrome. *J Psychosom Res* (2005) 58(1):55–60. doi:10.1016/j.jpsychores.2004.05.004
42. Littner MR, Kushida C, Wise M, Davila G, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* (2005) 28(1):113–21. doi:10.1093/sleep/28.1.113

43. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage* (2011) 58(1):91–9. doi:10.1016/j.neuroimage.2011.06.021
44. Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, et al. Is there "One" DLPFC in cognitive action control? Evidence for heterogeneity from co-activation-based parcellation. *Cereb Cortex* (2013) 23(11):2677–89. doi:10.1093/cercor/bhs256
45. Mori S, Wakana S, van Zijl PCM, Nagae-Poetscher LM. *MRI Atlas of Human White Matter*. Amsterdam: Elsevier (2005).
46. Bekiesinska-Figatowska M, Duczkowska A, Szkudlinska-Pawlak S, Duczkowski M, Madzik J, Cabaj A, et al. Diffusion restriction in the corticospinal tracts and the corpus callosum in neonates after cerebral insult. *Brain Dev* (2016) 39(3):203–10. doi:10.1016/j.braindev.2016.10.003
47. Huang X, Du X, Song H, Zhang Q, Jia J, Xiao T, et al. Cognitive impairments associated with corpus callosum infarction: a ten cases study. *Int J Clin Exp Med* (2015) 8(11):21991–8.
48. Mierzwa AJ, Marion CM, Sullivan GM, McDaniel DP, Armstrong RC. Components of myelin damage and repair in the progression of white matter pathology after mild traumatic brain injury. *J Neuropathol Exp Neurol* (2015) 74(3):218–32. doi:10.1097/NEN.0000000000000165
49. Winocur G. The hippocampus and thalamus: their roles in short- and long-term memory and the effects of interference. *Behav Brain Res* (1985) 16(2–3):135–52. doi:10.1016/0166-4328(85)90088-9
50. Aggleton JP, O'Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur J Neurosci* (2010) 31(12):2292–307. doi:10.1111/j.1460-9568.2010.07251.x
51. Stokum JA, Sours C, Zhuo J, Kane R, Shanmuganathan K, Gullapalli RP. A longitudinal evaluation of diffusion kurtosis imaging in patients with mild traumatic brain injury. *Brain Inj* (2015) 29(1):47–57. doi:10.3109/02699052.2014.947628
52. Menzler K, Belke M, Unger MM, Ohletz T, Keil B, Heverhagen JT, et al. DTI reveals hypothalamic and brainstem white matter lesions in patients with idiopathic narcolepsy. *Sleep Med* (2012) 13(6):736–42. doi:10.1016/j.sleep.2012.02.013
53. Feldman HM, Yeatman JD, Lee ES, Barde LH, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. *J Dev Behav Pediatr* (2010) 31(4):346–56. doi:10.1097/DBP.0b013e3181dcaa8b
54. Alkozei A, Smith R, Pisner DA, Vanuk JR, Berryhill SM, Fridman A, et al. Exposure to blue light increases subsequent functional activation of the prefrontal cortex during performance of a working memory task. *Sleep* (2016) 39(9):1671–80. doi:10.5665/sleep.6090
55. Rosenblum WI. Cytotoxic edema: monitoring its magnitude and contribution to brain swelling. *J Neuropathol Exp Neurol* (2007) 66(9):771–8. doi:10.1097/nen.0b013e3181461965
56. Browne KD, Chen XH, Meaney DF, Smith DH. Mild traumatic brain injury and diffuse axonal injury in swine. *J Neurotrauma* (2011) 28(9):1747–55. doi:10.1089/neu.2011.1913
57. Viano DC, Casson IR, Pellman EJ, Zhang L, King AI, Yang KH. Concussion in professional football: brain responses by fin te element analysis: part 9. *Neurosurgery* (2005) 57(5):891–916; discussion 891–916. doi:10.1227/01.NEU.0000186950.54075.3B
58. Miller KE, Heidemann SR. What is slow axonal transport? *Exp Cell Res* (2008) 314(10):1981–90. doi:10.1016/j.yexcr.2008.03.004
59. Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: clues to axon and myelin repair capacity. *Exp Neurol* (2016) 275(Pt 3):328–33. doi:10.1016/j.expneurol.2015.02.011
60. Duffy JF, Czeisler CA. Effect of light on human circadian physiology. *Sleep Med Clin* (2009) 4(2):165–77. doi:10.1016/j.jsmc.2009.01.004
61. Carpenter JS, Abelmann AC, Hatton SN, Robillard R, Hermens DF, Bennett MR, et al. Pineal volume and evening melatonin in young people with affective disorders. *Brain Imaging Behav* (2016):1–10. doi:10.1007/s11682-016-9650-2
62. Kumar R, Chavez AS, Macey PM, Woo MA, Yan-Go FL, Harper RM. Altered global and regional brain mean diffusivity in patients with obstructive sleep apnea. *J Neurosci Res* (2012) 90(10):2043–52. doi:10.1002/jnr.23083
63. Benedetti F, Melloni EMT, Dallaspezia S, Bollettini I, Locatelli C, Poletti S, et al. Night sleep influences white matter microstructure in bipolar depression. *J Affect Disord* (2017) 218:380–7. doi:10.1016/j.jad.2017.05.008
64. Clarner T, Diederichs F, Berger K, Denecke B, Gan L, van der Valk P, et al. Myelin debris regulates inflammatory responses in an experimental demyelination animal model and multiple sclerosis lesions. *Glia* (2012) 60(10):1468–80. doi:10.1002/glia.22367
65. Jiang C, Zhang L, Zou C, Long X, Liu X, Zheng H, et al. Diurnal microstructural variations in healthy adult brain revealed by diffusion tensor imaging. *PLoS One* (2014) 9(1):e84822. doi:10.1371/journal.pone.0084822
66. Elvsashagen T, Norbom LB, Pedersen PO, Quraishi SH, Bjornerud A, Malt UF, et al. Widespread changes in white matter microstructure after a day of waking and sleep deprivation. *PLoS One* (2015) 10(5):e0127351. doi:10.1371/journal.pone.0127351
67. Foote SL, Berridge CW, Adams LM, Pineda JA. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. *Prog Brain Res* (1991) 88:521–32. doi:10.1016/S0079-6123(08)63831-5
68. Florin-Lechner SM, Druhan JP, Aston-Jones G, Valentino RJ. Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. *Brain Res* (1996) 742(1–2):89–97. doi:10.1016/S0006-8993(96)00967-5
69. Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. *J Head Trauma Rehabil* (2009) 24(3):155–65. doi:10.1097/HTR.0b013e3181a0b281
70. Yeh FC, Vettel JM, Singh A, Poczos B, Grafton ST, Erickson KI, et al. Quantifying differences and similarities in whole-brain white matter architecture using local connectome fi gerprints. *PLoS Comput Biol* (2016) 12(11):e1005203. doi:10.1371/journal.pcbi.1005203

Confl ct of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or fi ancial relationships that could be construed as a potential confli t of interest.

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Daily administered blue light therapy reduces daytime sleepiness and improves somatic symptoms following mild traumatic brain injury

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Background: Mild traumatic brain injury (mTBI) is one of the most prevalent injuries in military personnel. While most mTBIs recover quickly, without complications, between 30-90% of those who are injured will continue to show some manner of sleep related problem up to 3 years post-injury. Poor sleep can slow recovery from mTBI and can also result in excessive daytime sleepiness. Daytime sleepiness slows psychomotor response times, disrupts sustained attention, impairs emotional awareness and responsiveness, and limits visuo-motor, postural, and proprioceptive control. These deleterious effects can affect day-to-day functioning of injured military personnel and can dramatically increase the likelihood of poor mission-related outcomes, including increased injury risk, possibility resulting in fatality, as well as mission failure. Given the deleterious effects of daytime sleepiness on recovery, training, and mission-critical cognitive awareness and function, it is essential to proactively treat post-mTBI sleep disruptions to support not only job performance but also potentially shorten recovery times. Short-wavelength blue light is effective at improving several disrupted sleep conditions (e.g., jet lag, seasonal affective disorder), and additionally has positive effects on cognitive performance and affect. Furthermore, the identification of non-pharmacologic sleep interventions would effectively minimize sleep-promoting substance dependence and abuse and encourage more natural internal homeostatic sleep regulation. Here, we evaluate the effects of a six-week intervention using short-wavelength (469-nm) blue light or a placebo (566-nm) amber light daily for 30-minutes in the morning in individuals with a recent mTBI. Outcome measures of interest included measures of daytime sleepiness and concussion symptom improvement. Consistent with prior research, we hypothesized that blue light therapy would be associated with reduced daytime sleepiness.

Methods: 27 individuals (age: 26.85±8.39y; 18 females; days post-injury: 275.42±167.04 days) were recruited and randomly assigned to receive blue or amber light therapy. All individuals underwent a comprehensive in-lab assessment including neuroimaging, as well as a neuropsychological and self-report assessment battery at both pre- and post-treatment. This battery included self-report measures of daytime sleepiness (Epworth Sleepiness Scale, ESS) and post-concussion symptoms (Rivermead Post-concussion Symptom Questionnaire, RPCSQ). All individuals completed six weeks of daily light treatment (30 minutes each morning) via direct exposure to a light box. The interventional specifically consisted of the following: Individuals were provided a Phillips goLITE BLU (peak λ = 464-467 nm) or custom amber goLITE (peak λ = 566 nm). Participants were instructed to place the light device 12-24 inches away from their faces and to allow light to enter the eyes through the periphery rather than directly (to reduce glare and adverse effects associated with looking directly into the light). Total dosage was 30 minutes per day within two hours of waking for 6 weeks.

The primary outcomes were change scores from pre- to post-treatment on the ESS and the RPCSQ. Two sample T-tests were used to statistically compare the between-group post-treatment changes in ESS scores and RPCSQ subscale scores (somatic, emotional, cognitive). Further analyses included bivariate correlations between change scores to uncover potentially informative relationships explaining treatment-related changes.

Results: Both groups reported similar pre-treatment ESS and RPCSQ subscale scores, suggesting a homogenous effect of mTBI on both daytime sleepiness and symptom burden. After treatment, ESS scores in the blue light treatment group exhibit decreased daytime sleepiness compared to the amber group ($t = 2.46$, $p = 0.025$). Additionally, both somatic ($t = 2.04$, $p = 0.053$) and cognitive ($t = 0.082$) RPCSQ subscale scores demonstrated a trend toward reduced symptom burden in the blue light group. Critically, improved daytime sleepiness via the ESS was associated with the improvement in somatic symptoms ($r = 0.49$, $p = 0.014$).

Conclusions: Individuals with a history of mTBI exhibit improved daytime sleepiness and reduced post-concussion symptom burden following focused, daily blue light therapy. Importantly, no adverse effects of this method of treatment were noted by any of the participants, suggesting that this is a safe and well-tolerated treatment. These findings replicate our previous trial using the same approach and provide a strong indication that a six-week, daily blue light intervention improves self-reported daytime sleepiness following mTBI. Furthermore, these improvements were associated with reduced symptom reporting and are likely to have substantial effects on individuals' daytime functioning, including sustained cognitive-, physical-, emotional-, and job-related performance as well as an overall improved quality of life.

Operational demands often dictate that Warfighters sleep in unnatural or inhospitable environments, or in shifts that are out-of-phase with natural homeostatic rhythms. These perturbations to natural sleep are exacerbated further by mTBIs, which may occur both in theater and in garrison. Collectively, these effects may significantly erode capabilities essential to meeting operational demands. Even with a small dosage (30 minutes daily), blue light therapy provides a safe, well-tolerated, non-pharmacological means for reducing daytime sleepiness following mTBI. Such improvement likely will contribute to optimizing the injured Service member's capability to return to duty more quickly and to perform consistently at the highest levels during critical operations, thereby reducing operational errors, injuries, morbidity, and mortality.

Impact of Blue-Wavelength Light Therapy on Cortical Volume and Simple Reaction Time following Mild TBI

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Introduction

Mild traumatic brain injury (mTBI) ~~accounts for approximately 75% of all traumatic brain injury cases each year in the United States~~is the most prevalent injury among returning Service members from the recent conflicts in Iraq and Afghanistan. Recent statistics suggest that over 390,000 military personnel have experienced a traumatic brain injury since the year 2000, with 82.3% of these being mTBI (DVBIC; 2018 Q1). Also, specific changes in cortical structure following an mTBI are often associated with impaired cognitive abilities. Previous studies have shown that the frontal lobe, particularly the prefrontal cortex, is ~~more~~ particularly vulnerable to mTBI. In addition, ~~role of~~ the prefrontal cortex ~~has been linked to~~plays a critical role in attention and the ability to respond quickly to a stimulus. Emerging evidence suggests that short-wavelength light therapy, such as blue-light therapy, may facilitate sleep, circadian realignment, and recovery from mTBI. Blue light has been shown to specifically activate intrinsically photosensitive retinal ganglion cells that project to the suprachiasmatic nucleus of the hypothalamus, thus regulating the circadian rhythm. However, the effect of blue-light exposure on cognitive performance and brain structure in mTBI populations remains poorly characterized. The present study focused on determining the effect of daily morning exposure to BLT on reaction time (RT) ~~indicating attention abilities~~ during a simple stimulus task and structural changes in the brain following an mTBI. The aims of this study were threefold: 1) to identify brain regions where individuals with an mTBI may have lower normalized cortical volume (NCV) than healthy controls and determine whether these regions, once identified, exhibit volumetric changes following six-weeks of short-wavelength morning BLT compared to a placebo amber light treatment; 2) to determine whether there is an improvement in RT during a simple stimulus task; and 3) to investigate whether structural changes in targeted brain areas were associated with changes in RT, in each treatment condition. We hypothesized that brain regions affected following an mTBI would show normalization in their morphometry as well as an improvement in associated cognitive abilities following BLT.

Methods

Participants. Neuroanatomical data were collected from 28 post-mTBI individuals (mean age = 21.50±3.76 years, 15 F) and 34 healthy controls (HCs) (mean age = 25.19±3.38 years, 20 F). Participants with mTBI had to have experienced at least one traumatic injury or blow to the head resulting in altered consciousness, complete loss of consciousness (less than 30 minutes), or post-traumatic amnesia (no longer than 24 hours) within the preceding 18 months. MTBI Participants with any history of a neurological or psychiatric disorder with an onset before the mTBI were excluded. The HCs were included as a comparison group for anatomical morphometry. All HCs ~~were recruited as part of a separate study but~~ completed an identical structural scanning sequence in the same scanner. All HCs were screened via a comprehensive telephone interview indicating no self-reported history of head injury/concussion, psychiatric, neurological, or significant medical problems.

Procedure. Individuals with mTBI underwent six-weeks of blue-light therapy (BLT) (n = 14, mean age = 20.78±4.42 years, 8 F) or placebo amber light therapy (ALT) mTBI (n = 14, mean age = 21.21±3.09 years, 7 F). The Automated Neuropsychological Assessment Metrics (ANAM4) battery was used to quantify mTBI participants' cognitive functioning before and following treatment. Only the raw Simple Reaction Time (SRT) and Simple Reaction Time Repeated (SR2) data were used for the present analysis. The SRT task requires participants to press a button while they are shown a series of asterisks ~~"*" symbol~~ on the computer screen and are asked to respond as quickly as possible when the symbol appears. Reaction time is the measure, in milliseconds, from stimulus onset to button press. This stimulus is repeated 40 times and average RT over 40 trials was calculated for each participant for each task – SRT and SR2.

Data analysis. Simple reaction time data, collected on both occasions, i.e. SRT and SR2, were screened for outliers. Two data points due to extremely slow responses – during the pre-treatment condition for SRT and during the post-treatment condition for SR2 were identified as extreme outliers (i.e., with a value more than 3.0 inter-quartile range above the upper quartile) and were excluded from further data analysis. The standard cross-sectional "recon-all" pipeline was used to process anatomical images for all participants. However, to determine the changes from pre-treatment to post-treatment condition, the longitudinal "recon-all" pipeline was used to preprocess images for all mTBI participants. The measures of NCV were evaluated for 34 regions per hemisphere (using the Desikan atlas) for each participant. For comparison between RT and NCV before and after therapy, 'age', 'days light used' and 'time since injury' were included as covariates. Subject-wise variability was accounted for by using normalized values of cortical volume. Therefore, 'sex' was not used as a covariate for comparison of NCV. However, 'sex' was used as an additional covariate for comparing RT. To determine the association between changes in NCV and changes in RT, residualized change scores were derived by regressing post-treatment measures of NCV and RT on pre-treatment measures of NCV and RT respectively, and partial correlation between the two was

estimated using the same three covariates – ‘age’, ‘days light used’ and ‘time since injury’.

Results

At baseline, three regions, including the caudal middle frontal gyrus (MFG), inferior parietal cortex and middle temporal cortex (MTC) within the left hemisphere and five regions, including the lateral orbitofrontal cortex, pars orbitalis (R.ParsOrb), MTC, precentral gyrus and rostral MFG within the right hemisphere, which showed significantly lower normalized cortical volume (NCV) in mTBI patients than HCs (Cohen’s $d \geq 0.5$). These areas of differing volume were then considered regions of interest in the subsequent analysis. There was significant reduction in RT following BLT ($p = 0.008$), but not following ALT ($p = 0.09$). There was a significant group (ALT/BLT) x time (pre/post) interaction for NCV within the R.ParsOrb ($p = 0.035$), suggesting that NCV within R.ParsOrb increased following BLT, but not following ALT. Moreover, following BLT, increased NCV of the R.ParsOrb was significantly correlated with decreased RT ($r = -0.54$, $p = 0.04$).

Conclusions

Our findings show identifiable group-level differences in NCV within the frontal, parietal and temporal lobes in individuals with mTBI. Our findings also indicate that regular morning exposure to blue-light may increase NCV in a region within the prefrontal gyrus, which may further lead to improved attention, as suggested by a correlated improvement in mean reaction time over a sustained period. While we speculate that many of the positive benefits that emerge from exposure to blue light result from its effects on sleep and circadian processes, further work will be necessary to identify the underlying mechanisms and the inter-individual difference factors that may contribute to the effectiveness of this approach. Further research is also required to quantify the effects of light exposure on neurocognitive performance during more complex attention tasks. With continued research, this treatment may prove useful for facilitating recovery from mTBI among military personnel.

Blue-wavelength Light Strengthens the Default Mode Network following Mild TBI: A DCM-DTI Study

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Introduction. Mild traumatic brain injury (mTBI) is often associated with lingering post-concussive symptoms, *including* sleep problems and mood fluctuations. Previous reports suggest that regular morning exposure to blue light therapy (BLT) may improve some aspects of sleep problems and enhance mood. We hypothesized that these previously observed effects may be due to alterations in underlying brain structure and function following treatment. Here we examined the effect of BLT on directed brain connectivity (DC) within the default-model network (DMN) in conjunction with quantitative anisotropy (QA) reflecting compactness of white-matter fibers, and happiness (HAP) in mTBI individuals. Here, HAP mood data were included because of strong association between DMN connectivity and levels of HAP reported in the past.

Methods. Resting-state MRI data were collected from 41 healthy controls (HCs) and 28 individuals with mTBI. MTBI individuals either underwent six-weeks of BLT or placebo amber light therapy (ALT), at two occasions: before (BPre and APre) and after treatment (BPost and APost). Diffusion-weighted and mood data using Automated Neuropsychological Assessment Metrics (ANAM) battery were also collected from mTBI individuals on both occasions. Spectral dynamic causal modeling was used to invert graphs comprising six nodes - the posterior cingulate cortex (PCC), middle prefrontal cortex (MPFC), left and right middle temporal cortex (LMTC/RMTC) and left and right lateral parietal cortex (LLPC/RLPC) within the DMN. DSI Studio was used to estimate QA. 'Age' and 'sex' were used as covariates for comparisons between the mTBI group and HCs. 'Days light used' and 'time since injury' were used as additional covariates for comparisons between pre and post-treatment conditions. For simplicity, self-connections were not interpreted in the analysis.

Results.

DC

HCs vs. mTBI: At posterior probability (Pp) > 0.95, compared to HCs, weaker (shown in red boxes in left column in Fig 1A) as well as hyper DC (shown in blue boxes in left column in Fig 1A) was observed for mTBI individuals. We noticed that the weaker connectivity in mTBI individuals was more dominant within the left hemisphere (LH), *involving* the LMTC, LLPC, and the PCC (right column in Fig 1A).

APost vs. APre: At Pp > 0.95, no improvement in DC was observed in mTBI population for APost compared to APre as shown in Fig 1B. Here, blue boxes show connections, which are weaker for APost compared to APre.
BPost vs. BPre: At Pp > 0.95, improvement in DC from LMTC to LLPC was observed following BLT as shown in Fig 1C. Here, red boxes show connections, which are stronger for BPost compared to BPre and blue boxes show connections, which are weaker for BPost compared to BPre.
HCs vs. APost and BPost: At Pp > 0.95, several connections within both hemispheres showed stronger DC for HCs compared to APost (shown in red boxes in Fig 1D, upper row), *especially* within the LH (Fig 1D, lower row). At Pp > 0.95, fewer connections showed stronger DC for HCs compared to BPost (shown in red boxes in Fig 1E, upper row). However, for most of the connections, *especially* within the LH, no differences were observed for HCs compared to BPost (Fig 1E, lower row).

QA, DC and HAP
QA measures for tracts connecting LMTC and LLPC (Figs 2A-B) showed that there was (i) significant group (ALT/BLT)-time (PRE/POST) interaction, and (ii) significant increase in residualized QA following BLT (Fig 2C). However, for HAP scores, we did not observe any such differences following either therapy (Fig 2D). Both residualized changes in DC from LMTC to LLPC (Fig 2E) as well as QA (Fig 2F) between the two showed significant negative association with residualized changes in HAP following BLT, but not following ALT.

Conclusions. Morning BLT may strengthen the excitataory influence as well as the compactness of white matter bundles connecting specific regions within the DMN. Stronger connectivity within the DMN could also be responsible for lower levels of happiness.

Figure 1. Group-level differences in directed brain connectivity within the DMN.
Figure 2. Here we show white-matter tracts connecting LMTC and LLPC for ALT (A) and BLT (B) groups, impact of ALT and BLT on QA (C), HAP (D), and association of HAP with DC (E) and QA (F).

Effect of Blue Light Therapy on Cortical Volume and Reaction Time following Mild TBI

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Limit: 4000 characters

Introduction. Changes in cortical structure following a mild traumatic brain injury (mTBI) are often associated with impaired cognitive abilities. There is previous evidence suggesting that short-wavelength light therapy, such as blue-light therapy (BLT) may facilitate sleep, circadian realignment, and recovery from mTBI. However, the effect of blue-light exposure on cognitive performance and brain structure in mTBI population remains poorly characterized. In this study, we hypothesized that brain regions affected following an mTBI would show normalization in their morphometry as well as an improvement in associated cognitive abilities following BLT.

Methods. Neuroanatomical data were collected from 34 healthy controls (HCs) (mean age = 25.19±3.38 years, 20 F) and 28 post-mTBI individuals (mean age = 21.50±3.76 years, 15 F). Individuals with mTBI underwent six-weeks of blue-light therapy (BLT) or placebo amber light therapy (ALT). The Automated Neuropsychological Assessment Metrics (ANAM4) battery was used to quantify mTBI participants' cognitive functioning before and following treatment. Only the raw Simple Reaction Time (SRT) and Simple Reaction Time Repeated (SR2) data were used for the present analysis. The SRT task requires participants to press a button when they are shown a series of "*" symbol on the computer screen and are asked to respond as quickly as possible when the symbol appears. Reaction time is the measure, in milliseconds, from stimulus onset to button press. This stimulus is repeated 40 times and average reaction time (RT) over 40 trials was calculated for each participant for each task – SRT and SR2. For comparison between RT and normalized cortical volume (NCV) before and after therapy, 'age', 'days light used' and 'time since injury' were included as covariates. Subject-wise variability was accounted for by using normalized values of cortical volume (CV). Therefore, 'sex' was not used as a covariate for comparison of NCV. However, 'sex' was used as an additional covariate for comparing RT. To determine the association between changes in NCV and changes in RT, residualized change scores were derived by regressing post-treatment measures of NCV and RT on pre-treatment measures of NCV and RT respectively, and partial correlation between the two was estimated using the same three covariates – 'age', 'days light used' and 'time since injury'.

Results. At baseline, three regions, including the caudal middle frontal gyrus (MFG), inferior parietal cortex and middle temporal cortex (MTC) within the left hemisphere (Figure 1A) and five regions, including the lateral orbitofrontal cortex, pars orbitalis (R.ParsOrb), MTC, precentral gyrus and rostral MFG within the right hemisphere (Figure 1B and 1C), which showed significantly lower normalized cortical volume (NCV) in mTBI patients than HCs (Cohen's $d \geq 0.5$). These areas of differing volume were then considered regions of interest in the subsequent analysis. There was significant reduction in RT following BLT ($p = 0.008$), but not following ALT ($p = 0.09$) (Figure 2A). There was a significant group (ALT/BLT) x time (pre/post) interaction for NCV within the R.ParsOrb ($p = 0.035$)(Figure 2B), suggesting that NCV within R.ParsOrb increased following BLT, but not following ALT. Moreover, following BLT, increased NCV of the R.ParsOrb was significantly correlated with decreased RT ($r = -0.54$, $p = 0.04$) (Figure 2C). Error bars in figures 1 and 2 represent standard error of mean.

Conclusions. Our findings show identifiable group-level differences in NCV within the frontal, parietal and temporal lobes in individuals with mTBI. Our findings also indicate that regular morning exposure to blue-light may increase NCV in a region within the prefrontal gyrus, which may further lead to improved attention, as indicated by a correlated improvement in mean reaction time over a sustained period. Further research is required to quantify the effects of light exposure on neurocognitive performance during more complex attention tasks.

Figure 1. Differences in NCV between HCs and individuals with mTBI
Figure 2. Impact of ALT and BLT on RT and NCV

Daily Blue Light Therapy Reduces Daytime Sleepiness and Post-concussion Symptoms After Mild Traumatic Brain Injury

Adam C. Raikes, Brieann C. Satterfield, Sahil Bajaj, Michael A. Grandner, William D. S. Killgore

Background: An estimated 30-80% of individuals report long-term sleep disruption following a mild traumatic brain injury (mTBI). Given the critical role of high-quality sleep on optimal cognitive, emotional, sport, and physical performance, ameliorating these adverse mTBI effects is essential. The purpose of this randomized controlled trial was to evaluate the effects of daily blue light therapy (BLT) in comparison to amber light therapy (ALT) in a post-mTBI sample. We hypothesized that individuals receiving blue light would exhibit improved self-reported sleep outcomes.

Method: 27 individuals (age: 26.85±8.39y; 18 females; days post-injury: 275.42±167.04 days) were recruited and randomly assigned to receive BLT or ALT. Individuals in both groups underwent a comprehensive neuropsychological and self-report assessment battery at pre-treatment and post-treatment. This battery included self-report measures of daytime sleepiness (Epworth Sleepiness Scale, ESS) and post-concussion symptoms (Rivermead Post-concussion Symptom Questionnaire, RPCSQ). All individuals completed six weeks of daily light treatment (30 morning minutes direct exposure via light box). Two sample T-tests compared between-group post-treatment changes in ESS scores and RPCSQ subscale scores (somatic, emotional, cognitive). Additional analyses included bivariate correlations between change scores.

Results: The light groups exhibited no differences in baseline ESS or RPCSQ subscale scores. At post-treatment, individuals in the BLT group had significantly improved daytime sleepiness ($t=2.46$, $p = 0.025$), somatic ($t = 2.04$, $p = 0.053$) and cognitive symptoms ($t = 1.82$, $p = 0.082$) compared to those in the ALT group. Bivariate correlations indicated that improvements in ESS scores were significantly associated with improvements in somatic symptoms ($r = 0.49$, $p = 0.014$).

Conclusion: Daily BLT effectively reduced mTBI-related daytime sleepiness and self-reported somatic and cognitive symptoms. These improvements are likely to have significant positive effects on individuals' daytime functioning (cognitive, physical, emotional, sport) and overall quality of life. Further research is needed to uncover the directionality of these findings (decreased daytime sleepiness leads to improved symptoms or vice versa) as well as the neurological mechanisms underpinning these improvements.

Support: Funded by USAMRMC grant W81XWH-14-1-0571 to Dr. Killgore.

(HSATs) and a structured diagnostic interview for sleep disorders (SIS-D).
Methods: Data collection is ongoing as part of a study testing the efficacy of behavioral insomnia treatment in patients with mild to moderate TBI. Presently, 33 participants have completed baseline self-report measures of sleep (ISI, ESS, PSQI) and mood (GAD-7, PHQ-9), 7-14 days of actigraphy and Fitbit™ monitoring, 1-night of ambulatory sleep EEG monitoring, 1-night of HSAT, 7-14 days of sleep diaries, and the SIS-D.
Results: The participant sample has a mean age of 39.9 ± 12.7 years, and is predominantly female (70%), white (67%), at least college educated (52%), and unemployed (58%). Subjects endorse moderately severe insomnia symptoms (ISI: μ=18.7, SD=5.4), above-normal daytime sleepiness (ESS: μ=6, SD=3.8), poor sleep quality (PSQI: μ=12.7, SD=3.2), and moderately severe symptoms of depression (PHQ-9: μ=18.2, SD=5.3) and anxiety (GAD-7: μ=12.5, SD=4.8). Insomnia severity and reduced sleep quality were associated with self-reported depression (r=.59, p=.001 & r=.42, p=.02, respectively) but not with anxiety. Mean sleep efficiency (self-report based) was 59.7% ± 21.3%. When data collection is complete, descriptive statistics and standard sleep metrics will be compared among the objective sleep-tracking modalities utilized.
Conclusion: To date, study participants endorse and display associations between moderately severe sleep disturbance and affective distress, both of which are common in TBI. Hence, effective treatment of sleep disturbance in TBI patients may improve both sleep and emotional distress. However, these results should be considered preliminary, as data collection is ongoing. When complete, this study will contribute to the literature by providing extensive objective characterization of sleep in patients with TBI.
Support (If Any): ASMF Strategic Research Award; American Heart Association Mentored Clinical Research Award

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PRE- AND POST-INJURY SLEEP QUALITY AND SLEEP PROPENSITY PREDICTS RESILIENCE AND SYMPTOM RECOVERY IN HIGH-PERFORMING ATHLETES WITH CONCUSSION.

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Introduction: Disrupted sleep and sleep propensity are common sequelae of concussion in high-performing athletes. Although the summative effect of head injuries is widely accepted, the role of sleep quality and sleepiness in resilience and recovery is still poorly understood. This study quantified pre- and post-injury sleep quality and sleep propensity in high-performing athletes with concussion.
Methods: Forty-six athletes (20.8 y/o ± 3.60; 48% male) with concussion (n=27) and healthy, matched controls (n=19) completed self-report surveys on sleep quality, sleep propensity, and concussive symptoms before and immediately following an in-season concussion, and again at three follow up time points. Summary scores from The Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the British Columbia Postconcussion Symptom Inventory (BC-PSI) were analyzed using t-tests, ANOVAS, and regression models.
Results: We predict that during the off-season, those who did not go on to sustain a concussion would have both better sleep quality and lower sleep propensity than those who did go on to sustain a subsequent in-season concussion. In athletes who sustained an in-season concussion, we predict that sleep quality will be lower and propensity for sleep will be higher immediately following injury when compared to pre-injury data. Further, we expect sleep quality to decline and sleep propensity to increase gradually over the 6-month recovery tracking period. Finally, it is predicted that pre- and immediately post-injury sleep quality and sleep propensity will both individually and synergistically predicted concussion symptom recovery at 3-6 months.
Conclusion: Given the hypotheses are supported by the evidence, this study will demonstrate sleep quality and sleep propensity as targets for resilience and improving symptom recovery in high-performing athletes with concussion. Future research will examine the contribution of objective sleep/wake patterns and neurological factors in concussion resilience and recovery.
Support (If Any): Support for this study came from the Military Operational Medicine Research Program (MOMRP) of the United States Army Medical Research and Materiel Command (USAMRMC) and John Hopkins University School of Medicine.

0941

IMPACT OF LIGHT THERAPY ON BRAIN STRUCTURE AND SIMPLE REACTION TIME FOLLOWING MILD TRAUMATIC BRAIN INJURY

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Introduction: Mild traumatic brain injury (mTBI) is often associated with persistent post-concussive symptoms and sleep disruption. Emerging evidence suggests that circadian timing and some aspects of sleep quality may be improved through daily morning exposure to blue light therapy (BLT). However, the effect of BLT on brain structure in the mTBI population remains unknown.
Methods: Neuroanatomical data were collected from 34 healthy controls (HCs) and 28 mTBI individuals. Individuals with mTBI either underwent six-weeks of BLT or placebo amber light therapy (ALT). MTBI participants were administered the Automated Neuropsychological Assessment Metrics (ANAM4) battery both before and following treatment. For the purpose of this study, only the simple reaction time (RT) data from ANAM4 battery were analyzed.
Results: Compared to HCs, individuals with mTBI showed significantly lower normalized cortical volume (NCV) at baseline assessment (Cohen's d 0.5) in several brain regions. These included the caudal middle frontal gyrus (MFG), inferior parietal cortex and middle temporal cortex (MTC) within the left hemisphere and five regions, including the lateral orbitofrontal cortex, pars orbitalis (R.ParsOrb), MTC, precentral gyrus and rostral MFG within the right hemisphere. These areas of differing volume were then utilized as regions of interest (ROIs) in the main analysis of mTBI participants. There was significant reduction in RT following BLT ($p = 0.008$), but not following ALT ($p = 0.09$). There was a significant group (ALT/BLT) x time (pre/post) interaction for NCV within the R.ParsOrb ($p = 0.035$), suggesting that NCV within R.ParsOrb increased following BLT, but not following ALT. Moreover, following BLT, increased NCV of the R.ParsOrb was significantly correlated with decreased RT ($r = -0.54$, $p = 0.04$).

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Conclusion: Morning BLT may increase NCV within prefrontal areas and contribute to reductions in RT among individuals with mTBI. The primary effect of blue-light could be on sleep and circadian rhythms. This could cause observed improvements in cortical structure and reaction time, which can be considered as secondary consequence of improved sleep.
Support (If Any): W81XWH-11-1-0056 (WDK) and W81XWH-12-1-0109 (SLR)

0942

EFFECTS OF TIMED LIGHT ON MOOD AND COGNITION IN ALZHEIMER`S DISEASE

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Introduction: Circadian disturbances are often associated with cognitive decline in patients with Alzheimer's disease(AD). Reduced light exposure in addition to the degeneration of circadian clock in AD might lead to depression. Light therapy(LT) has been known to improve depression and cognitive function by stabilizing the circadian rhythm. We aimed to examine the effects of timed LT on mood and cognition in AD patients.
Methods: We recruited mild to moderate AD patients with Pittsburgh Sleep Quality Index score ≥ 5. They were randomly assigned to treatment group(TG) and control group(CG). The dim light melatonin onset(DLMO) was determined from seven hourly saliva samples obtained before sleep onset measured by actigraphy. Home-based one-hour blue-enriched light was applied between 9to 10h after DLMO for 2 weeks. The CG patinets wore blue-blocked glasses during timed LT. The Cornell Scale for Depression in Dementia(CSDD), Global Vigor(GVS) and Affect Scale(GAS) were administered before and immediately after timed LT. The MMSE in the Korean version of CERAD Packet(MMSE-KC), Trail Making Test-A(TMT-A), Digit Span Forwards(DSF) and Backwards(DSB) tests were also assessed. Changes in the values assessed before and after timed LT were analyzed for 15 patients(76.9±5.5years) of TG and 11 patients(78.3±7.7years) of CG. The effects of group and time were evaluated using two-way repeated measures ANOVA.
Results: There were no significant changes in the scores of the GVS and GAS after timed LT in both groups, while the TG showed reduced CSDD scores with an expected trend(7.6±5.7to 5.2±3.8, p=.1). The CG had significantly increased MMSE-KC scores($p<.05$) after timed LT, and the MMSE-KC scores yielded a significant time effect($F_{1, 22}=9.94$, $p<.01$) with no significant group effect or interactions. No significant changes in the scores of the TMT-A, DSF and DSB were found after timed LT in both groups.
Conclusion: Our finding suggests that timed LT would be beneficial for improving the overall cognitive function in AD patients. And LT might influence reducing their depressive symptoms.
Support (If Any): Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science, ICT & Future Planning(2017R1A2B4003493)

0943

PAP ADHERENCE IN VETERANS WITH MODERATE TO SEVERE TRAUMATIC BRAIN INJURY (TBI)

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Introduction: Sleep apnea is prevalent following TBI, though little is known about treatment adherence. Disordered sleep following acute injury may be associated with greater morbidity and early mortality after TBI. The purpose of this study is to describe PAP adherence and variability during acute neurologic recovery after TBI.
Methods: Retrospective electronic chart reviews were conducted on a cohort of all participants prescribed PAP therapy following PSG (N=33; ER GCS quartiles [3/3/14]; age quartiles [37/48/58]) and enrolled in a prospective longitudinal study of TBI following inpatient neurorehabilitation (VA TBI Model Systems).
Results: A majority of participants prescribed PAP had symptomatic mild obstructive sleep apnea (AHI quartiles, 9/13/23). Nine (27%) refused PAP. Nine (27%) were adherent to the treatment per CMS guidelines (=/>4hrs for =/> 70% of days). Among those accepting PAP and were non-adherent (N=15), the median PAP usage was 3 (3-5, Q1-Q3) hours/night. The median days used was 43 (18-192, Q1-Q3) which was 79% (46-91%, Q1-Q3) of total days monitored. The adherent group used PAP for a median of 6 (6-8, Q1-Q3) hours/night. The median days used was 30 (23-180, Q1-Q3) which was 96% of the total days used (95-100%, Q1-Q3). A subset (n=8) had subsequent downloads of data. Fifty percent were non-compliant on the most recent download with half (25%) originally meeting criteria for compliance. A large proportion (38%) remained compliant with 12% improving to compliance relative to the initial download.
Conclusion: TBI patients undergoing acute neurologic recovery commonly refuse PAP therapies or are non-adherent to PAP upon initial download. Rates of adherence are lower compared to the general population. Nonadherence may influence neurologic recovery and long-term morbidity from TBI. Reasons for non-adherence warrant further investigation. For a small subset with follow-up, adherence was not static over time. Patients worsening (25%) or improving (12%) PAP adherence suggesting the need for ongoing treatment monitoring in persons with moderate to severe TBI. Future research is needed to examine the relationship between recovery and PAP adherence in this population.
Support (If Any): PCORI (CER-1511-33005), GDHS (W91YTZ-13-C-0015) for DVBIC.

0944

A COMPARISON OF MEDICAL-GRADE ACTIGRAPHY DEVICES WITH POLYSOMNOGRAPHY DURING INPATIENT REHABILITATION FOR TRAUMATIC BRAIN INJURY (TBI).

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Daily Blue Light Therapy Reduces Persistent Post-Mild Traumatic Brain Injury Daytime Sleepiness and Post-concussion

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Context: As many as 30-80% of individuals report long-term sleep disruption following a mild traumatic brain injury (mTBI). Given the critical role of high-quality sleep on optimal cognitive, emotional, sport, and physical performance, reducing adverse mTBI effects is essential to improved functional outcomes and quality of life. Prior research demonstrates that blue light therapy (BLT) is effective for improving sleep timing and reducing daytime sleepiness in individuals with jet lag, seasonal affective disorder, and other circadian dysrhythmias. The purpose of present randomized controlled trial was to evaluate the effects of daily BLT in comparison to amber light therapy (ALT) in a post-mTBI sample. We hypothesized improved self-reported sleep outcomes in individuals receiving blue light.

Method: 27 individuals (age: 26.85±8.39y; 18 females; days post-injury: 275.42±167.04 days) were recruited and randomly assigned to receive BLT or ALT. All individuals completed a comprehensive neuropsychological and self-report assessment battery at pre- and post-treatment. This battery included self-report measures of daytime sleepiness (Epworth Sleepiness Scale, ESS) and post-concussion symptoms (Rivermead Post-concussion Symptom Questionnaire, RPCSQ). All individuals completed six weeks of daily light treatment (30 minutes direct exposure via light box in the morning). We used a two sample T-test to compare between-group post-treatment changes in ESS scores and RPCSQ subscale scores (somatic, emotional, cognitive). Additional analyses included bivariate correlations between these change scores.

Results: The light groups exhibited no differences in baseline ESS or RPCSQ subscale scores. At post-treatment, individuals in the BLT group had significantly improved daytime sleepiness (t=2.46, p = 0.025, 95% CI: 0.370-4.83), somatic (t = 2.04, p = 0.053, 95% CI: 0.043-6.21) and cognitive symptoms (t = 1.82, p = 0.082, 95% CI: 0.32-5.02) compared to those in the ALT group. Bivariate correlations indicated that improvements in ESS scores were significantly associated with improvements in somatic symptoms (r = 0.49, p = 0.014, 95% CI: 0.108-0.720).

Conclusion: Daily BLT reduces persistent daytime sleepiness and self-reported somatic and cognitive symptoms after mTBI. Improvements in these domains are likely to have significant positive effects on individuals' daytime functioning (cognitive, physical, emotional, sport) and overall quality of life. Further research is needed to uncover the directionality of these findings (decreased daytime sleepiness leads to improved symptoms or vice versa) as well as the neurological mechanisms underpinning these improvements.

Anterior Cingulate Gyrus Volume Predicts Changes in Post-mTBI Daytime Sleepiness Following Blue Wavelength Light Therapy

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Objective

Mild traumatic brain injuries (mTBIs) are often associated with increased daytime sleepiness and the onset of depressive symptoms. Prior work suggests that morning blue wavelength light (BLT) exposure may have positive effects on both sleepiness and depression via changes in circadian rhythms of hormone release. However, the neural underpinnings of post-injury changes and treatment-related improvements are unclear. We hypothesized that BLT treatment would improve daytime sleepiness and depressive symptoms and that gray matter volume (GMV) in regions important for focused attention, sleep disruption, and mood would predict these improvements.

Participants and Methods

Twenty-three adults with a recent mTBI (age: 25.39±7.28y; months post-injury: 9.17±5.42) participated in a 6-week light-therapy intervention. Individuals were randomized to receive either blue wavelength or placebo amber wavelength light (30 min/day in the morning). Participants self-reported daytime sleepiness (Epworth Sleepiness Scale, ESS) and depression (Beck Depression Inventory, BDI) at pre- and post-treatment. Voxel-based morphometry was used to identify pre-treatment correlates of treatment-related daytime sleepiness improvements.

Results

Individuals receiving blue light, but not amber light, had significantly lower ESS (p=0.03) and BDI (p=0.007) post-treatment scores. Improved daytime sleepiness was associated with less Anterior Cingulate Gyrus (ACG) GMV at pre-treatment. Additionally, lower ACG GMV was associated with greater improvement in BDI scores following blue but not amber light therapy ($\eta^2 = 0.292$) in a linear regression.

Conclusion

BLT is effective for improving daytime sleepiness and depression in some people following mTBI. We observed improvement in these following blue light therapy for those with smaller ACG volumes. The ACG plays critical roles in both sleep and depression and these findings suggest that smaller ACG volumes may play a role in responsiveness to BLT.

The present study examined the relationships among neurobehavioral symptoms, insomnia severity, and memory in OEF/OIF veterans with and without PTSD.

Methods: Thirty combat exposed OEF/OIF Veterans with (n=20) or without (n=10) PTSD were participants in a study examining neurobiological and neuropsychological factors resulting from combat exposure. Participants completed the Insomnia Severity Index (ISI) and the Neurobehavioral Symptom Inventory (NSI). Laboratory polysomnography was examined for sleep continuity [total sleep time (TST)] and sleep architecture [Stages N1, N2, and N3; and rapid eye movement (REM) sleep]. Computerized neuropsychological testing [Letter-N back (LNB), Penn word memory (PWM)] was conducted to evaluate verbal (LNB) and working (PWM) memory. The associations among neurobehavioral symptoms and other variables were examined using correlational analyses.

Results: Veterans who reported greater severity of neurobehavioral symptoms (i.e., NSI scores) had more severe insomnia symptoms ($r(29) = .67$, $p < .001$), lower percentage of REM sleep ($r(19) = -.51$, $p = .026$), more awakenings ($r(19) = .58$, $p = .010$), and increased deficits in verbal ($r(30) = -.54$, $p = .002$) and working memory ($r(23) = -.43$, $p = .042$). However, insomnia severity was not associated with verbal or working memory.

Conclusion: These results indicate that neurobehavioral symptoms, that are common outcomes of TBI exposure, are associated with both impaired memory function and sleep disturbances. The impact of neurocognitive function does not appear to be indirectly due to the effects of poor sleep. These results suggest that, while sleep-focused intervention may be warranted, one might not expect improved sleep to result in improved memory.

Support (If Any): This work was funded by the Defense Advanced Research Projects Agency under a grant from the US Army Research Office (grant number W911NF1010093).

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IMPACT OF BLUE LIGHT THERAPY ON CORTICAL STRUCTURE, SLEEP, AND ANXIETY SYMPTOMS FOLLOWING MILD TRAUMATIC BRAIN INJURY

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Introduction: Cortical abnormalities following a mild traumatic brain injury (mTBI) are often associated with abnormal sleep and increased anxiety. Both fatigue and altered mood may be improved through daily morning exposure to blue wavelength light therapy (BLT). The present study focused on identifying the effect of BLT compared to the placebo amber-light therapy (ALT) on cortical volume (CV), anxiety, and sleep-onset latency (SOL) following a recent mTBI, as well as the correlations between changes in these measures.

Methods: Neuroanatomical data were collected from 33 healthy controls (HCs) and 27 mTBI participants. Individuals with mTBI underwent six-weeks of BLT or ALT. For the mTBI group, State (S) and Trait (T) Anxiety Inventory (STAI) scores were collected at baseline and post-treatment. Actigraphy data were collected one week prior to each participant's baseline visit and throughout the intervening six weeks. The FreeSurfer toolbox was used to identify regions of interest (ROIs) showing significant baseline differences in CV between HCs and mTBI participants (cluster-forming threshold, $p < 0.01$, corrected for multiple comparisons). Identified ROIs were used in subsequent analyses to capture the effect of BLT and ALT in mTBI group.

Results: CV was significantly lower in the mTBI participants compared to HCs in two brain regions: the right inferior parietal cortex and lateral orbitofrontal cortex (rLOFC). There was a trend towards a group (ALT/BLT) x time (pre/post) interaction ($p = 0.09$) for CV within the rLOFC, suggesting that rLOFC volume tended to increase following BLT, but not following ALT. Following BLT, mTBI participants showed a significant decrease ($p < 0.05$) in STAI-S and STAI-T scores. Moreover, following BLT but not ALT, increased rLOFC volume was significantly correlated with decreased STAI-T scores and SOL ($p < 0.05$).

Conclusion: Six-weeks of morning BLT may increase CV within the orbitofrontal cortex and is associated with reduced trait anxiety and improved sleep latency following mTBI. Future work will be necessary to identify the underlying mechanisms that may contribute to the effectiveness of this promising treatment approach.

Support (If Any): USAMRMC W81XWH-11-1-0056

1027

DAILY MORNING BLUE LIGHT EXPOSURE ENHANCES EXECUTIVE FUNCTIONING IN INDIVIDUALS WITH MILD TRAUMATIC BRAIN INJURY

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Introduction: Mild traumatic brain injury (mTBI) often leads to persistent disruptions in mood, sleep, and cognition, but no reliable and effective treatments for post-concussive symptoms have been developed. Notably, sleep and circadian rhythm problems are particularly common following mTBI and may affect recovery from the injury. Because the circadian system is strongly regulated by light, we hypothesized that daily morning exposure to blue-wavelength light would improve circadian entrainment, sleep, and executive functioning.

Methods: Individuals with a recent mTBI in the past 18 months (15 male; 16 female; Age=23.3, SD=7.2) were randomly assigned to receive either blue (469 nm; n=16) or amber (478 nm; n=15) morning light therapy for 30-minutes daily for 6-weeks. Participants completed baseline and post-treatment assessments including the Tower of London (TOL), an executive function task requiring planning and sequencing. Participants completed ten TOL puzzles that involved moving 3 colored beads on three pegs of differing lengths to match a pre-set goal pattern. The number of moves the participant made to complete the puzzles and the time per move were recorded by computer.

Results: We calculated a throughput metric that accounts for time and accuracy (i.e., % Correct moves/average move time] x 0.60), which provides an output reflecting the number of correct bead placements per minute. After controlling for covariates, there was a significant light condition x session interaction (p=.016). Simple effects comparisons showed that BLT was associated with a significant pre-to post-treatment increase in TOL throughput (p<.0001), whereas ALT showed no significant improvement (p=.094).

Conclusion: Compared to a placebo condition, 6-weeks of daily morning exposure to blue-wavelength light was associated with improved planning and sequencing ability, as indicated by the number of correct bead placements per unit of time. These findings are consistent with recent evidence suggesting that BLT can reduce fatigue, improve sleep timing, and facilitate brain repair processes among patients recovering from concussion. Further research will be necessary to determine the extent to which these findings are associated with changes in sleep and circadian rhythms.

Support (If Any): USAMRMC (W81XWH-11-1-0056).

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Neural and Neurocognitive Correlates of Responsiveness to Blue Light Therapy Following Mild Traumatic Brain Injury

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BACKGROUND

Approximately 1.5 to 3 million traumatic brain injuries (TBIs) are reported by emergency rooms in the United States each year and the annual incidence is rising [1,2]. Approximately 75% of these injuries are ultimately classified as mild (mTBIs), suggesting transient symptoms with limited long-term deficits. However, this definition is challenged by emerging evidence of persistent, though often subtle, deficits in cognitive, neuromechanical, and behavioral function. Optimal cognitive function depends on high quality sleep, yet self-reported degradation of sleep quality, quantity, and increased daytime sleepiness are among the most commonly reported persistent post-mTBI changes [3,4]. Therefore, mTBI-related sleep degradation may result in impaired cognitive function as well as prolong physiological and clinical recovery. It is, therefore, needful to identify methods for reducing the profound effects of mTBI on sleep. Short-wavelength blue light has been previously used to improve sleep, as well as alertness and vigilance, in individuals with and without previously identified sleep disruption [5–7]. Additionally, non-pharmacologic interventions for sleep are essential for reducing substance-dependence and creating better internal self-regulation of homeostatic sleep. However, uses to date in mTBI have been limited, though positive effects on sleep and cognition have been observed. Here, we provided a six-week intervention using short-wavelength (469-nm) blue light or a placebo (566-nm) amber light daily for 30-minutes in the morning to individuals with a recent mTBI. Outcome measures of interest included self-reported daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS). Specifically, we hypothesized that individuals receiving daily morning blue light would demonstrate lower daytime sleepiness after treatment than those receiving a matched placebo treatment with amber light.

METHODS

Twenty-three individuals with a recent history of mTBI (25.4±7.3 years; 15 females; 39.3±23.2 weeks post-injury) participated in this study. Participants were randomly assigned to the blue (n = 10; 6 females, 35.7±17.5 weeks post-injury) or amber (n = 13, 9 females, 41.8±26.9 weeks post-injury) light intervention. We computed the reliable change index ($\Delta > 2.4$ between sessions) for the ESS based on reported normative samples and classified individuals after intervention as responders or non-responders.

We performed an exploratory whole-brain gray matter volume (GMV) analysis to identify differences between responders ($n = 5$) and non-responders ($n = 5$) in the blue light group. High-resolution T1-weighted magnetic resonance imaging scans were segmented and normalized following an automated procedure implemented in CAT12 (http://dbm.neuro.uni-jena.de/cat12/). Baseline and post-treatment scans were analyzed separately. We fit a 3-group (amber, blue responder, blue non-responder) full factorial analysis in CAT12, controlling for age, sex, and total intracranial volume. Volumetric data from common cluster between baseline and post-treatment was exported for further analysis.

Finally, to evaluate behavioral correlates, we compared blue responders and non-responders on the Automated Neuropsychological Assessment Metrics (ANAM) math processing subscale, a complex cognitive task requiring both fast and accurate responses to mathematics problems.

RESULTS

There were no demographic differences (age, sex, days post-injury) between the amber and blue groups. Overall, we observed a statistically significant decrease in ESS scores in the blue group ($p = 0.032$) compared to the amber group ($p = 0.165$) from baseline to post-treatment. No individuals in the amber group demonstrated improvement in daytime sleepiness following treatment whereas 5 individuals in the blue group did improve (responders) and 5 did not (non-responders). This response rate was statistically significant. (Fisher's exact $p = 0.007$). The whole-brain GMV analysis further revealed a cluster with significantly lower GMV in the responders compared to the non-responders at both baseline (k = 2077; family-wise error (FWER) correct $p = 0.004$) and post-treatment (k = 1773; FWER $p = 0.004$ located in the inferior frontal gyrus, including Broca's area.

Post-hoc exploratory correlations in the group receiving blue light between GMV in this cluster and post-treatment ANAM math processing scores revealed a significant positive correlation between GMV and mean reaction time ($\rho = 0.697$, $p = 0.031$. A significant negative correlation was observed between GMV and math processing throughput (correct responses/minute; $\rho = -0.729$, $p = 0.017$). Group differences were not statistically significant for these measures.

CONCLUSIONS

We observed that blue light therapy is an effective intervention approach at a group-wide level for reducing daytime sleepiness in individuals following an mTBI, providing support for a non-pharmacological treatment option for individuals with mTBI-related sleep disturbances. However, not all individuals respond to this method of intervention. Individuals who did respond exhibited lower gray matter volume at both baseline and post-treatment in the inferior frontal gyrus, an area associated with both language processing as well as other complex cognitive task processing, including mathematics processing. Furthermore we observed that lower GMV in this cluster was significantly associated with *better* performance on a math processing task, including faster reaction times and more correct responses per minute. These findings suggest that a.) individual morphometric properties may predispose individuals to respond, or not, to blue light therapy and b.) that these same predisposing factors may be associated with improved mathematical processing. Given the observed relationship between GMV and mathematical processing on the ANAM, it may be possible to use the ANAM to prospectively identify individuals likely to respond to blue light therapy for reducing daytime sleepiness without needing sophisticated imaging.

Acknowledgements

This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs and the Defense Health Agency J9, Research and Development Directorate, through the US Army Medication Research and Materiel Command (USAMRMC) under Award No. (W81XWH-14-0571), awarded to Dr. W.D.S. Killgore. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense.

References

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006;21: 375–378. doi:10.1097/00001199-200609000-00001

2. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. Clin Sports Med. 2011;30: 1–17. doi:10.1016/j.csm.2010.08.006

3. Gosselin N, Lassonde M, Petit D, Leclerc S, Mongrain V, Collie A, et al. Sleep following sport-related concussions. Sleep Med. 2009;10: 35–46. doi:10.1016/j.sleep.2007.11.023

4. Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. J Head Trauma Rehabil. 2006;21: 199–212. doi:10.1097/00001199-200605000-00001

5. Chellappa SL, Steiner R, Blattner P, Oelhafen P, Götz T, Cajochen C. Non-Visual Effects of Light on Melatonin, Alertness and Cognitive Performance: Can Blue-Enriched Light Keep Us Alert? PLOS ONE. 2011;6: e16429. doi:10.1371/journal.pone.0016429

6. Lockley SW, Evans EE, Scheer FAJL, Brainard GC, Czeisler CA, Aeschbach D. Short-Wavelength Sensitivity for the Direct Effects of Light on Alertness, Vigilance, and the Waking Electroencephalogram in Humans. Sleep. 2006;29: 161–168. doi:10.1093/sleep/29.2.161

7. Motamedzadeh M, Golmohammadi R, Kazemi R, Heidarimoghadam R. The effect of blue-enriched white light on cognitive performances and sleepiness of night-shift workers: A field study. Physiology & Behavior. 2017;177: 208–214. doi:10.1016/j.physbeh.2017.05.008

Blue light therapy improves self-reported sleep quality in individuals with a recent mild traumatic brain injury

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Background: In warfare, it is essential that military personnel obtain sufficient amounts of high quality sleep. High quality, recuperative sleep is necessary for efficient combat operations, particularly those requiring sustained mental, cognitive, and physical performance – all of which are imperative for efficient combat operation. Acute and chronic sleep loss degrades response times and decreases the ability to maintain attention. These lapses in responsiveness and attention dramatically increase the likelihood of poor mission-related outcomes, including increased risk of injury, fatality, and failure. Among the contributors to sleep loss in military settings is the high prevalence of mild traumatic brain injury (mTBI). mTBIs are associated with short- and long-term changes in self-reported sleep quality and quantity. Indeed, 30-80% of individuals report insomnia following mTBI at least 3 years following injury. Given the dependence of numerous cognitive functions on high quality sleep, it is likely that mTBI-related insomnia results in degraded cognitive function and delays full recovery. It is, therefore, needful to identify methods for reducing the profound effects of mTBI on sleep. Short-wavelength blue light has been previously used to improve sleep, as well as alertness and vigilance, in individuals with and without previously identified sleep disruption. Additionally, non-pharmacologic interventions for sleep are essential for reducing substance-dependence and creating better internal self-regulation of homeostatic sleep. However, uses to date in mTBI have been limited, though positive effects on sleep and cognition have been observed. Consequently, the ability to ameliorate mTBI-related sleep loss or degraded sleep quality may help improve multi-domain battlespace safety and efficiency. Here, we provided a six week intervention using short-wavelength (469-nm) blue light or a placebo (566-nm) amber light daily for 30-minutes in the morning to individuals with a recent mTBI. Outcome measures of interest included self-reported sleep quality and quantity indicators via the Pittsburgh Sleep Quality Index (PSQI). Specifically, we hypothesized that individuals receiving blue light would demonstrate better self-reported indices of sleep quality (better sleep efficiency, fewer disturbances, better overall score) than those in the placebo group.

Methods: 23 individuals with a recent history of mTBI (25.4±7.3 years; 15 females; 39.3±23.2 weeks post-injury) participated in this study. Participants were randomly assigned to the blue (n = 10; 6 females, 35.7±17.5 weeks post-injury) or amber (n = 13, 9 females, 41.8±26.9 weeks post-injury) light intervention. All participants completed a comprehensive neuropsychological and self-report battery, including the PSQI, and neuroimaging session at pre- and post-treatment. We report only report PSQI-related outcomes here.

During the intervention period, individuals were provided a Phillips goLITE BLU (peak λ = 464-467 nm) or goLITE fitted with amber lights (peak λ = 566 nm). Participants were instructed to place the light device 12-24 inches away from their faces and to allow light to enter the eyes

through the periphery rather than directly (to reduce glare and adverse effects associated with looking directly into the light). Total dosage was 30 minutes per day within two hours of waking for 6 weeks. To model PSQI-related outcomes, we fit individual linear models with post-treatment PSQI scores as the dependent measures, group (amber, blue) and pre-treatment scores plus their interaction as independent measures, and controlling for total numbers of mTBIs and weeks post-injury. Given the small sample size, we report statistical outcomes for predictors of interest even for models not achieving statistical significance ($\alpha < 0.05$).

Results and Conclusions: We observed statistically significant models for PSQI reported sleep disturbance ($R^2 = 0.476$, $p = 0.047$) but not for sleep efficiency ($R^2 = 0.370$, $p = 0.154$) or total sleep scores ($R^2 = 0.421$, $p = 0.091$). The interaction between pre-treatment scores and group (e.g., the slope of the relationship between pre- and post-treatment) was statistically significant for sleep disturbance ($p = 0.008$; partial $\eta^2 = 0.365$; power = 0.854) and sleep efficiency ($p = 0.028$; partial $\eta^2 = 0.268$; power = 0.674) but not for total sleep scores ($p = 0.223$; partial $\eta^2 = 0.091$; power = 0.244). Additionally, the group effect was not significant for the total sleep scores ($p = 0.138$; partial $\eta^2 = 0.132$; power = 0.344). However, our observations for the total sleep scores were under-powered in this small sample. Generally, we observed that individuals in the blue light group had increased sleep efficiency, decreased incidence of sleep disturbance, and lower overall total sleep scores at post-treatment after controlling for pre-treatment scores, total prior mTBIs, and weeks post-injury. These trends were reversed in the placebo group.

Additionally, among individuals self-reporting insomnia at pre-treatment (total PSQI score ≥ 8; $n = 13$; n blue light = 7; n amber light = 6), a greater proportion of those in the blue light group self-reported non-insomnia at post-treatment than in the amber group (71.4% vs 50%). While this response rate was not statistically significant (Fisher's exact $p = 0.592$; odds ratio = 2.324) in this small sample, there is the early indication that blue light may help to reduce the incidence of post-mTBI self-reported insomnia.

We have identified that individuals with a history of mTBI respond positively to a six week daily blue light intervention. No adverse effects or perceptions of the treatment were noted. Blue light therapy was associated with maintaining or improving self-reported sleep quality and overall sleep as compared to amber light. Additionally, there is the indication that for individuals self-reporting insomnia, blue light may be associated with an increased odds of self-reporting non-insomnia after treatment than those receiving amber light. Therefore, there is the early indication that a six week intervention with a 30 minute daily dosage improves self-reported sleep outcomes following mTBI.

Warfighters are placed into situations of increased sleep burden and demand due to job-related short sleep durations, unusual sleeping environments that may inhibit high quality sleep, and increased operationally-relevant cognitive demands. In the presence of mTBI, these detrimental effects on the warfighter's sleep may be further compromised. Daily blue light therapy, even in small dosages (30 minutes) provides a non-pharmacological means for improving perceived sleep. Such improvement in perceived sleep quality helps to ensure that individuals that are capable of performing at the highest levels during critical operations, thereby reducing operational errors, injuries, morbidity, and mortality.

Executive Functioning in Individuals with Mild Traumatic Brain Injury is Enhanced by Daily Morning Blue Light Therapy

William D. S. Killgore[1]
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Background: Mild traumatic brain injury (mTBI) is one of the most common injuries currently sustained during military operations. Moreover, mTBI often leads to persistent disruptions in mood, sleep, and cognition, but no reliable and effective treatments for post-concussive symptoms have been developed. Notably, sleep and circadian rhythm problems are particularly common following mTBI and may affect recovery from the injury. Recent evidence suggests that blue wavelength light may be particularly effective at resetting and regulating the circadian rhythm, we hypothesized that daily morning exposure to blue-wavelength light would improve circadian entrainment, sleep, and executive functioning.

Methods: Individuals with a recent mTBI in the past 18 months (15 male; 16 female; Age=23.3, SD=7.2) were randomly assigned to receive either blue (469 nm; n=16) or amber (478 nm; n=15) morning light therapy for 30-minutes daily for 6-weeks. Participants completed baseline and post-treatment assessments including the Tower of London (TOL), an executive function task requiring planning and sequencing. Participants completed ten TOL puzzles that involved moving 3 colored beads on three pegs of differing lengths to match a pre-set goal pattern. The number of moves the participant made to complete the puzzles and the time per move were recorded by computer.

Results: We calculated a throughput metric that accounts for time and accuracy (i.e., % Correct moves/average move time] x 0.60), which provides an output reflecting the number of correct bead placements per minute. After controlling for covariates, there was a significant light condition x session interaction (p=.016). Simple effects comparisons showed that BLT was associated with a significant pre-to post-treatment increase in TOL throughput (p<.0001), whereas ALT showed no significant improvement (p=.094).

Conclusions: Compared to a placebo condition, 6-weeks of daily morning exposure to blue-wavelength light was associated with improved planning and sequencing ability, as indicated by the number of correct bead placements per unit of time. These findings are consistent with recent evidence suggesting that BLT can reduce fatigue, improve sleep timing, and facilitate brain repair processes among patients recovering from concussion. Further research will be necessary to determine the extent to which these findings are associated with changes in sleep and circadian rhythms. Nonetheless, these preliminary findings are particularly encouraging and suggest that blue light therapy may provide an easy to use and effective method for restoring some aspects of cognitive functioning following mTBI.

Support: USAMRMC (W81XWH-11-1-0056).

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Background

- Mild traumatic brain injury (mTBI) is a highly prevalent injury among Service members.
- While mTBI typically resolves rapidly with few associated complications, a significant proportion of individuals complain of persisting post-concussive symptoms such as poor attention and concentration, irritability, headaches, and balance problems.
- Moreover, approximately 50% of individuals who experience an mTBI will subsequently develop sleep problems and lingering fatigue that may continue for years after their injury.
- A primary factor leading to these sleep problems may be the perturbation of the circadian rhythm induced by the injury.
- Because the daily circadian rhythm is regulated predominantly by exposure to light, we recently completed a clinical trial using blue wavelength light therapy to enhance sleep and circadian rhythmicity in patients with recent mTBIs.
- It was hypothesized that daily exposure to blue light each morning would re-entrain the circadian rhythm, which would enhance sleep quality, thus facilitating brain repair processes.

Methods & Materials

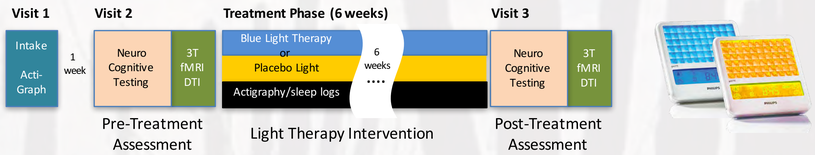
SUBJECTS

Thirty-two individuals (15 male; 17 female; aged 18-48 years) who experienced an mTBI during the preceding 18 months.

STUDY DESIGN AND PROCEDURE

Participants completed a comprehensive neuropsychological evaluation, multiple sleep latency test (MSLT), and neuroimaging, including voxel based morphometry (VBM), resting state functional connectivity (rsFC), and Diffusion Tensor Imaging (DTI).

Participants were then randomly assigned in double-blind fashion to undergo daily morning exposure with a light device fitted with a 10 x 6 array of light emitting diodes in either the BLUE- (active; n=16) or AMBER-wavelength (placebo; n=16).



Treatment was conducted at home and lasted **6 weeks** (30-minutes daily, prior to 11:00am).

At the conclusion of treatment, participants returned to the lab for a follow-up assessment, MSLT, and neuroimaging session.

Results

Group Demographics

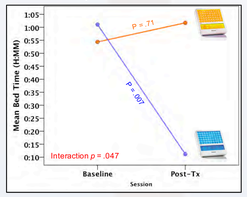
	λ = 469 nm	λ = 566 nm
n	16	16
% Male	44%	50%
Age	23.2 (SD = 7.1)	23.3 (SD = 7.4)
Education	15.0 (SD = 2.4)	14.6 (SD = 2.2)
# Concussions	2.4 (SD = 1.8)	2.2 (SD = 1.6)
Months since injury	6.8 (SD = 4.4)	6.7 (SD = 3.6)

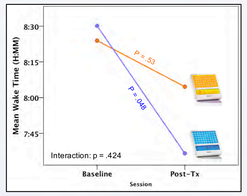
BLUE light is known to suppress melatonin production and morning exposure has the effect of phase advancing the circadian rhythm (i.e., signaling the brain that it is later than the clock time.

The active BLUE and AMBER placebo groups were closely matched in terms of demographic variables.

Actigraphic Sleep Measures

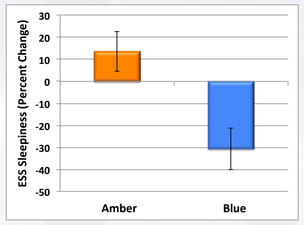
Sleep onset time showed a significant change from baseline to post-treatment for those in the BLUE, but not the AMBER placebo condition.



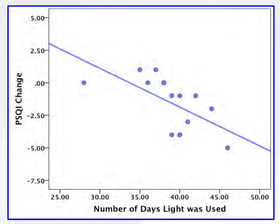


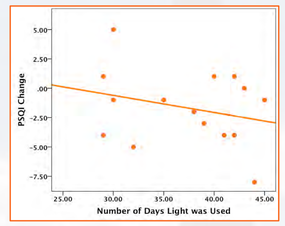
Wake time showed a significant change from baseline to post-treatment for those in the BLUE, but not the AMBER placebo condition.

Daytime Sleepiness



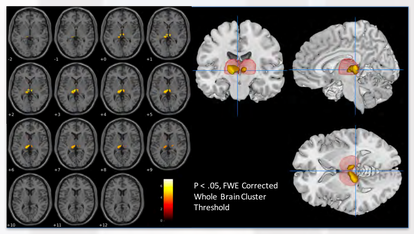
Blue light treatment reduced daytime sleepiness relative to the amber placebo



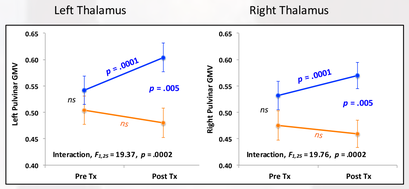


Mean sleep problems (i.e., Pittsburg Sleep Quality Index) did not differ between groups, but sleep problems decreased with greater use of the BLUE but not AMBER placebo light.

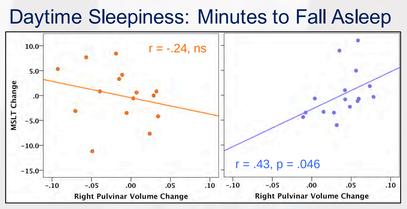
Voxel Based Morphometry (VBM)



Whole brain analysis comparing pre- and post-treatment structural brain scans revealed a significant increase in gray matter volume in the bilateral thalamus for the BLUE light group, whole brain FWE corrected ($p < .05$). There was no change for AMBER.



Participants receiving BLUE light treatment for six weeks showed a significant increase in gray matter volume from pre- to post-treatment for both thalami, while there was no significant change for those undergoing the AMBER placebo treatment.

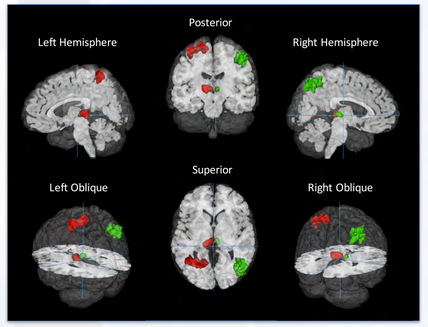


The association between changes in thalamic volume (i.e., pulvinar nucleus) and changes in sleep latency on the multiple sleep latency test (MSLT). While there was no association for the AMBER placebo group, there was a significant association for the BLUE group.

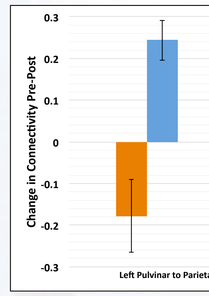
Results (cont.)

Resting State Functional Connectivity

Pulvinar regions from the preceding VBM analysis were used as seed regio functional connectivity (rsFC) analysis comparing change from pre- to pos BLUE vs AMBER groups.

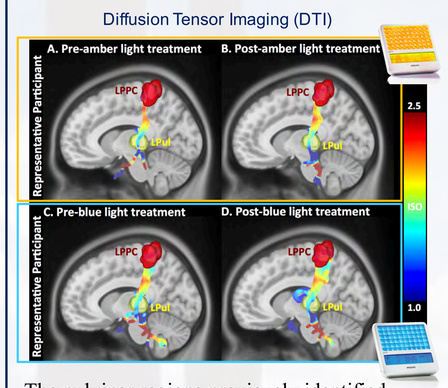


Each pulvinar region showed significant functional connectivity to its own ipsilateral parietal cortex region.

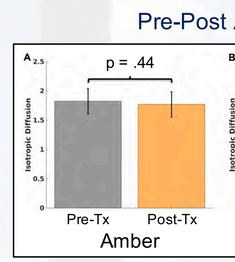


Strength of ipsilateral significantly from pre- the BLUE group ($p<.0$

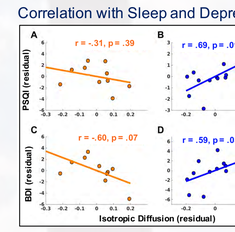
Diffusion Tensor Imaging



The pulvinar regions previously identified were then used as end-points within individual fiber tractography analyses using Diffusion Tensor Imaging (DTI) and fiber strands were connected for each individual. The mean Isotropic Diffusion was extracted for each participant and a change score was calculated.



Isotropic Diffusion (IsoD pre- to post-treatment for significantly decreased fo



Conclusions

- In a sample of patients recovering from mTBI, daily m wavelength light therapy for 6 weeks led to significant in circadian timing as well as functional and structural connectivity, and associated neurocognitive performanc
- These preliminary findings support prior research sugg light therapy may improve fatigue among patients with further suggest that regular morning blue light exposur an effective treatment for re-entraining the circadian rh enhancing brain repair following mTBI.

Effect of blue light therapy on cortical volume, sleep, and anxiety symptoms following mild traumatic brain injury

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Introduction

A mild traumatic brain injury (mTBI) occurs when an individual experiences a blow to the head that leads to a temporary alteration in consciousness or cognition[1]. The dynamic physical forces involved in sustaining an mTBI may lead to abnormal changes in cortical structure. Such abnormalities are associated with post-concussion symptoms, *including* abnormal sleep and increased anxiety. Emerging evidence suggests that some symptoms of fatigue and mood alteration may be improved through daily morning exposure to blue wavelength light therapy (BLT)[2]. The present study focused on identifying the effect of daily morning exposure to BLT on cortical structure and potential correlations with changes in anxiety and actigraphically-measured sleep onset latency (SOL) following a recent mTBI. The aims of this study were threefold: 1) to identify brain regions where individuals with a recent mTBI may have lower cortical volume (CV) than healthy controls (HCs); 2) to determine whether these regions, once identified, exhibit volumetric changes following six-weeks of short-wavelength morning BLT compared to a placebo condition of amber light treatment (ALT); and 3) to investigate how structural changes in these targeted brain areas were associated with changes in anxiety (state and trait) and SOL in each treatment condition. We hypothesized that BLT would increase CV and reduce anxiety and SOL in individuals with mTBI compared to the placebo condition.

Methods

High-resolution neuroanatomical data were collected form 33 HCs (mean age = 24.52±3.03 years, 19 F) and 27 mTBI participants (mean age = 21.00±2.72 years, 14 F). The mTBI participants were randomized to undergo six-weeks of BLT or a placebo ALT. For the mTBI group, State (S) and Trait (T) Anxiety Inventory (STAI) scores were collected at baseline and post-treatment. Actigraphy data were collected one week prior to each participant's baseline visit and throughout the intervening six weeks. The FreeSurfer toolbox (https://surfer.nmr.mgh.harvard.edu) was used to identify clusters (regions of interest) showing significant differences in CV between HCs and the mTBI group. The effects of age and sex were regressed out while estimating these differences. A cluster-forming threshold of $p < 0.01$ with a smoothing kernel of 15 mm was used for all the analysis. Multiple comparisons were corrected using a clusterwise threshold of $p < 0.05$ (Monte-Carlo Simulation). Identified regions of interest were used in subsequent analyses to capture the effect of BLT and ALT in mTBI group. Additionally, we covaried for age, gender, body-mass index (BMI), time-since injury (TSI), and light compliance.

Results

CV in the right inferior parietal cortex and the right lateral orbitofrontal cortex (rLOFC) was significantly lower in the mTBI participants compared to HCs at baseline (Figure 1). There was a trend towards a group (ALT/BLT) x time (pre/post) interaction ($p = 0.09$) for CV within the rLOFC, suggesting that rLOFC volume tended to increase following BLT, but not following ALT (Figure 2A-2B). Following BLT, the mTBI participants showed a significant decrease ($p < 0.05$) in STAI-S and STAI-T scores, which was not observed following ALT. Moreover, following BLT, increased volume of the rLOFC was significantly correlated with decreases in STAI-T (Figure 2C) scores and SOL ($p < 0.05$) (Figure 2D), but not following ALT.

Conclusion: Our findings suggest that 6-weeks of morning BLT may increase CV within the orbitofrontal cortex and is associated with reduced trait anxiety and improved sleep latencies among individuals recovering from an mTBI. Future work will be necessary to identify the underlying mechanisms that may contribute to the effectiveness of this approach.

Figure 1

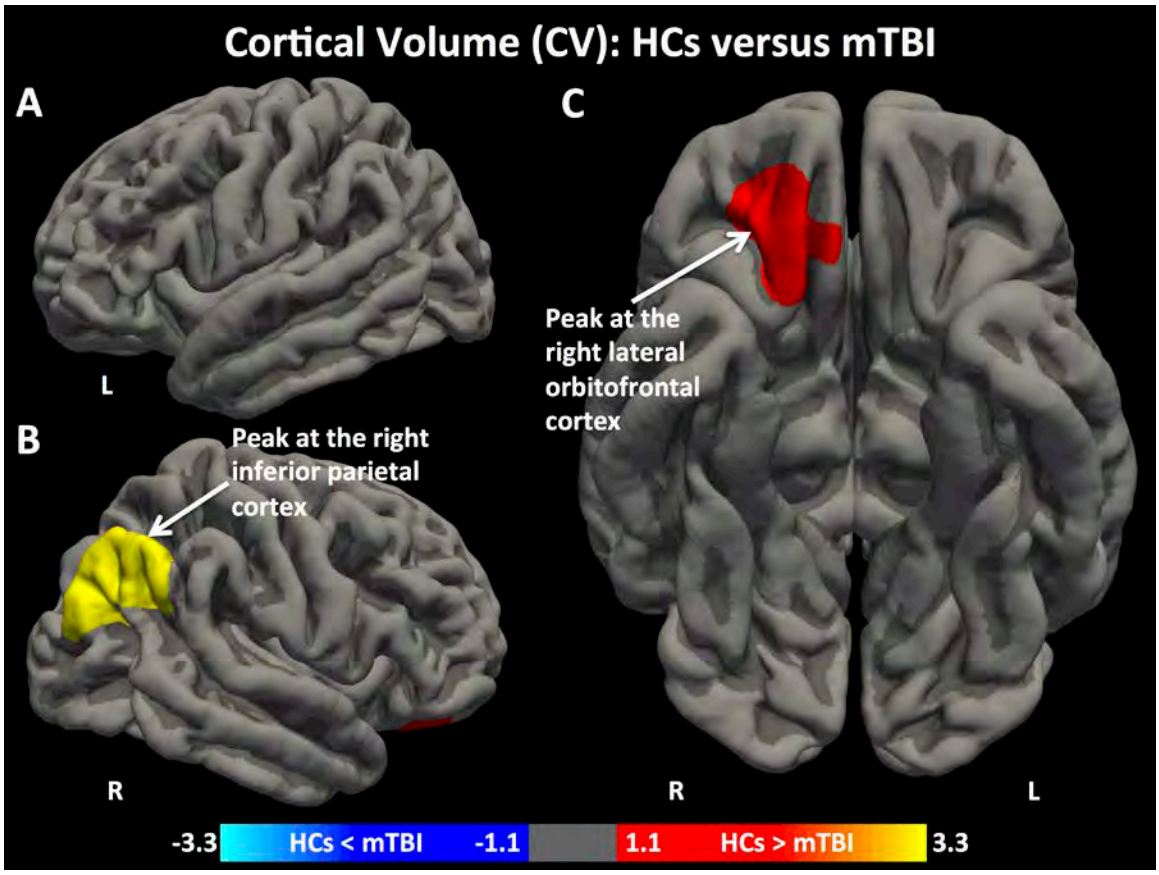
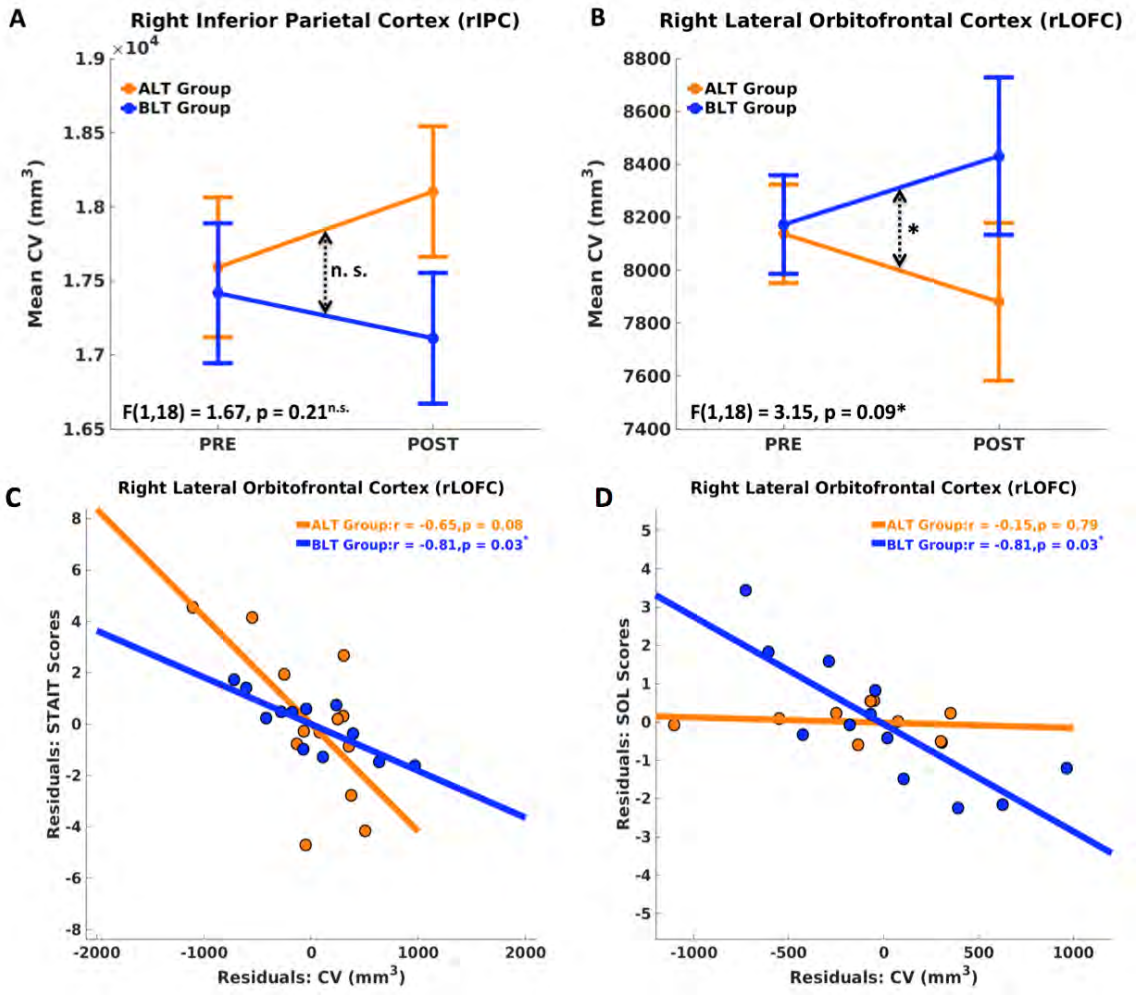


Figure 2



References

1 Blyth, B. J. & Bazarian, J. J. Traumatic alterations in consciousness: traumatic brain injury. *Emerg Med Clin North Am* **28**, 571-594, doi:10.1016/j.emc.2010.03.003 (2010).

2 Sinclair, K. L., Ponsford, J. L., Taffe, J., Lockley, S. W. & Rajaratnam, S. M. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair* **28**, 303-313, doi:10.1177/1545968313508472 (2014).

3 Desikan, R. S. *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980, doi:10.1016/j.neuroimage.2006.01.021 (2006).

- **Hypothesis:** Six weeks of morning BLT, compared to an amber light therapy (ALT), would lead to greater normalization of white matter abnormalities and associated improvements in neurocognitive status.

Methods

Participants

28 individuals (mean age = 21.48±3.76 years, 15 F) with mTBI participated in the study.

Data Collection

At baseline and after the light therapy, each participant underwent diffusion tensor imaging and completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Delayed Memory (DM), Immediate Memory, Attention, Visuospatial/Constructional, and Language abilities.

Analysis

- Half of the participants were randomly assigned to ALT and half were assigned to BLT.
- Normalized Quantitative Anisotropy (NQA) was estimated, using DSI Studio[5], from fibers crossing 11 regions of interest: Dorsolateral prefrontal cortex, corpus callosum (CC) (genu, body, and splenium), bilateral uncinate fasciculus, bilateral superior longitudinal fasciculus, bilateral anterior corona radiata (ACR) and thalamus.

Results

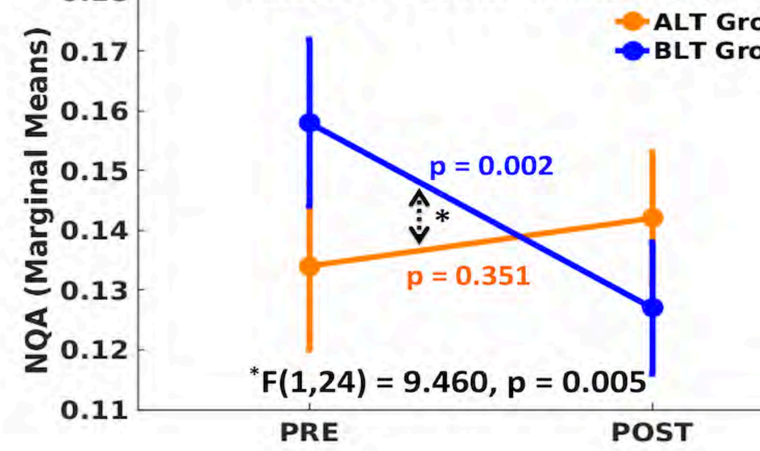
Effect of light therapy on:

Diffusion measures following mTBI

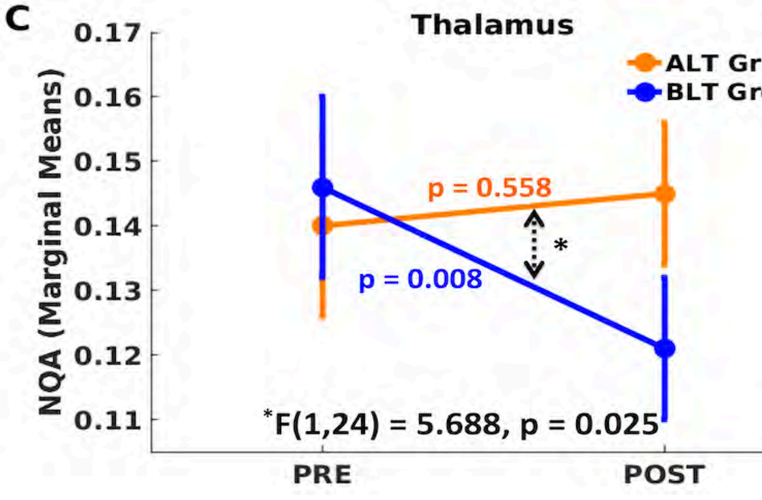
- Using a mixed ANCOVA (time since injury and light compliance as covariates), we found: **A significant time x group interaction such that following BLT, but not ALT, individuals showed a significant decrease in NQA for the fibers crossing the body of CC, left ACR and thalamus.**
- Pairwise comparison showed that **following BLT (but not ALT), there was a significant decrease in NQA for the fibers crossing the body of CC, left ACR and thalamus.**

Neuropsychological function following mTBI

- **We did not find significant associations between change in NQA and change in any behavioral measures following ALT.**



C



- **For BLT, a significant negative association was observed between residualized changes in RBANS DM scores and NQA for fibers crossing the body of the CC and the thalamus.**



Co

- BLT helps to normalize water diffus cognitive recovery among individu
- NQA is a sensitive measure to anal

References

1. Levin, H. S. *et al. 1987 J of neurosurgery.*
2. Silver, J. M. et al. 2009 *Am J Psychiatry.*
3. Matsushita, M. *et al. 2011 J of neurosurgery*
4. Golden, R. N. *et al. 20*
5. http://dsi-studio.labs

Impact of blue light therapy on cortical structure, sleep, and anxiety symptoms following mild traumatic brain injury

Sahil Bajaj[1,*], Adam Raikes[1], Natalie S. Dailey[a], John Vanuk[a], Brieann C. Satterfield[a], Anna Alkozei[a], , Mareen Weber[1, 2], Isabelle M. Rosso[2], Scott L. Rauch[2], Michael A. Grandner, [1] & William D. S. Killgore[1, 2]

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Limit: 350 words

Introduction
Cortical abnormalities following a mild traumatic brain injury (mTBI) are often associated with abnormal sleep and increased anxiety. Both fatigue and altered mood may be improved through daily morning exposure to blue wavelength light therapy (BLT). The present study focused on identifying the effect of BLT on cortical volume (CV), anxiety, and sleep-onset latency (SOL) following a recent mTBI, as well as the correlations between changes in these measures. We hypothesized that BLT would increase CV and reduce anxiety and sleep disturbances in individuals with mTBI compared to the placebo amber-light therapy (ALT).

Methods
Neuroanatomical data were collected from 33 healthy controls (HCs) and 27 mTBI participants. Individuals with mTBI underwent six-weeks of BLT or ALT. For the mTBI group, State (S) and Trait (T) Anxiety Inventory (STAI) scores were collected at baseline and post-treatment. Actigraphy data were collected one week prior to each participant's baseline visit and throughout the intervening six weeks. The FreeSurfer toolbox was used to identify regions of interest (ROIs) showing significant baseline differences in CV between HCs and mTBI participants (cluster-forming threshold, $p < 0.01$, *corrected for multiple comparisons*). Identified ROIs were used in subsequent analyses to capture the effect of BLT and ALT in mTBI group.

Results
CV was significantly lower in the mTBI participants compared to HCs in two brain regions: the right inferior parietal cortex and lateral orbitofrontal cortex (rLOFC). There was a trend towards a group (ALT/BLT) x time (pre/post) interaction ($p = 0.09$) for CV within the rLOFC, suggesting that rLOFC volume tended to increase following BLT, but not following ALT. Following BLT, mTBI participants showed a significant decrease ($p < 0.05$) in STAI-S and STAI-T scores. Moreover, following BLT but not ALT, increased rLOFC volume was significantly correlated with decreased STAI-T scores and SOL ($p < 0.05$).

Conclusion: Our findings suggest that six-weeks of morning BLT may increase CV within the orbitofrontal cortex and is associated with reduced trait anxiety and improved sleep latency following mTBI. Future work will be necessary to identify the underlying mechanisms that may contribute to the effectiveness of this promising treatment approach.

Changes in Morning Salivary Melatonin Correlate with Prefrontal Responses During Working Memory Performance

Anna Alkozei, Haley C. Kent, Sara A. Knight, & William D. S. Killgore,

Background: Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle. Profound increases in circulating levels of melatonin are observed during the nighttime but these drop to nearly non-existent levels during daylight hours. While melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning salivary melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and behavioral control.

Methods: We measured the change in salivary melatonin from mid- to late-morning in 26 healthy young adults (12 male; 13 female) who were also exposed to a 30-minute period of blue or amber light followed by functional magnetic resonance imaging (fMRI) at 3T during a working memory task (N-Back). Brain activation during the N-Back task was regressed on change in melatonin scores and the role of light exposure was also assessed.

Results: Although overall melatonin levels did not change significantly over the morning at the group level, individual declines in salivary melatonin from 0945 to 1245 were associated with significant increases in activation within the left dorsomedial and right inferior lateral prefrontal cortex ($p < .05$, cluster corrected) during the N-Back working memory task. Medial prefrontal activation also correlated modestly with better vigilance performance during the 0-Back ($p < .05$), but not the 1-Back or 2-Back conditions. Light condition did not affect the outcomes.

Conclusions: Changes in morning salivary melatonin were associated with functional brain responses during a working memory task. The magnitude of decline in salivary melatonin during the late morning hours was associated with increased brain activation within dorsomedial and lateral prefrontal cortex, brain regions involved in vigilance, action selection, and cognitive control. We interpret these associations as reflecting individual differences in circadian phase of melatonin and their potential impact on the morning establishment of prefrontal functioning in the hours following awakening.

Support: USAMRMC (W81XWH-11-1-0056).

Presented at the: 32nd Annual Meeting of the Associated Professional Sleep Societies; June 2-6, 2018; Baltimore, MD.

Changes in Morning Salivary Melatonin Correlate with Prefrontal Responses During Working Memory Performance

William D. S. Killgore, Haley C. Kent, Sara A. Knight, Anna Alkozei

Background: Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle, with profound increases in circulating levels during the nighttime and nearly non-existent levels during daylight hours. While melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and behavioral control.

Methods: We measured the change in salivary melatonin from mid- to late-morning in 26 healthy young adults (13 female) who were also exposed to a 30-minute period of blue or amber light followed by functional magnetic resonance imaging (fMRI) during a working memory task (N-Back). Brain activation was regressed on change in melatonin scores and the role of light exposure was also assessed.

Results: Although overall melatonin levels did not change significantly over the morning at the group level, individual declines in salivary melatonin were associated with significant increases in activation within the left dorsomedial and right inferior lateral prefrontal cortex ($p < .05$, cluster corrected). Medial prefrontal activation also correlated modestly with better vigilance performance during the 0-Back ($p < .05$), but not the 1-Back or 2-Back conditions. Light condition did not affect the outcomes.

Conclusions: These findings suggest declining melatonin levels in the morning are associated with increased prefrontal cortex functioning, and may play a role in the increased frontal activation that occurs following awakening.

Support: USAMRMC (W81XWH-14-1-0571).

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April 10, 2018; 90 (15 Supplement) APRIL 27, 2018

Behavioral and Brain Imaging Changes in Patients Receiving Bright Light Therapy Following a Mild Traumatic Brain Injury (mTBI) (S49.003)

Bradley Shane, Johnny Vanuk, Sahil Bajaj, Melissa Millan, William Killgore

First published April 9, 2018,

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Abstract

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Objective: We hypothesized that morning blue light therapy (MBLT) will cause changes in the brain's function and structure that align with improved cognitive performance, mood, and sleep in patients recovering from an mTBI.

Background: Patients who suffer an mTBI may develop post-concussion syndrome symptoms including issues with concentration, mood, and sleep. Research shows that morning blue light exposure leads to regular entrainment of one's circadian rhythm, resulting in improved sleep efficiency and daytime alertness.

Design/Methods: In this double-blind randomized control trial, thirty-one participants with sleep disturbances following documented mTBI in the past 18 months were assigned to the active treatment of MBLT (7M, 8F, mean age = 23 ± 7.5 years) or placebo condition of amber light therapy (ALT) (7M, 9F, mean age = 23 ± 7.1 years). Neurocognitive testing and brain magnetic resonance imaging were conducted at baseline and after 6 weeks of treatment.

Results: In the MBLT group, voxel based morphometry showed increased gray matter volume in the left ($p < .001$) and right pulvinar ($p = .009$) between pre-and post treatment. Resting state functional connectivity demonstrated a significant positive correlation between the pulvinar and parietal area in the left (p-FDR=.003) and right (p-FDR<.001) hemispheres in the MBLT group. Further, the MBLT group showed a significant relationship between right pulvinar connectivity change and Epworth Sleepiness Scale residual change ($r = 0.59$), left pulvinar connectivity change and patient health questionnaire score residual change ($r = -0.56$), and left pulvinar connectivity change and Repeatable Battery for the Assessment of Neuropsychological Status residual change ($r = 0.44$). ALT did not show any significant brain changes or correlations with behavior.

Conclusions: MBLT appears to promote structural and functional pathways within the visuospatial processing system after an mTBI. The improvement in the brain's functional and structural strength, daytime alertness, mood, and neurocognitive performance suggests MBLT may be an effective and safe non-pharmacological treatment for mTBI.

Disclosure: Dr. Shane has nothing to disclose. Dr. Vanuk has nothing to disclose. Dr. Bajaj has nothing to disclose. Dr. Millan has nothing to disclose. Dr. Killgore has nothing to disclose.

Disputes & Debates: Rapid online correspondence

No comments have been published for this article.

Impact of blue light therapy on cortical volume, sleep and anxiety symptoms following mild traumatic brain injury

Sahil Bajaj[1], Natalie S. Dailey[1], John R. Vanuk[1], Adam Raikes[1], Mareen Weber[1, 2], Isabelle M. Rosso[2], Scott L. Rauch[2], & William D. S. Killgore[1, 2]

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Background: The dynamic physical forces involved in sustaining a mild traumatic brain injury (mTBI) may lead to abnormal changes in brain structure. Such abnormalities are often associated with significant cognitive impairments and post-concussion symptoms, including excessive daytime sleepiness and increased anxiety. At present, there are few, if any, widely accepted treatments for the post-concussive symptoms that often occur after an mTBI. Emerging evidence suggests that some symptoms of fatigue and mood alteration may be improved through daily morning exposure to blue wavelength light therapy, although the effect of light exposure on brain structure in this population remains unknown.

Methods: This study involved a whole-brain comparison of cortical volume (CV) between 33 healthy controls (HCs) and 27 mTBI patients who either underwent six-weeks of blue light therapy (BLT) or a placebo amber light therapy (ALT). High-resolution neuroanatomical data, as well as State (S) and Trait (T) Anxiety Inventory (STAI) scores were collected at baseline and post-treatment. Actigraphic data were collected one week prior to each participant's baseline visit and throughout the intervening six weeks.

Results: There were two brain regions, the right inferior parietal cortex and the right lateral orbitofrontal cortex (rLOFC), that showed significantly reduced CV in mTBI patients compared to HCs ($p < 0.05$, *corrected for multiple comparisons*). Following BLT, mTBI patients showed a significant decrease ($p < 0.05$) in STAI-S and STAI-T scores, which was not observed following ALT. There was a trend towards a group (ALT/BLT) x time (pre/post) interaction ($p = 0.09$) for CV within the rLOFC, suggesting that rLOFC volume tended to increase following BLT, but not following ALT. Moreover, following BLT, increased volume of the rLOFC was significantly correlated with decreases in STAI-T scores and sleep onset latency ($p < 0.05$), but not following ALT.

Conclusion: These preliminary findings suggest that 6-weeks of morning BLT may increase CV within the orbitofrontal cortex and is associated with reduced trait anxiety and improved sleep latencies among individuals recovering from concussion. Future work will be necessary to identify the underlying mechanisms that may contribute to the effectiveness of this approach.

Exposure to Blue Wavelength Light During Memory Consolidation Improves Long-Delay Verbal Memory Performance

Anna Alkozei, Ryan Smith, Natalie S. Dailey, Sahil Bajaj, Sara A. Knight, & William D.S. Killgore

Objective

Exposure to blue wavelength light has been shown to lead to increased alertness and improved performance on reaction time tasks, possibly due to noradrenergic influences. However, whether higher-order aspects of cognition can also be improved remains to be determined. The aim of this study was to investigate the effects of thirty minutes of blue versus placebo wavelength light exposure during memory consolidation on verbal memory performance.

Participants and Methods

Thirty healthy men and women (17 female; Mean age = 21.9± 3.7) completed the five learning trials of the California Verbal Learning Test (CVLT-II). Sixty minutes later, participants were randomized to receive either 30 minutes of blue (n=12) or amber (n=18) wavelength light. Fifteen minutes after light cessation, participants completed the long-delay verbal recall portion of the CVLT-II. Participants also completed the Wechsler Abbreviated Scale of Intelligence as a measure of general intelligence (IQ) and the Beck Depression Inventory as a measure of depressive symptoms.

Results

Blue light was associated with significantly better long-delay verbal recall compared to amber placebo, while controlling for the effects of depressive symptoms and IQ ($F(1, 26)=5.23$, $p=.03$). While participants in the blue light group forgot an average of 0.23 words, participants in the amber light group forgot an average of 1.81 words from short-delay to long-delay memory recall.

Conclusions

Exposure to blue light during consolidation enhanced memory recall. Memory consolidation is facilitated by increased norepinephrine release, which has been shown to be stimulated by exposure to blue light. This has important implications for the potential use of blue light as a safe way to improve memory in healthy and clinical populations with memory deficits. Future research will be necessary to extend these findings to clinical populations, and to identify the optimal timing and dose of blue light exposure in this context.

Changes in cortical structure, sleep, and anxiety symptoms following blue-wavelength light therapy in individuals with mild traumatic brain injury

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Introduction
The dynamic physical forces involved in sustaining an mild traumatic brain injury (mTBI) may lead to abnormal changes in cortical structure. Such abnormalities are often associated with post-concussion symptoms, *including* abnormal sleep and increased anxiety. Symptoms of fatigue and mood alteration may be improved through daily morning exposure to blue wavelength light therapy (BLT). The present study focused on identifying the effect of daily morning exposure to BLT on cortical volume (CV) and potential correlations with changes in anxiety and actigraphically-measured sleep onset latency (SOL) following a recent mTBI. In this study, we identified brain regions where individuals with a recent mTBI may have significantly different cortical volume (CV) than healthy controls (HCs) and determined whether these regions, once identified, exhibit volumetric changes following six-weeks of morning BLT compared to a placebo condition of amber light treatment (ALT). Further, we investigated how CV changes in these targeted brain areas were associated with changes in anxiety (state and trait) and SOL in each treatment condition.

Methods
High-resolution neuroanatomical data were collected form 33 HCs (mean age = 24.52±3.03 years, 19 F) and 27 mTBI participants (mean age = 21.00±2.72 years, 14 F). The mTBI participants were randomized to undergo six-weeks of BLT or a placebo ALT. For the mTBI group, State (S) and Trait (T) Anxiety Inventory (STAI) scores were collected at baseline and post-treatment. Actigraphy data were collected one week prior to each participant's baseline visit and throughout the intervening six weeks. The FreeSurfer toolbox was used to identify clusters (regions of interest) showing significant differences in CV between HCs and the mTBI group. The effects of age and sex were regressed out while estimating these differences. A cluster-forming threshold of $p < 0.01$ with a smoothing kernel of 15 mm was used for all the analysis. Multiple comparisons were corrected using a clusterwise threshold of $p < 0.05$ (Monte-Carlo Simulation). Identified regions of interest were used in subsequent analyses to capture the effect of BLT and ALT in mTBI group. Additionally, we covaried for age, gender, body-mass index (BMI), time-since injury (TSI), and light compliance.

Results
CV in the right inferior parietal cortex and the right lateral orbitofrontal cortex (rLOFC) was significantly lower in the mTBI participants compared to HCs at baseline. There was a trend towards a group (ALT/BLT) x time (pre/post) interaction ($p = 0.09$) for CV within the rLOFC, suggesting that rLOFC volume tended to increase following BLT, but not following ALT. Following BLT, the mTBI participants showed a significant decrease ($p < 0.05$) in STAI-S and STAI-T scores, which was not observed following ALT. Moreover, following BLT, increased volume of the rLOFC was significantly correlated with decreases in STAI-T scores and SOL ($p < 0.05$), but not following ALT.

Conclusion: Our findings suggest that 6-weeks of morning BLT may increase CV within the orbitofrontal cortex and is associated with reduced trait anxiety and improved sleep latencies among individuals recovering from an mTBI. Future work will be necessary to identify the underlying mechanisms that may contribute to the effectiveness of this approach.

Short wavelength light therapy following mild traumatic brain injury: Can we normalize the abnormal diffusion and quantity of water within brain?

Sahil Bajaj[1], Anna Alkozei[1], Natalie Dailey[1], William D. S. Killgore[1]

[1]University of Arizona, Tucson, AZ, USA.

Introduction

Mild Traumatic Brain Injury (mTBI) is known to affect the functional and structural integrity of the brain, leading to multiple post-concussion symptoms, including lack of concentration and sleep disturbances. Short wavelength bright light therapy may be effective at reducing these symptoms and re-entraining the circadian rhythm in patients with mTBI. Here, we explored the effect morning blue light therapy (BLT) versus amber placebo light therapy (ALT) on brain function and structure following mTBI.

Methods

28 mTBI survivors underwent diffusion tensor imaging on two occasions, separated by 6-weeks of light therapy i.e. either ALT or BLT. Half of the mTBI survivors were randomly assigned to ALT and the rest were assigned to BLT. In order to estimate diffusion parameters such as fractional anisotropy (FA) and quantitative anisotropy (QA), we limited the white-matter tracts to 11 regions of interest, namely- the dorsolateral prefrontal cortex, genu, body and splenium of the corpus callosum (CC), the left uncinate fasciculus (L: UF), the right uncinate fasciculus (R: UF), the left superior longitudinal fasciculus, the right superior longitudinal fasciculus, the left anterior corona radiata (L: ACR), right anterior corona radiata (R: ACR) and the thalamus. We investigated whether individuals in the ALT and BLT groups showed significant changes in FA and QA and whether these changes from pre-to-post treatment were correlated with changes in executive function (memory and attention).

Results

FA: Using repeated measures analysis of variance (RM-ANOVA), we found that following BLT, the splenium of the CC showed a significant decrease ($p < 0.05$) in FA, but not following ALT. There was also significant treatment-group interaction (i.e., there was an overall significant difference between ALT and BLT profiles) for the splenium of the CC.

NQA: Using RM-ANOVA, we found that following BLT, four brain areas (i.e., body of CC, R: UF, L: ACR and thalamus) showed a significant decrease ($p < 0.05$) in QA. But, following ALT, none of the areas showed any significant change in QA. We found that there was a significant treatment-group interaction (i.e. that was an overall significant difference between ALT and BLT profiles) for three brain areas (body of CC, L: ACR and thalamus).

Cognition: For FA, we did not find any significant correlation between change in any area and change in cognitive metrics following either therapy. For QA, however, significant negative correlations were observed between change in RBANS Delayed Memory scores and change in QA for two brain areas: the body of the CC ($r = -0.664$, $p = 0.009$) and the thalamus ($r = -0.577$, $p = 0.031$) for the BLT group. In contrast, for ALT, there was no significant correlation in any possible combination between diffusion measures and cognitive measures for mTBI survivors.

Conclusions

Our findings show BLT as an effective means of non-pharmacological intervention for improving structural and functional aspects of brain recovery among mTBI survivors. These findings support the proposition that the brain's white matter properties, especially QA, can be considered as broadly applicable, sensitive and reliable neuro-markers for recovery in mTBI therapies.

Increases in Prefrontal Activation After Exposure to Blue versus Amber Wavelength Light During Cognitive Load

Anna Alkozei[1], Ryan Smith, Sarah M. Berryhill, Sara A. Knight, & William D.S. Killgore[1]

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Objective

Consistent long-term exposure to blue enriched white light has been associated with increases in self-reported alertness, concentration, work performance and decreases in fatigue and daytime sleepiness. Blue light has also been shown to lead to immediate functional brain changes during the light exposure, but the effects of blue light on functional brain responses during cognitive tasks *after* cessation of light exposure remain unclear.

Participants and Methods

Thirty-five healthy 18-32 year olds (18 females, mean age = 21.79) were randomized to receive a 30-minute exposure to either blue (active) (n=17) or amber (placebo) light (n=18), immediately followed by a working memory task (N-Back task) during functional magnetic resonance imaging (fMRI). All exposure was completed in the morning, following normal sleep at home.

Results

In contrast to placebo, participants in the blue light group showed significantly greater activation within the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) with increases in working memory load. Participants in the blue group responded faster during conditions of high cognitive load than participants in the placebo group. In addition, with increases in activation within the VLPFC, participants showed faster reaction times (r = -.35, p = .04) and more efficient responding (i.e., answered more items correctly per second) (r = .40, p = .01) during conditions of greater cognitive load.

Conclusions

The results suggest that a short single exposure to blue light is sufficient to produce measurable changes within the DLPFC and VLPFC, brain areas recruited during heavy cognitive load. This may explain why previous studies have reported increases in subjective alertness and performance after long-term blue light exposure. These findings may have important implications for using blue light as a tool to increase alertness, and response times in a variety of work settings that require alertness, and quick decision-making.

Poster presented at the: University of Arizona Junior Investigator Poster Forum; November 17, 2017; Tucson, AZ.

Blue Wavelength Light Therapy Increases Axonal Myelination in Mild Traumatic Brain Injury

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Background: Mild traumatic brain injury (mTBI) is a highly prevalent injury among Service members. While mTBI typically resolves rapidly with few associated complications, a significant proportion of individuals complain of persisting post-concussive symptoms such as poor attention and concentration, irritability, headaches, and balance problems. Moreover, approximately 50% of individuals who experience an mTBI will subsequently develop sleep problems and lingering fatigue that may continue for years after their injury. A primary factor leading to these sleep problems may be the perturbation of the circadian rhythm induced by the injury. Because the daily circadian rhythm is regulated predominantly by exposure to light, we recently completed a clinical trial using blue wavelength light therapy to enhance sleep and circadian rhythmicity in patients with recent mTBIs. It was hypothesized that daily exposure to blue light each morning would re-entrain the circadian rhythm, which would enhance sleep quality, thus facilitating brain repair processes.

Methods: Thirty-two individuals (15 male; 17 female; aged 18-48 years) who experienced an mTBI during the preceding 18 months completed a comprehensive neuropsychological evaluation and neuroimaging, including Diffusion Tensor Imaging (DTI). Participants were then randomly assigned in double-blind fashion to undergo daily morning exposure with a light device fitted with a 10 x 6 array of light emitting diodes in either the blue- (active; n=16) or amber-wavelength (placebo; n=16). Treatment was conducted at home and lasted 6 weeks (30-minutes daily, prior to 11:00am). At the conclusion of treatment, participants returned to the lab for a follow-up assessment and neuroimaging session.

Results: Compared to amber placebo, blue light tratment was associated with a significant phase advance in sleep onset ($p = .007$) and wake times ($p = .048$). Structural magnetic resonance imaging (MRI) showed that active blue-light treatment was associated with increased volume of the pulvinar nucleus bilaterally ($p<.05$, FWE corrected), while no difference was observed for the amber placebo condition. Blue light was also associated with increased functional connectivity between the pulvinar and parietal regions compared to placebo ($p < .05$). Moreover, using the DTI data, we conducted fiber tractography of the axonal tracts connecting the pulvinar and parietal cortex and were able to define left hemisphere tracts connecting these regions in 10 participants in each group. This analysis revealed significantly increased fractional anisotropy (FA) of these fiber tracts after 6 weeks of treatment in the blue but not amber

groups ($p<.05$, FWE corrected). Changes in structural connectivity correlated with improved neurocognitive performance on the Immediate Memory and Total score on the Repeatable Battery of Neuropsychological Status (RBANS).

Conclusion: In a sample of patients recovering from mTBI, daily morning blue-wavelength light therapy for 6 weeks led to significant improvements in circadian timing as well as functional and structural brain connectivity, and associated neurocognitive performance. These preliminary findings support prior research suggesting that blue light therapy may improve fatigue among patients with concussion, but further suggest that regular morning blue light exposure therapy may be an effective treatment for re-entraining the circadian rhythm and enhancing brain repair following mTBI.

Abstract 1 for Organization for Human Brain Mapping (OHBM) 2017

Title: Impact of Bright Light Therapy on Structural Abnormalities following a mild Traumatic Brain Injury

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Introduction

Mild Traumatic Brain Injury (mTBI) may affect the functional and structural integrity of the brain, leading to post-concussion symptoms. White matter (WM) abnormality is believed to contribute to the underlying pathophysiology of mTBI and its deficits. Bright light exposure, especially in the blue wavelengths, may be effective at reducing fatigue and re-entraining the circadian rhythm in patients with mTBI. Here, we explored the effect of morning bright light therapy: amber light therapy (ALT) and blue light therapy (BLT) on brain structure and function following mTBI. To our knowledge, this is the first study where affected brain areas following a brain injury were identified based on quantitative measure of anisotropy[1], followed by their recovery following a light therapy. We hypothesized that morning BLT would help to recover brain's structural integrity and improve the behavior (Repeatable Battery for the Assessment of Neurological Status (RBANS) scores, Epworth Sleepiness Scale (ESS) reflecting day-time sleepiness and Patient Health Questionnaire reflecting depression (PHQ)) of mTBI survivors.

Methods

We collected diffusion tensor imaging (DTI) data from 31 mTBI survivors (mean age=22.1±5.6 years, 16 F) and 39 healthy-controls (HCs) (mean age=27.1±5.9, 19 F). Due to abnormal clinical scans; data from three mTBI survivors were excluded. The remainder of the mTBI survivors underwent

two DTI scans. Prior to the second scan, half of the mTBI survivors (N = 14, mean age=21.2±3.1 years, 10 F) were randomly assigned for six weeks of morning ALT and the rest half (N = 14, mean age=21.8±4.4 years, 8 F) were given six weeks of morning BLT. A battery of neurocognitive tests was administered before and after the therapy. Using DSI Studio (http://dsistudio.labsolver.org), diffusion parameters such as raw quantitative anisotropy (QA), normalized QA (NQA) and isotropic (ISO) diffusion were estimated for 11 regions of interest (ROIs): the dorsal lateral prefrontal cortex (DLPFC), the genu, the splenium and the body of corpus callosum (CC), the left/right uncinate fasciculus (L/R UF), the left/right superior longitudinal fasciculus (L/R SLF), the left/right anterior corona radiata (L/R ACR) and the thalamus.

Results

Using two-sample t-tests, we found that all 11 ROIs (a) had significantly higher ($p < 0.05$) QA and (b) except the splenium, the LSLF and the thalamus, had significantly higher ($p < 0.05$) ISO for mTBI than HCs. Compared to pre-treatment measures, following ALT, we noticed that none of the 11 areas, which were found to be affected following an mTBI, showed any significant change (paired t-test, $p < 0.05$) in normalized QA (NQA) (Figure 1A) or ISO, although there was some decrease in ISO for 8 areas, except the DLPFC, the L: UF and the thalamus (Figure 1B). Following BLT, however, we noticed that four areas i.e. the body of CC, the L/R: UF (L) and the L: ACR, which were found to be affected following mTBI, showed significant decrease (paired t-test, $p < 0.05$) in NQA (Figure 1C). While none of the affected areas showed significant change in ISO, there was some decrease in ISO observed for L/R: UF following BLT (Figure 1D). After a careful visual inspection of NQA maps of these 4 areas, we identified the presence of new fibers visible following BLT, indicated by white/blue dashed circles (Figure 2). For the BLT group, we also found significant negative correlations ($p < 0.05$) between residualized change scores of NQA and residualized change scores of delayed memory (DM) RBANS scores for 3 ROIs (the body of CC and the L/R: UF).

Conclusion

Our findings show that blue-wavelength bright light (BLT) can be an effective non-pharmacological intervention for improving some aspects of brain recovery among mTBI survivors and support the proposition that the brain's white matter properties can be considered as broadly applicable and reliable neuro-markers for recovery in mTBI therapies.

References

1. Yeh, F. C., Verstynen, T. D., Wang, Y., Fernandez-Miranda, J. C. & Tseng, W.Y. Deterministic diffusion fiber tracking improved by quantitative anisotropy. Plos One 8, e80713, doi:10.1371/journal.pone.0080713 (2013).

Figure 1: Effect of amber-light therapy (ALT) (A-B) and blue-light therapy (BLT) (C-D) on normalized QA (NQA) and ISO measures following mTBI.

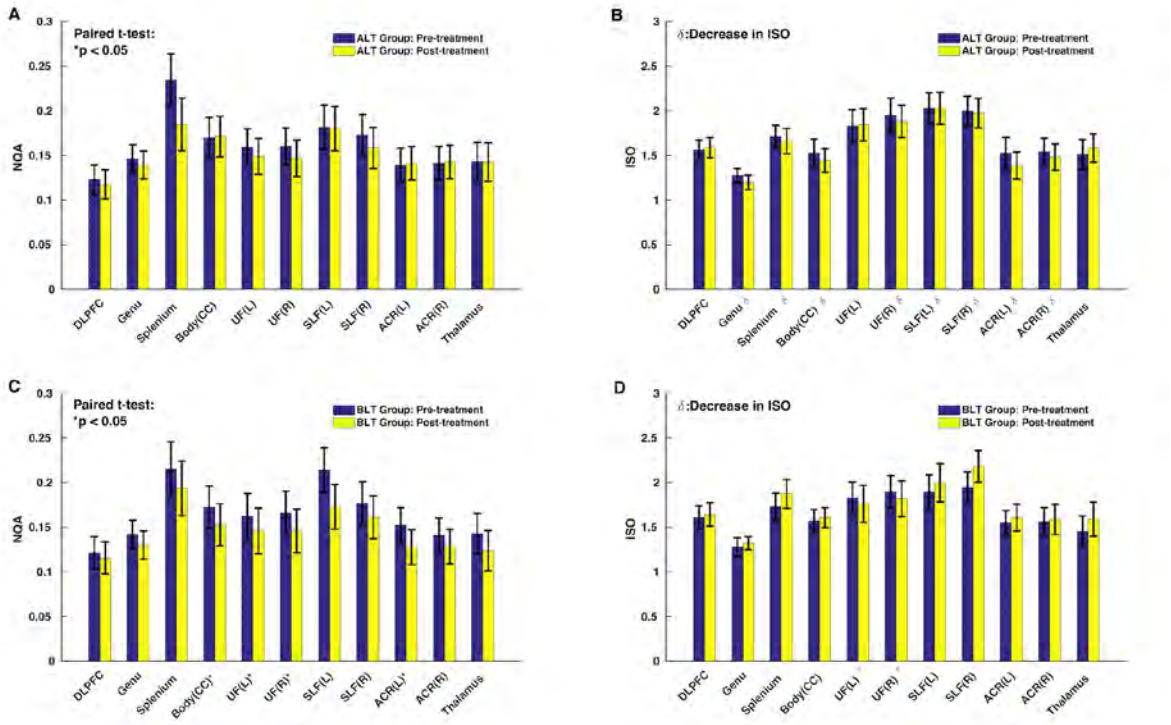
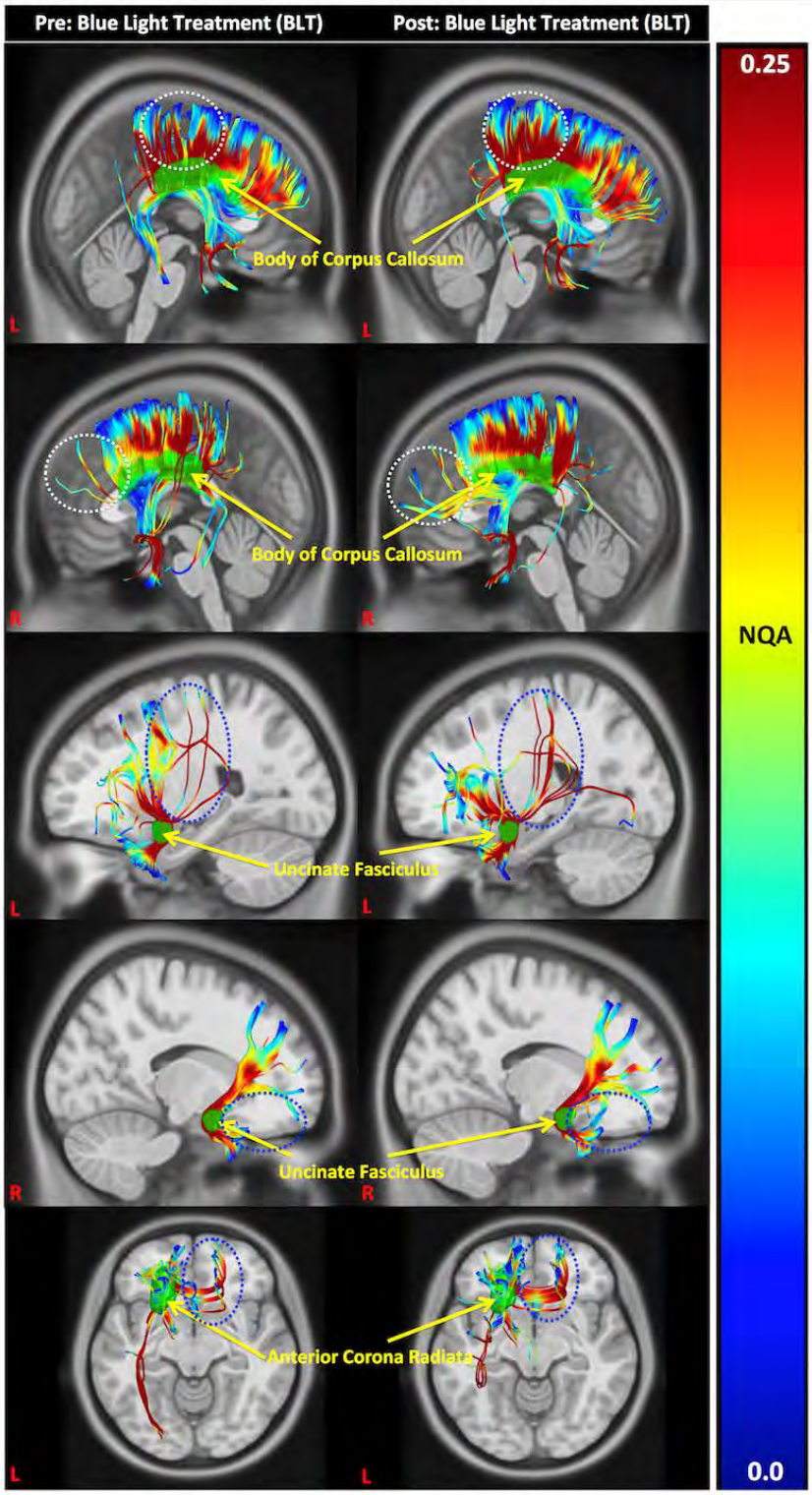


Figure 2: Inspection of four brain areas (the body of corpus callosum, the L/R: UF and the L: ACR) of a representative participant, which showed a

significant improvement in NQA following BLT, indicates degeneration of some new fibers, indicated by white/blue dashed circles.



Abstract 2 for Organization for Human Brain Mapping (OHBM) 2017

Title: Dynamics of brain's cortical measures following a mild traumatic brain injury

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Introduction

The physical forces involved in sustaining a mild Traumatic Brain Injury (mTBI) may lead to abnormal structural changes in the brain. These structural changes are also associated with persistent post-concussion symptoms such as daytime sleepiness and depression. Due to the rapid pace of recovery and inconsistent pattern of structural changes following an mTBI, fully characterizing the pattern of these abnormalities over time has been difficult. Here we examined brain morphometric changes at three time points following an mTBI and correlated those with cognitive function.

Methods

We collected anatomical data from 54 individuals (mean age=22.1±5.6 years, 16 F) suffering from sleep disorders following documented mTBI within last 18 months. Using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki), anatomical images were pre-processed for each participant, followed by whole brain parcellation and calculation of cortical thickness (CT), cortical volume (CV) and cortical surface area (CSA). Comparisons of whole brain's CT, CV, CSA and neuropsychological behavior were done for mTBI survivors- within and across three time-points (TPs) (N=18, mean age=24.6±6.1 years, 11 F, TP1: 0-3 months post mTBI; N=22, mean age=21.8±3.5 years, 14 F, TP2: 3-6 months post mTBI and N=14, mean age=20.6±2.6 years, 8 F, TP3: 6 months or longer post mTBI). Monte Carlo simulations were used to detect the

significant clusters of significant vertex-wise CT, CV and SA group differences ($p<.05$) between 3 TPs for mTBI survivors.

Participants completed measures such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) of attention (ATT)[1] (measure of speed of information processing), Pittsburgh Sleep Quality Assessment (PSQI)[2] (measure of multiple sleep related behaviors, where lower scores represent healthier sleep), Beck Depression Inventory (BDI)[3] (measure of symptoms related to depression) and Epworth Sleepiness Scale (ESS)[4] (measure of typical or trait-like daytime sleepiness, where a high-score represents greater daytime sleepiness).

Results

CT: We find that CT remains unchanged across three time-points (i.e. between TP1 and TP2, TP1 and TP3 and TP2 and TP3).

CV: We find that CV increases significantly for several brain areas from TP1 to TP3 and from TP2 to TP3 but not from TP1 to TP2 as shown in Figure 1.

CSA: Here, we find that CSA also is significantly increased for several brain areas from TP2 to TP3 but not from TP1 to TP2 and TP1 to TP3 as shown in Figure 1.

Overall, we find that CT does not change significantly after 3 months of mTBI but CV increases significantly after 3 months of mTBI and continues increasing even after 6 months. Also, CSA does not change before 6 months of mTBI but gets significantly increased after 6 months of mTBI compared to first 3 months.

Cortical measures versus behavioral measures: For several areas, CT shows positive as well as negative significant correlations with behavioral scores as well as with time since injury (TSI). So there is no particular pattern of correlations between CT and behavioral scores (Table 1).
For several areas, CV shows increases with TSI. Also, ESS becomes significantly reduced with increase in CV for several areas (Table 1).
For several areas, CSA gets increased with TSI. Also, ESS and BDI get significantly reduced with increase in CSA for several areas whereas ATT gets significantly increased and PSQI gets significantly decreased with increase in CSA (Table 1).

Hence, findings suggest that with time, changes in CV and CSA tend to be associated with improved cognitive functioning.

Conclusions

Findings suggest that brain recovery may continue for up to 6 months following an mTBI. This time-line may help to facilitate development effective rehabilitation techniques for concussion survivors. A comparison of these functional and cortical measures of mTBI survivors with a control data set would further strengthen these findings. Such comparisons are underway in our lab.

References

1 Randolph, C., Tierney, M. C., Mohr, E. & Chase, T. N. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* **20**, 310-319, doi:10.1076/jcen.20.3.310.823 (1998).

2 Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* **28**, 193-213 (1989).

3 Beck, A. T., Steer, R. A. & Brown, G. K. *Manual for the Beck Depression Inventory-II*. (The Psychological Corporation, 1996).

4 Johns, M. W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* **14**, 540-545 (1991).

Figure 1. Clusters indicating either significant increase or significant decrease in cortical volume (CV) and cortical surface area (CSA) between three time-points.

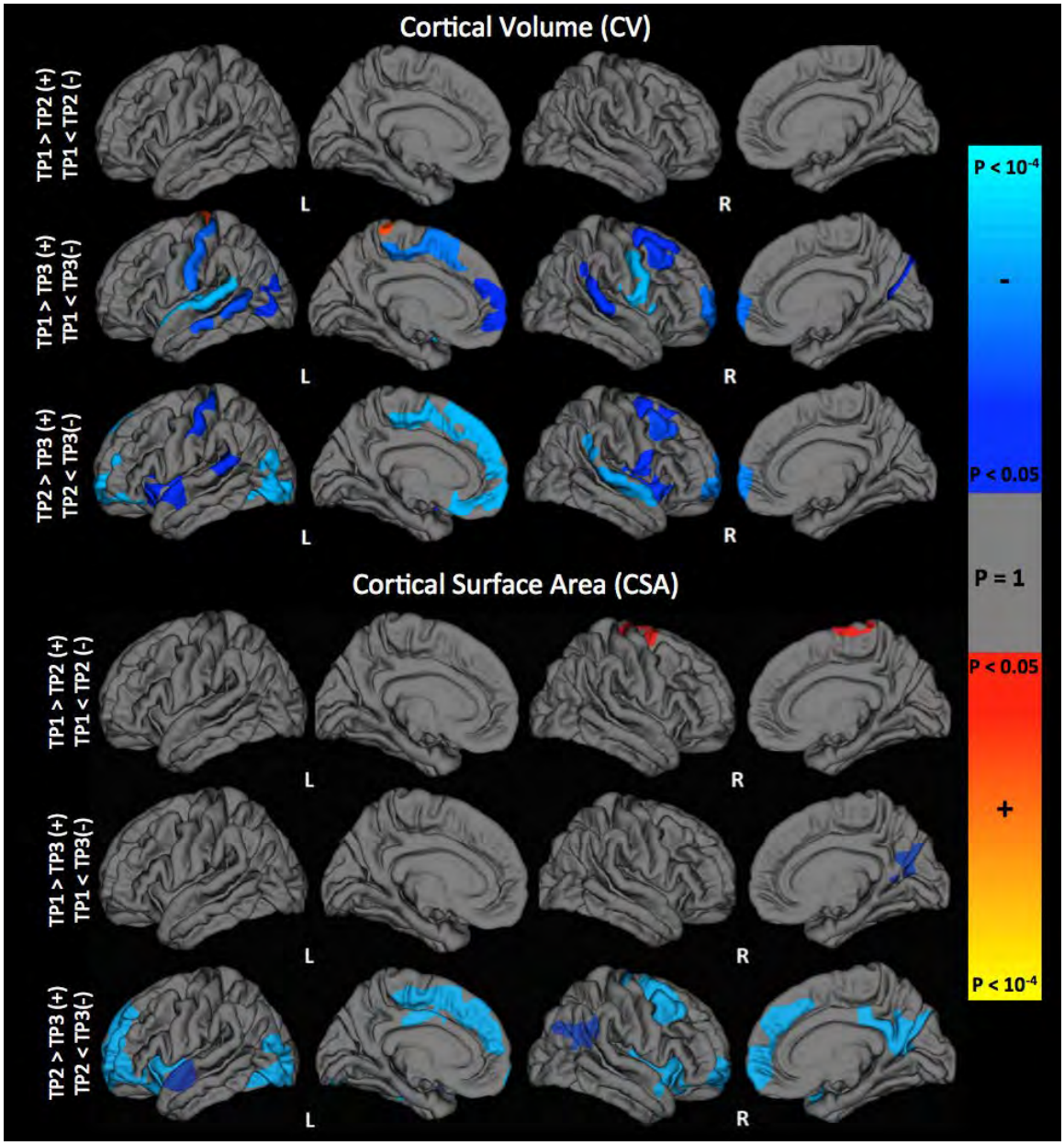


Table 1 Correlations between cortical measures and behavioral measures

#	Clusters	Hemisphere	Correlation (r, p) between CT and				
			TSI	ATT	PSQI	BDI	ESS
1	Bankssts	L	N.S	N.S	N.S	**0.29, 0.03**	N.S
2	Inferior temporal	R	N.S.	**-0.32,0.02**	N.S.	N.S.	N.S.
3	Isthmus cingulate	L	N.S.	N.S.	N.S.	N.S.	**0.34, 0.01**
4	Lateral occipital	R	N.S.	N.S.	N.S.	N.S.	**-0.30, 0.03**
5	Lateral orbitofrontal	L	N.S.	**-0.28, 0.04**	N.S.	N.S.	N.S.
6	Parahippocampal	L	N.S.	N.S.	N.S.	**-0.28, 0.04**	N.S.
7	Parsopercularis	R	N.S.	N.S.	**-0.28, 0.04**	N.S.	N.S.
8	Pericalcarine	L	N.S.	**0.28, 0.04**	N.S.	N.S.	N.S.
9	Precentral	L	N.S.	N.S.	N.S.	**-0.28, 0.04**	N.S.
10	Precuneus	L	N.S.	N.S	N.S	**-0.33, 0.02**	N.S
11	Rostral anterior cingulate	R	**-0.36, 0.01**	N.S.	N.S.	N.S.	N.S.
12	Frontal pole	L	**0.33, 0.02**	N.S.	N.S.	N.S.	N.S.
13	Transverse temporal	R	**0.30, 0.03**	N.S.	N.S	N.S.	N.S.
#	Clusters	Hemisphere	Correlation (r, p) between CV and				
			TSI	ATT	PSQI	BDI	ESS
1	Bankssts	R	**0.37, 0.00**	N.S	N.S.	N.S	N.S.
2	Bankssts	L	N.S.	N.S.	**0.28, 0.04**	N.S.	N.S.
3	Caudal middle frontal	R	**0.30, 0.03**	N.S.	N.S.	N.S.	**-0.31, 0.02**
4	Entorhinal	R	N.S.	N.S.	**-0.32, 0.02**	N.S.	**-0.29, 0.04**
5	Entorhinal	L	N.S.	N.S.	N.S.	N.S.	**-0.31, 0.03**
6	Inferior parietal	R	**0.27, 0.05**	N.S.	N.S.	N.S.	N.S.
7	Lateral occipital	R	N.S.	N.S.	N.S.	N.S.	**-0.38, 0.00**
8	Medial orbitofrontal	R	N.S.	N.S.	N.S.	N.S.	**-0.27, 0.05**
9	Parsopercularis	L	N.S.	N.S.	N.S.	N.S.	**0.27, 0.05**
10	Parsorbitalis	R	N.S.	**-0.29, 0.04**	N.S.	N.S.	N.S.
11	Precentral	L	N.S.	N.S.	N.S.	N.S.	**-0.30, 0.03**
12	Rostral anterior cingulate	R	N.S	N.S	N.S	N.S	**0.28, 0.04**
13	Superior frontal	L	N.S.	N.S.	N.S.	N.S.	**-0.29, 0.03**
14	Supramarginal	L	N.S.	N.S.	N.S.	N.S.	**-0.31, 0.03**
15	Frontal pole	L	N.S.	N.S.	N.S.	**-0.30, 0.03**	N.S.
16	Frontal pole	R	N.S.	N.S.	N.S.	N.S.	**-0.27, 0.05**
17	Insula	L	**0.28, 0.04**	N.S	N.S	N.S	N.S
#	Clusters	Hemisphere	Correlation (r, p) between SA and				
			TSI	ATT	PSQI	BDI	ESS
1	Bankssts	R	**0.36, 0.00**	N.S.	N.S.	N.S.	N.S.
2	Caudal middle frontal	R	**0.27, 0.05**	N.S.	N.S.	N.S.	N.S.
3	Entorhinal	L	N.S.	N.S.	N.S.	N.S.	**-0.32, 0.02**
4	Entorhinal	R	N.S.	N.S.	**-0.32, 0.02**	**-0.38, 0.00**	N.S.
5	Inferior parietal	R	**0.28, 0.04**	N.S.	N.S.	N.S.	N.S.
6	Isthmus cingulate	R	**0.29, 0.03**	N.S.	N.S.	N.S.	N.S.
7	Lateral occipital	R	N.S.	N.S.	**-0.29, 0.04**	N.S.	N.S.
8	Parahippocampal	L	N.S.	**0.27, 0.05**	N.S.	N.S.	N.S.
9	Supramarginal	L	N.S.	N.S.	N.S.	N.S.	**-0.33, 0.01**
10	Frontal pole	L	N.S.	N.S.	N.S.	**-0.36, 0.00**	N.S.
11	Insula	L	N.S.	N.S.	N.S.	N.S.	**-0.32, 0.02**

Short-Wavelength Light Therapy as a Way of Improving Sleep, Cognition, and Functional Connectivity Following a Mild Traumatic Brain Injury

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Mild traumatic brain injury (mTBI) has been associated with disruptions in sleep, limbic function, and increases in symptoms related to anxiety as a consequence of the injury. Evidence suggests that there is a relationship between improvements in neurobehavioral impairments and more regulated sleep architecture, but this relationship is not well understood. We hypothesized that among patients recovering from an mTBI, daily morning blue light therapy (BLT) would yield improvement in brain function, as evidenced by greater post-treatment functional connectivity between the medial prefrontal cortex (MPFC) and amygdala, and this would be associated with improvements in sleep and anxiety.

Twenty-six adults (12 male; M age: 21.6±3.9) with self-reported sleep disturbances subsequent to a documented mTBI within the preceding 18 months were recruited to receive either BLT or a placebo amber light therapy (ALT) for 30-minutes each morning over a six-week period. Participants underwent a six-minute resting state functional magnetic resonance imaging (fMRI) scan at 3T and completed neurocognitive testing at baseline and again at the conclusion of treatment. Regions of interest were placed in the amygdala (bilateral) and MPFC. Functional connectivity was analyzed utilizing the CONN toolbox with SPM12, $p<.05$, FDR corrected.

BLT was associated with significant increases in functional connectivity between the left amygdala and MPFC, whereas no change was observed for ALT. The increase in connectivity for BLT was associated with significant decreases in sleep onset latency, state anxiety, and perceived invincibility from baseline to post treatment.

A six-week period of BLT produced improvements in sleep onset latency and anxiety that were associated with increased functional connectivity between the left amygdala and MPFC. BLT may provide an effective method for regulating the sleep wake cycle and improving cognition and emotion among individuals recovering from mTBI. Better sleep may serve to strengthen mPFC to amygdala connectivity, thereby improving emotional functioning.

Abstract 1 for SLEEP Meeting 2017

Title: Effect of Bright Light Therapy on Brain and Behavioral Abnormalities following a mild Traumatic Brain Injury

Sahil Bajaj*[1], Anna Alkozei[1], Michael A. Grandner[1], William D. S. Killgore[1]

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Introduction: Mild traumatic brain injury (mTBI) can lead to alterations in sleep, circadian function, and cognition. Evidence suggests that blue wavelength light can alter circadian timing and fatigue in patients with mTBI, but no studies have examined the structural brain correlates of these effects. Here, we explored the impact of morning bright (amber/blue) light exposure therapy (ALT/BLT) on white matter structure and its neurocognitive correlates.

Methods: 28 mTBI survivors underwent diffusion tensor imaging (DTI) before and after six weeks of either ALT or BLT. 39 healthy-controls (HCs) were used as a normal comparison group. First, for both groups, raw quantitative anisotropy (QA) and normalized QA (NQA) were estimated for 11 regions of interest (ROIs): the dorsal-lateral prefrontal cortex (DLPFC), genu, splenium and body of the corpus callosum (CC), the left/right uncinate fasciculus (UF), the left/right superior longitudinal fasciculus, the left/right anterior corona radiata (ACR) and the thalamus. Finally, impact of light on changes in diffusion parameters of these ROIs was analyzed among those with mTBI.

Results: At baseline, all 11 ROIs had significantly higher QA ($p<0.05$) for mTBI than HCs. There was no significant improvement in NQA for any ROI following ALT. Following BLT, four ROIs (the body of CC, the L/R UF and the left ACR) showed significant decreases in NQA ($p<0.05$). For ALT, pre-post changes in these ROIs were associated with worsening neurocognitive and mood scores, while changes were generally associated with improvements for those in the BLT group, potentially reflecting a positive impact of BLT on brain and behavior.

Conclusion: Compared to ALT, BLT led to improve structural integrity, neurocognition, and mood of mTBI survivors. Given the known role of light in the entrainment of the circadian rhythm, our findings suggest that BLT may be a useful approach for improving circadian function to facilitate brain recovery from concussion.

(Sleep)

Short Wavelength Light Therapy Facilitates Recovery from Mild Traumatic Brain Injury

William D.S. **Killgore**, Bradley R. Shane, John R. Vanuk, Jenna Franco, Amaris Castellanos, Melissa Millan, Michael A. Grandner, & Sahil Bajaj

University of Arizona, Tucson, AZ

Introduction: Mild traumatic brain injury (mTBI) or "concussion" is often associated with persistent problems with sleep and fatigue in up to 50% of those injured. We hypothesized that regular morning blue light exposure therapy may re-entrain the circadian rhythm and improve overall sleep quality, potentially enhancing brain repair, thereby improving brain functioning, symptom expression, and neurocognitive problems.

Methods: Twenty-eight individuals (15 female; aged 18-48 years) who experienced an mTBI during the preceding 18 months underwent a comprehensive neuropsychological assessment and multi-modal neuroimaging. In a double-blind design, participants were randomly assigned to complete daily morning exposure with a light device fitted with an array of light emitting diodes in the blue (n=14) or amber wavelength (placebo; n=14). Participants used the device for 6-weeks at home (30-minutes daily, prior to 11:00am), and returned for follow-up assessment and imaging.

Results: Blue light exposure led to an earlier bedtime and rise time, lower daytime sleepiness, and improved balance stability compared to placebo light ($p<.05$). Structural magnetic resonance imaging (MRI) showed that active blue-light treatment was associated with increased volume of the pulvinar nucleus bilaterally ($p<.05$, FWE corrected), while no difference was observed for the amber placebo condition. Blue light was also associated with increased functional connectivity and greater integrity of white matter axonal pathways connecting the pulvinar to parietal regions compared to placebo ($p<.05$, FWE corrected). Changes in functional and structural connectivity correlated with improved neurocognitive performance.

Conclusion: Daily morning exposure to blue-wavelength light for 6-weeks led to improved sleep and associated alterations in thalamo-cortical structure, connectivity, and function compared to amber placebo light exposure. Findings are consistent with recent evidence that light exposure may improve fatigue in this population. These preliminary findings raise the possibility that blue-light treatment may provide a novel method for improving recovery from some aspects of mTBI.

Support: This study was supported by USAMRAA grant W81XWH-11-1-0056 to WDSK.

Abstract 1 for SLEEP Meeting 2017

Title: Effect of Bright Light Therapy on Brain and Behavioral Abnormalities following a mild Traumatic Brain Injury

Sahil Bajaj*[1], Anna Alkozei[1], Michael A. Grandner[1], William D. S. Killgore[1]

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Introduction: Mild traumatic brain injury (mTBI) can lead to alterations in sleep, circadian function, and cognition. Evidence suggests that blue wavelength light can alter circadian timing and fatigue in patients with mTBI, but no studies have examined the structural brain correlates of these effects. Here, we explored the impact of morning bright (amber/blue) light exposure therapy (ALT/BLT) on white matter structure and its neurocognitive correlates.

Methods: 28 mTBI survivors underwent diffusion tensor imaging (DTI) before and after six weeks of either ALT or BLT. 39 healthy-controls (HCs) were used as a normal comparison group. First, for both groups, raw quantitative anisotropy (QA) and normalized QA (NQA) were estimated for 11 regions of interest (ROIs): the dorsal-lateral prefrontal cortex (DLPFC), genu, splenium and body of the corpus callosum (CC), the left/right uncinate fasciculus (UF), the left/right superior longitudinal fasciculus, the left/right anterior corona radiata (ACR) and the thalamus. Finally, impact of light on changes in diffusion parameters of these ROIs was analyzed among those with mTBI.

Results: At baseline, all 11 ROIs had significantly higher QA ($p<0.05$) for mTBI than HCs. There was no significant improvement in NQA for any ROI following ALT. Following BLT, four ROIs (the body of CC, the L/R UF and the left ACR) showed significant decreases in NQA ($p<0.05$). For ALT, pre-post changes in these ROIs were associated with worsening neurocognitive and mood scores, while changes were generally associated with improvements for those in the BLT group, potentially reflecting a positive impact of BLT on brain and behavior.

Conclusion: Compared to ALT, BLT led to improve structural integrity, neurocognition, and mood of mTBI survivors. Given the known role of light in the entrainment of the circadian rhythm, our findings suggest that BLT may be a useful approach for improving circadian function to facilitate brain recovery from concussion.

SoBP

Blue Light Therapy Following a Mild Traumatic Brain Injury Improves MPFC-Amygdala Functional Connectivity and Mood

John R. Vanuk[1,2], Melissa Millan[1], Bradley R. Shane[1], Sahil Bajaj[1], William D.S. Killgore[1,2]

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2. Department of Psychology, University of Arizona, Tucson, AZ

Mild traumatic brain injury (mTBI) has been associated with increases in anxiety subsequent to the injury. Dysfunction in functional connectivity of the medial prefrontal cortex (MPFC) and amygdala has been postulated to contribute to this incidence, perhaps via sleep disruption. We hypothesized that daily blue light therapy (BLT) would stabilize sleep for individuals recovering from a mTBI and this would contribute to increases in MPFC to amygdala functional connectivity and decreases in anxiety.

Twenty-six adults (14 female; M age: 21.6±3.9) who experienced a documented mTBI within the previous 18 months were enrolled. Subjects underwent six weeks of either BLT or a placebo amber light therapy (ALT) each morning for 30 minutes. Neurocognitive testing and a six-minute resting state functional magnetic resonance imaging scan occurred at baseline and following treatment. Regions of interest were placed in the MPFC and bilateral amygdala. Functional connectivity was analyzed utilizing the CONN toolbox, $p<.05$, FDR corrected.

Significant increases in functional connectivity between the left amygdala and MPFC for individuals that received BLT were observed relative to ALT. This increase was associated with significant decreases in state anxiety and sleep onset latency between baseline and the conclusion of treatment.

BLT contributed to increased functional connectivity between the left amygdala and MPFC, which was associated with decreased anxiety symptoms. Findings suggest that BLT may facilitate entrainment the sleep wake cycle, which may facilitate cognitive and emotional recovery following a mTBI. Future work may examine the durability of this effect beyond the conclusion of treatment.

(SoBP)

Light Therapy Facilitates Thalamo-Cortical Brain Recovery from Mild Traumatic Brain Injury

William D.S. **Killgore**, Bradley R. Shane, John R. Vanuk, Jenna Franco, Amaris Castellanos, Melissa Millan, Michael A. Grandner, & Sahil Bajaj

University of Arizona, Tucson, AZ

Introduction: Mild traumatic brain injury (mTBI) or "concussion" is often associated with persistent problems with sleep for up to 50% of patients. We hypothesized that regular morning blue light exposure therapy may re-entrain the circadian rhythm and improve sleep, potentially enhancing brain repair and neuropsychological recovery.

Methods: Twenty-eight individuals (15 female; 18-48 years) with a documented mTBI during the preceding 18 months underwent a comprehensive neuropsychological assessment and multi-modal neuroimaging. Participants completed 6-weeks of daily morning light exposure (30 min/day) with a light device fitted with blue (n=14) or amber wavelength (placebo; n=14) diodes, and returned for follow-up assessment and imaging.

Results: Blue light exposure led to an earlier bedtime and rise time, lower daytime sleepiness, and improved balance compared to placebo light ($p<.05$). Structural magnetic resonance imaging (MRI) showed that active blue-light treatment was associated with increased volume of the pulvinar nucleus bilaterally ($p<.05$, FWE corrected), while no difference was observed for amber placebo. Blue light was also associated with increased functional connectivity and greater integrity of white matter axonal pathways connecting the pulvinar to parietal regions compared to placebo ($p<.05$, FWE corrected). Changes in functional and structural connectivity correlated with improved neurocognitive performance.

Conclusion: Daily morning exposure to blue-wavelength light for 6-weeks led to improved sleep and associated alterations in thalamo-cortical structure, connectivity, and function compared to amber placebo light exposure. These preliminary findings raise the possibility that blue-light treatment may provide a novel method for improving recovery from some aspects of mTBI.

Support: This study was supported by USAMRAA grant W81XWH-11-1-0056 to WDSK.

Abstract 1 for Society of Biological Psychiatry (SOBP) Meeting 2017

Title: Effect of Bright Light Therapy on White Matter Abnormalities following a mild Traumatic Brain Injury

Sahil Bajaj*[1], Anna Alkozei[1], & William D. S. Killgore[1]

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Background: White matter (WM) integrity still needs to be explored to determine the structural and cognitive impairment following an mTBI. We aim to explore such WM abnormalities and analyze the impact of morning bright (amber/blue) light therapy (ALT/BLT) on WM integrity.
Methods: 39 healthy-controls (HCs) and 28 mTBI survivors (before and after six weeks of either ALT or BLT) underwent diffusion tensor imaging. Raw quantitative anisotropy (QA), normalized QA (NQA) and isotropic (ISO) diffusion were estimated for 11 regions of interest (ROIs): the dorsal-lateral prefrontal cortex (DLPFC), genu, splenium and body of the corpus callosum (CC), the left/right uncinate fasciculus (L/R UF), the left/right superior longitudinal fasciculus (L/R SLF), the left/right anterior corona radiata (L/R ACR) and the thalamus.
Results: Using two-sample t-tests ($p < 0.05$), we found that all ROIs (a) had significantly higher QA and (b) except the splenium, the LSLF and the thalamus, had significantly higher ISO for mTBI than HCs. There was no significant improvement in NQA for any ROI following ALT. Following BLT, four ROIs (the body of CC, the L/R UF and the LACR) showed significant decrease in NQA (paired t-test, $p < 0.05$) and three ROIs (the body of CC and the L/R UF) showed significant ($p < 0.05$) negative correlation between residuals of NQA and residuals of delayed memory Repeatable Battery for the Assessment of Neuropsychological Status scores.
Conclusions: BLT helped to improve WM integrity and behavior of mTBI survivors, indicating that BLT can be an effective treatment for mTBI survivors.

Blue Wavelength Light Therapy Improves Balance following Mild Traumatic Brain Injury

William D.S. Killgore[1,3], Mareen Weber[2], Michael A. Grandner[1], & David M. Penetar[3]

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Introduction

Individuals with mild traumatic brain injury (mTBI) often complain of several common cognitive and psychomotor symptoms, including persistent difficulties with balance and stance stability. Furthermore, up to 50% of people with an mTBI report sleep problems and fatigue. Blue wavelength light therapy has previously been shown to improve fatigue in mTBI patients. We hypothesized that blue light exposure therapy may re-entrain the circadian rhythm and improve overall sleep quality, potentially enhancing brain repair and therefore be associated with improvement in balance problems following mTBI.

Methods

Twenty-eight individuals (15 female; aged 18-48 years) who experienced an mTBI during the preceding 18 months underwent balance and stance-stability (BSS) testing while standing on a platform with feet together, eyes open, arms extended, and palms up. In a double-blind design, participants were randomly assigned to daily morning exposure with a blue-wavelength (active; n=14) or amber-wavelength (placebo; n=14) light device for 6 weeks at home (30-minutes daily, prior to 11:00am). Following treatment, participants again returned to the lab to undergo the BSS test.

Results

After 6 weeks of treatment, the active blue light group decreased body sway movement by 9.89% while the amber placebo light placebo group increased by 23.98%, $F(1,25)=4.31$, $p=.048$. Moreover, the improvement in balance/stability was found to be significantly correlated with the change in subjective sleepiness from baseline to post-treatment, but only among those in the active light group ($r=.58$, $p=.03$), but not for the placebo light condition ($r=-.31$, $p=.31$).

Conclusions

Daily morning exposure to blue light for 6 weeks led to an improvement in balance and stance stability compared to a matched light placebo and this improvement corresponded directly to the reduction in daytime sleepiness. These preliminary findings suggest that morning blue light therapy may be an effective treatment for balance problems following mTBI by improving sleep and thereby enhancing potential brain repair.

CONTROL ID: 2611220
CONTACT (NAME ONLY): Bradley Shane
PRESENTATION TYPE: Abstract
CURRENT CATEGORY: Neuroscience
Abstract

TITLE: MULTIMODAL BRAIN IMAGING IN PATIENTS RECEIVING BRIGHT LIGHT THERAPY FOLLOWING A MILD TRAUAMTIC BRAIN INJURY
AUTHORS (FIRST NAME INITIAL LAST NAME): B. R. Shane[1], J. R. Vanuk[1], S. Bajaj[1], M. Millan[1], W. D. Killgore[1]
INSTITUTIONS (ALL):
1. University of Arizona , Tucson, AZ, United States.
ABSTRACT BODY:
Purpose of Study: Individuals who suffer an mTBI may develop post-concussion syndrome symptoms including issues with attention, mood, and sleep. Research shows that morning blue light exposure leads to regular entrainment of one's circadian rhythm, resulting in improved sleep efficiency and daytime alertness. We hypothesized that morning blue light therapy (MBLT) will cause changes in the brain's function and structure that align with improved cognitive performance, mood, and sleep in patients recovering from an mTBI.
Methods Used: Thirty-one participants with sleep disturbances following documented mTBI in the past 18 months were randomly assigned to the active treatment of MBLT (7M, 8F, mean age=23±7.5 years) or placebo condition of amber light therapy (ALT) (7M, 9F, mean age=23±7.1 years). Neurocognitive testing and brain magnetic resonance imaging were conducted at baseline and after 6 weeks of treatment.
Summary of Results: In the MBLT group, voxel based morphometry showed increased gray matter volume in the left (p<.001) and right pulvinar (p=.009) between pre-and post treatment. Resting state functional connectivity demonstrated a positive significant correlation between the pulvinar and parietal area in the left (p-FDR=.003) and right (p-FDR<.001) hemispheres. Diffusion tensor imaging showed an increase in fractional anisotropy (FA) between the left parietal and pulvinar (2-sample t-test, p=.063). Cognitive performance analyses yielded a significant correlation between residual FA and residual Repeatable Battery for the Assessment of Neuropsychological Status total (r=.805, p=.016) and visuospatial constructive (r=0.865, p=.059) scores. Mood analysis showed a correlation (r=-.689, p=.059) between residual patient health questionnaire score, measuring depression, and residual FA. There were no significant correlations between brain changes and sleep data. ALT did not show significant brain changes or correlations with behavior.
Conclusions: MBLT appears to promote structural and functional pathways within the visuospatial processing system after an mTBI. The improvement in the brain's functional and structural strength, mood, and neurocognitive performance suggests MBLT may be an effective non-pharmacological treatment for mTBI. The extent to which these changes are mediated by sleep remains to be determined.
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AWARDS: WAFMR/WSPR Outstanding Student Research Awards

Abstract ID: 176762

HEART RATE VARIABILITY DURING LIGHT EXPOSURE AND SUBSEQUENT NETWORK CONNECTIVITY PATT

Presentation Type: Poster

Member Status: Student Member

Abstract Status: Complete / Locked

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Topic

1st choice: Behavioral Medicine
2nd choice: Individual Differences

Abstract Body

Heart rate variability (HRV) reflects, in part, parasympathetic control and may relate to alertness, as preliminary data suggest that lower study examined the association between changes in HRV following exposure to bright light and the strength of functional connectivity of internally focused default mode network or DMN; externally focused task positive network or TPN). This investigation was motivated by t between DMN and TPN. Twenty healthy young adults received 30 minutes of morning bright light; resting HRV was recorded for 5 minut state fMRI were then obtained for functional connectivity analysis. Increases in HRV in response to light predicted greater connectivity b cingulate cortex; left angular gyrus). Increased HRV in response to light exposure was associated with reduced vigilance, and aberrant f increase in HRV in response to light may index a propensity towards reduced vigilance that results from increased coupling and inefficie

Funding Information

USAMRMC/CDMRP

Comments

Lab Affiliation

Affiliation

University of Arizona Psychophysiology Lab;

Social, Cognitive, and Affective Neuroscience Lab

Short Wavelength Light Therapy Facilitates Recovery from Mild Traumatic Brain Injury

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Background: Mild traumatic brain injury (mTBI) or "concussion" is among the most common wounds experienced by military Service members. Most mTBIs resolve without complications, but a substantial minority of individuals complain of persisting cognitive and psychomotor symptoms, including poor attention and concentration, irritability, headaches, and difficulties with balance. Furthermore, up to 50% of people with an mTBI report sleep problems and fatigue that may persist for years after their injury. Many of these sleep-related problems may be due to perturbations of the normal circadian rhythm. We have been conducting a clinical trial of the efficacy of blue wavelength light therapy for improving sleep, circadian rhythmicity, and symptom recovery in patients with recent mTBIs. We hypothesized that regular morning blue light exposure therapy may re-entrain the circadian rhythm and improve overall sleep quality, potentially enhancing brain repair, potentially leading to improvement in brain functioning, symptom expression, vigilance, and balance problems.

Methods: Twenty-eight individuals (15 female; aged 18-48 years) who experienced an mTBI during the preceding 18 months underwent a comprehensive neuropsychological evaluation, assessment of morningness-eveningness chronotype, functional and structural neuroimaging, and balance and stance-stability (BSS) testing using a sensitive weight-displacement platform. In a double-blind design, participants were randomly assigned to daily morning exposure with a light device fitted with a 10 x 6 array of light emitting diodes in the blue- (active; n=14) or amber-wavelength (placebo; n=14). Participants used the device for 6 weeks at home (30-minutes daily, prior to 11:00am). Following treatment, participants again returned to the lab to undergo all assessments and scans.

Results: After 6 weeks of daily treatment, the active blue light group led to an increase in morning chronotype scores compared to the amber placebo light ($p = .044$). Functional connectivity analysis showed that the blue light condition showed a significant enhancement of connectivity between the left thalamus and rostral anterior cingulate gyrus ($p < .05$, FWE corrected), while no difference was observed for the amber placebo condition. Cortico-thalamic connectivity was correlated with greater vigilance at both time points, and the increased thalamo-cortical connectivity was directly correlated with change in morning chronotype ($r=.41$, $p=.039$) from pre-to post treatment, and with higher morning chronotype scores after the treatment period ($r=.61$, $p=.001$). In terms of balance and stance-stability, the blue light condition showed a 38.9% greater

improvement in stability relative to those receiving the amber placebo condition (p=.027).

Conclusion: Among a sample of patients with recent mTBI, daily morning exposure to blue-wavelength light for 6 weeks led to a shift in morning chronotype (i.e., greater morningness), which was associated with increased thalamo-cortical functional connectivity, reduced attentional lapses, and improvement in balance and stance-stability compared to a matched amber light placebo condition. These preliminary findings are consistent with recent evidence suggesting that blue light therapy may reduce fatigue among those with concussion but further suggest that morning blue light therapy may be an effective treatment for enhancing vigilance and improving balance problems following mTBI.

Blue Wavelength Light Therapy Reduces Daytime Sleepiness following Mild Traumatic Brain Injury

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Objective

Excessive daytime sleepiness and fatigue are some of the most common symptoms of mild traumatic brain injury (mTBI), affecting approximately 50% of patients with recent concussions. Emerging evidence suggests that exposure to blue wavelength light in the morning hours may provide an effective treatment for fatigue problems in many mTBI patients, but it is unclear whether this also affects self-reported sleepiness. Here we tested the effectiveness of a six-week regimen of morning blue wavelength light therapy on daytime sleepiness in individuals with mTBI.

Participants and Methods

Thirty participants (15 female; aged 18-45 years) with a history of mTBI during the previous 18 months completed the Epworth Sleepiness Scale (ESS) and several other questionnaires at baseline and again following 6 consecutive weeks of 30-minute daily treatment with either a blue-wavelength (active; n=15) or amber-wavelength (placebo; n=15) light device at home, within 2 hours of awakening each morning.

Results

Mixed ANOVA, with covariation for the number of days of light used, presence of baseline sleep disturbance, and total sleep obtained on the baseline night, showed a significant reduction in ESS scores for the blue compared to the amber light group ($p=.04$). Furthermore, 86% of those exposed to blue light showed a decline in sleepiness scores whereas only 40% of those exposed to amber light showed a decline ($p=.008$).

Conclusions

Among individuals with mTBI, six weeks of daily treatment with morning blue wavelength light led to a significant improvement in daytime sleepiness relative to placebo. Because morning exposure to blue light suppresses melatonin and phase advances the circadian rhythm, it is likely that these effects are due to improvement in sleep and daytime alertness due to entrainment of the circadian system. These preliminary findings suggest that blue wavelength light therapy may be an effective treatment for reducing sleepiness in patients with mTBI.

Changes in Heart Rate Variability Due to Light Exposure Predict Frontoparietal Connectivity

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Acute exposure to blue light increases alertness and performance on the Psychomotor Vigilance Task (PVT). Preliminary data from our lab has also shown that smaller changes in heart rate variability (HRV), a measure of cardiac reactivity, can predict PVT performance during bright light exposure. We hypothesized that individuals who show smaller increases in HRV during light exposure (presumably reflecting greater alertness and associated sympathetic tone) would have greater post-exposure frontoparietal connectivity.

Twenty healthy 18-30 year olds underwent a half-hour acclimation period at 9:45 a.m. in low amber light (baseline), followed by a half-hour exposure to bright light (blue or amber) at 10:15 a.m. Participants then underwent a six-minute resting state functional magnetic resonance imaging (fMRI) scan at 3T within 10 minutes of cessation of light exposure. Regions of interest were placed in frontal and parietal areas of the cortex as defined by the Automated Anatomical Labeling Atlas. Functional connectivity was analyzed utilizing the CONN toolbox and SPM12, with $p<.05$, FDR corrected.

Smaller change in HRV from baseline in response to the bright light exposure, and better PVT performance, correlated positively with increased functional connectivity between the Left Angular Gyrus, and Left Middle Frontal Gyrus; in contrast, it was associated with greater negative functional connectivity between the Left Middle Frontal Gyrus and Right Superior Frontal Orbital Gyrus.

During light exposure, attenuated change in HRV was associated with increased functional connectivity within the left fronto-parietal attention network, and better vigilance performance. Findings suggest a link between sympathetic vagal tone as measured by HRV and brain function that is directly associated with faster response times. The HRV response to light exposure might potentially serve as a trait marker of vulnerability to cognitive decline during sleepiness or fatigue.

The Effects of Light Exposure on Heart Rate Variability Predict Sleepiness and Vigilance

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Heart Rate Variability (HRV) has been shown to increase at the onset of sleep. Interestingly, exposure to blue wavelength light prior to sleep can inhibit this increase, suggesting a possible biomarker of increased alertness. In addition, acute exposure to blue light has been demonstrated to increase alertness, reduce sleepiness, and increase performance on the Psychomotor Vigilance Test (PVT), but this has not been directly associated with HRV. We hypothesized that blue light exposure would decrease HRV and increase performance on the PVT.

Twenty healthy 18-30 year olds underwent a half hour baseline acclimation period in low amber light at 9:45 a.m., followed by a half hour exposure to bright blue light (469 nm; n=10) or bright amber light (578 nm; n=10). HRV was assessed during a 5 minute resting condition at baseline and during bright light exposure. A change score was calculated between these two resting periods. As a measure of sustained attention, the PVT was administered during the final 10 minutes of the bright light exposure.

There was no significant difference in baseline HRV, performance on the PVT, or sleepiness between the two light conditions. Both groups showed an increase in HRV between baseline and the bright light exposure (p=.001). However, smaller HRV change scores were associated with fewer lapses in vigilance (p=.003) and faster reaction time (p=.001) on the PVT.

Contrary to expectations HRV increased for both wavelengths of bright light. However, consistent with our hypotheses, individuals with inhibited HRV increases during light exposure, regardless of wavelength, had better performance on the PVT. Findings suggest that smaller increases in HRV during bright light exposure, regardless of wavelength, may be associated with better sustained attention. Future work may focus on the role of individual differences in HRV during exposure to light on performance during various cognitive tasks.

Exposure to Blue Wavelength Light is Associated with Increased Dorsolateral Prefrontal Cortex Responses, and Increases in Response Times During a Working Memory Task

Anna Alkozei[1] , Sarah Markowski, Derek Pisner, Andrew Fridman & William D.S. Killgore[1]

[1] University of Arizona, Department of Psychiatry

Objective

Consistent long-term exposure to blue enriched white light has been associated with increases in self-reported alertness, concentration, work performance and decreases in fatigue and daytime sleepiness. Blue light has also been shown to lead to immediate functional brain changes during the light exposure, but the effects of blue light on functional brain responses during cognitive tasks *after* cessation of light exposure remain unclear.

Participants and Methods

Thirty-five healthy 18-32 year olds (18 females, mean age = 21.79) were randomized to receive a 30-minute exposure to either blue (active) (n=17) or amber (placebo) light (n=18), immediately followed by a working memory task (N-Back task) during functional magnetic resonance imaging (fMRI). All exposure was completed in the morning, following normal sleep at home.

Results

In contrast to placebo, participants in the blue light group showed significantly greater activation within the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) with increases in working memory load. Participants in the blue group responded faster during conditions of high cognitive load than participants in the placebo group. In addition, with increases in activation within the VLPFC, participants showed faster reaction times (r = -.35, p = .04) and more efficient responding (i.e., answered more items correctly per second) (r = .40, p = .01) during conditions of greater cognitive load.

Conclusions

The results suggest that a short single exposure to blue light is sufficient to produce measurable changes within the DLPFC and VLPFC, brain areas recruited during heavy cognitive load. This may explain why previous studies have reported increases in subjective alertness and performance after long-term blue light exposure. These findings may have important implications for using blue light as a tool to increase alertness, and response times in a variety of work settings that require alertness, and quick decision-making.

Presented at the: 30th Annual Meeting of the Associated Professional Sleep Societies; June 11-15, 2016; Denver, CO.

Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli

Anna Alkozei[1], Sarah Markowski, Derek Pisner, Andrew Fridman, & William D.S. Killgore[1]

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Introduction

Blue wavelength light has been used as an effective treatment for depression and seasonal affective disorder and is associated with increased arousal, reduced fatigue, and even re-entrainment of the circadian rhythm of sleep and wake. While the neurobiological mechanisms behind these effects remain unclear, blue light has been shown to influence the locus coeruleus, which in turn releases norephinephrine throughout the cortex, affecting a wide range of functions. We aimed to investigate how 30 minutes of blue light exposure affects subsequent functional brain responses during an emotional anticipation task.

Methods

Thirty-five healthy adults (18 females, mean age = 21.58) were randomized to receive a thirty-minute exposure to either blue (active) or amber (placebo) light. Within a half hour following cessation of the light, participants completed an emotional anticipation task (EAT) during fMRI at 3T. The EAT included conditions during which participants were anticipating certain reward, certain threat, and uncertain reward/threat. Data were analyzed using SPM12

Results

In contrast to the amber placebo light, participants in the blue light group showed significantly reduced activation within the rostral ACC during uncertain versus certain anticipation of reward ($p<.05$, false discovery rate corrected).

Conclusion

A single thirty-minute exposure to blue wavelength light versus exposure to a placebo amber wavelength light was associated with reduced activation within the ACC during a situation involving unpredictability of aversive or reward stimuli versus conditions with certain predictability of reward stimuli. These findings suggest that blue wavelength light, in addition to its effects on alertness, fatigue, and sleep, also has the potential to enhance emotional activation within the ACC during anticipation of rewarding stimuli, possibly due to an increase in norepinephrine and its effects on dopaminergic reward prediction-error signals. Future work should examine the effects of blue light on emotional processing during periods of insufficient sleep.

Presented at the: 32nd Annual Meeting of the Associated Professional Sleep Societies; June 2-6, 2018; Baltimore, MD.

Blue Wavelength Light Therapy Improves Balance following Mild Traumatic Brain Injury

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Objective

Mild traumatic brain injury (mTBI) is associated with a number of cognitive and psychomotor symptoms, including persistent difficulties with balance and stance stability, and sleep problems in up to 50% of patients. Blue wavelength light therapy has previously been shown to improve fatigue in mTBI patients. We hypothesized that improvement of sleep via circadian re-entrainment with blue light therapy would enhance brain repair and lead to improvement in balance problems following mTBI.

Participants and Methods

Twenty-eight individuals (15 female; aged 18-48 years) with a history of recent mTBI underwent balance and stance-stability (BSS) testing while standing on a platform with feet together, eyes open, with arms extended, palms up. Participants were randomly assigned to use either a blue-wavelength (active; n=14) or amber-wavelength (placebo; n=14) light device during 6 weeks of at-home light exposure therapy (30-minutes daily, prior to 11:00am). Following treatment, participants again returned to the lab to undergo the BSS test.

Results

Compared to baseline, the active blue light group decreased body sway movement by 9.89% while the amber placebo light placebo group increased by 23.98%(p=.048. The change in stance stability was correlated with the change in subjective sleepiness from baseline to post-treatment in the active light group (r=.58, p=.03), but not the placebo light condition (r=-.31, p=.31).

Conclusions

Six weeks of daily morning blue light therapy was associated with an improvement in stance stability compared to a matched placebo and this improvement corresponded directly to the reduction in daytime sleepiness. Blue light therapy may be an effective treatment for balance problems following mTBI.

Increases in Prefrontal Activation After Exposure to Blue versus Amber Wavelength Light During Cognitive Load

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Objective

Blue light exposure has been shown to lead to increases in alertness, and has been used as a treatment for depression. Considering difficulties concentrating are a symptom of a range of psychiatric disorders, the effects of blue light on cognitive performance are important to explore further. The aim of this study was to investigate differences in functional brain responses during a cognitive task after 30 minutes of blue versus placebo (amber) light exposure.

Participants and Methods

Thirty-five healthy 18-32 year olds (18 females, mean age = 21.79) were randomized to receive a 30-minute exposure to either blue (active) (n=17) or amber (placebo) light (n=18), immediately followed by a working memory task (N-Back task) during functional magnetic resonance imaging (fMRI).

Results

In contrast to placebo, participants in the blue light group showed significantly greater activation within the dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC), and showed faster reaction times with increases in cognitive memory load. In addition, increases in activation within the VLPFC correlated positively with reaction times (r = -.35, p = .04) during conditions of greater cognitive load.

Conclusions

The results suggest that a short single exposure to blue light is sufficient to produce measurable changes within the DLPFC and VLPFC, brain areas recruited during heavy cognitive load. These findings may have important implications for using blue light as a tool to increase alertness, and concentration in clinical populations who often report difficulties with attention as a symptom, including depression, generalized anxiety disorder, and post-traumatic stress disorder.

Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli

Anna Alkozei, Sarah M. Markowski, Derek Pisner, Andrew Fridman, Bradley R. Shane, John R. Vanuk, Sara A. Knight, & William D.S. Killgore

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Objective

Blue wavelength light has been used as an effective treatment for depression and seasonal affective disorder. While the neurobiological mechanism behind this effect remains unclear, blue light has been shown to influence the locus coeruleus, which in turn releases norephinephrine throughout the cortex, affecting a wide range of functions. We aimed to investigate how 30 minutes of blue light exposure affects functional brain responses during an emotional anticipation task.

Participants and Methods

Thirty-five healthy adults (18 females, mean age = 21.58) were randomized to receive a thirty-minute exposure to either blue (active) or amber (placebo) light, immediately followed by an emotional anticipation task during fMRI. The EAT included conditions during which participants were anticipating certain reward, certain threat and uncertain reward/threat.

Results

In contrast to amber light, participants in the blue light group showed significantly reduced activation within the rostral ACC during uncertain anticipation versus certain anticipation of reward, in comparison to individuals in the amber condition.

Conclusions

A single thirty-minute exposure to blue wavelength light versus exposure to a placebo amber wavelength light was associated with reduced activation within the ACC during a situation involving unpredictability of aversive and reward stimuli versus predictability of reward stimuli. The findings suggest that blue wavelength light has the potential to enhance activation within the ACC during certain reward anticipation, possibly due to an increase in norepinephrine, leading to an increase in the effectiveness of dopaminergic reward prediction-error signals. This increase may partly explain the beneficial effect of blue light as a treatment for individuals with depression.

Blue Wavelength Light Therapy Improves Balance following Mild Traumatic Brain Injury

William D.S. Killgore[1,3], Mareen Weber[2], & David M. Penetar[3]

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Objective

Mild traumatic brain injury (mTBI) is associated with a number of cognitive and psychomotor symptoms, including persistent difficulties with balance and stance stability. Additionally, mTBI has been associated with sleep problems and fatigue in up to 50% of patients. Blue wavelength light therapy has previously been shown to improve fatigue in mTBI patients. We hypothesized that improvement of sleep via circadian re-entrainment with blue light exposure therapy would enhance brain repair and therefore be associated with improvement in balance problems following mTBI.

Participants and Methods

Twenty-eight individuals (15 female; aged 18-48 years) with a history of mTBI during the preceding 18 months underwent balance and stance-stability (BSS) testing while standing erect on a platform with feet together, eyes open, with arms extended, palms up. In a double-blind design, participants were randomly assigned to use either a blue-wavelength (active; n=14) or amber-wavelength (placebo; n=14) light device. Participants then underwent 6 weeks of at-home light exposure therapy (30-minutes daily, prior to 11:00am). Following treatment, participants again returned to the lab to undergo the BSS test.

Results

Compared to baseline, the active blue light group decreased body sway movement by 9.89% while the amber placebo light placebo group increased by 23.98%, $F(1,25) = 4.31$, $p = .048$. Furthermore, the change in stance stability was found to be significantly correlated with the change in subjective sleepiness from baseline to post-treatment, but only for the active light group ($r = .58$, $p = .03$), but not for the placebo light condition ($r = -.31$, $p = .31$).

Conclusions

Six weeks of daily morning exposure to BLUE light was associated with an improvement in stance stability compared to a matched placebo and this improvement corresponded directly to the reduction in daytime sleepiness. Blue light therapy may be an effective treatment for balance problems following mTBI.

Blue Wavelength Light Therapy Reduces Daytime Sleepiness following Mild Traumatic Brain Injury

William D.S. Killgore[1,2] & Mareen Weber[3]

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Objective

Some of the most common symptoms of mild traumatic brain injury (mTBI) include excessive daytime sleepiness and fatigue, with approximately 50% of affected individuals reporting such problems. Some evidence suggests that morning blue wavelength light therapy may provide an effective treatment for fatigue problems in mTBI patients. Here we tested a six-week program of blue wavelength light therapy for its effectiveness at reducing daytime sleepiness in individuals with mTBI.

Participants and Methods

Thirty individuals (15 female; aged 18-45 years) with a history of mTBI during the preceding 18 months completed the Epworth Sleepiness Scale (ESS) and several other questionnaires at baseline and again after 6 consecutive weeks of treatment. Participants were randomly assigned to use either a blue-wavelength (active; n=15) or amber-wavelength (placebo; n=15) light device at home for 6 weeks (30-minutes each morning).

Results

Repeated measures ANOVA, controlling for the number of days of light used, baseline sleep disturbance, and total sleep obtained on the baseline night, showed a significant reduction in ESS scores for the blue light group but not the amber light group ($p=.04$). Furthermore, 86% of those receiving blue light showed a decline in sleepiness scores whereas only 40% of those receiving amber light showed a decline ($p=.008$).

Conclusions

Six weeks of daily morning treatment with blue wavelength light therapy was associated with a significant improvement in daytime sleepiness compared to placebo among individuals with mTBI. Because morning exposure to blue light has been shown to suppress melatonin and phase advance the circadian rhythm, it is likely that the observed effects are due to improvement in sleep and daytime alertness due to entrainment of the circadian system. Blue wavelength light therapy may be an effective means for reducing sleepiness in patients with mTBI.

Exposure to Blue Wavelength Light Suppresses Anterior Cingulate Cortex Activation in Response to Uncertainty During Anticipation of Negative or Positive Stimuli

Anna Alkozei[1] & William D.S. Killgore[1]

[1] University of Arizona, Department of Psychiatry

Objective

Blue wavelength light has been used as an effective treatment for some types of mood disorders, including depression and seasonal affective disorder. The neurobiological mechanism behind this effect, however, remains unclear. One possible explanation for this effect may be that blue light influences functioning of the emotion-regulation neurocircuitry when processing emotional stimuli. We hypothesized that acute exposure to blue wavelength light would directly affect the functioning of the ventromedial prefrontal cortex, amygdala, insula, and anterior cingulate cortex (ACC) during an emotional anticipation task.

Participants and Methods

Twenty-nine healthy 18-32 year olds (15 females, mean age = 21.57) were randomized to receive an acute thirty-minute exposure to either blue (active) (n=14) or amber (placebo) light (n=15), immediately followed by functional magnetic resonance imaging (fMRI). During scanning, participants completed a task that involved presentation of cues that portended an upcoming positive or negative emotional stimulus of certain or uncertain valence. Participants also reported on their depressive symptoms using the Beck Depression Inventory (BDI-II).

Results

In contrast to placebo light, participants in the blue light group showed significantly ($p < .003$) reduced activation within the rostral and dorsal ACC during uncertain anticipation (i.e., uncertainty regarding whether a positive or negative stimulus would be shown) in comparison to certain anticipation (i.e., assured exposure to a positive stimulus). Notably, within the blue, but not the placebo group, greater depressive symptoms correlated with deactivation within the rostral ACC ($r=-.59$, $p<.02$).

Conclusions

Findings suggest that blue light exposure may lead to suppression of emotional brain responses during anticipation of uncertain outcomes. As this effect was correlated with greater depressive symptoms, these findings may point to one potential neurobiological mechanism by which light exposure improves mood.

Exposure to Blue Wavelength Light is Associated with Increased Dorsolateral Prefrontal Cortex Responses During a Working Memory Task

Anna Alkozei[1] & William D.S. Killgore[1]

[1] University of Arizona, Department of Psychiatry

Objective

Consistent long-term exposure to blue enriched white light has been associated with increases in self-reported alertness, concentration, work performance and decreases in fatigue and sleepiness. The aim of this study was to investigate whether a short single exposure to blue light would lead to measurable changes in functional brain responses during a working memory task.

Participants and Methods

Twenty-nine healthy 18-32 year olds (15 females, mean age = 21.79) were randomized to receive a 30-minute exposure to either blue (active) (n=14) or amber (placebo) light (n=15), immediately followed by a working memory task (N-Back task) during functional magnetic resonance imaging (fMRI).

Results

In contrast to placebo, participants in the blue light group showed significantly greater activation within the dorsolateral prefrontal cortex (DLPFC) with increases in working memory load (two back>zero back) (k = 69; x = -48, y = 14, z = 22; p = .01, FWR corrected at the cluster level). There was a trend that participants in the blue group had faster reaction times during conditions of high cognitive load in comparison to participants in the placebo group (M_{Blue} = 574.09ms (203.81ms), $M_{Placebo}$ = 692.89ms (222.71ms), p = .10).

Conclusions

The results suggest that a short single exposure to blue light is sufficient to produce measurable changes within the DLPFC, a brain area recruited during heavy cognitive load. This may explain why previous studies have reported increases in subjective alertness and performance after long-term blue light exposure. Our results point in the direction that blue light exposure may be associated with better performance, albeit the results did not reach statistical significance. It is possible that while 30 minutes of blue light exposure is sufficient to lead to increases in activation within certain brain areas, longer exposure is necessary to produce objective behavioral changes. Replication with a larger sample size and varying durations of blue light exposure is therefore necessary.

The Effect of Bright Light Therapy on Improving Sleep Among Individuals with Mild Traumatic Brain Injury

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Background:
Sleep problems, including excessive daytime sleepiness, are seen in about 50% of patients with mild Traumatic Brain Injuries (mTBI), and can negatively affect mood and cognitive performance. Since blue wavelength light has a strong influence on sleep patterns, melatonin suppression, and circadian rhythmicity, we hypothesized that 6-weeks of daily exposure to Morning Blue Light Therapy (MBLT) compared to an amber Sham Placebo Light Treatment (SPLT) would significantly improve daytime sleepiness from pre- to post-treatment.

Methods:
Twenty-nine subjects (ages 18 -48), who experienced a mTBI in the past 18-months coupled with comorbid sleep difficulties, underwent an six-week light therapy using a bright light device every morning for 30 minutes. 14 subjects received MBLT and 12 subjects received SPLT. Participants also reported their daytime sleepiness using the Epworth Sleepiness Scale (ESS) before and after treatment. A mixed ANOVA was used to analyze ESS ratings between the two groups.

Results:
There was a significant treatment x time interaction on ESS scores ($F(1,24)=4.485$, $p=0.04$). Post-hoc comparisons showed that, on average, individuals in the MBLT group showed a 15.08% decrease in daytime sleepiness ratings on the ESS compared to a 4.26% increase for individuals in the SPLT group ($p<.05$).

Conclusions:
The findings suggest that MBLT is an effective treatment for reducing post-concussion daytime sleepiness. Further work will be necessary to evaluate the effectiveness of MBLT on objective measures of sleep and sleepiness and the underlying neural mechanisms, as well as whether these changes are associated with improvements in cognitive functioning and emotional wellbeing.

Abstract submitted for presentation at the SoBP 201, Toronto, Canada May 14-16, 2015.
Support: W81XWH-11-1-0056

Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli

Anna Alkozei[1] , Sarah Markowski, Derek Pisner, Andrew Fridman & William D.S. Killgore[1]

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Objective

Blue wavelength light has been used as an effective treatment for depression and seasonal affective disorder. While the neurobiological mechanism behind this effect remains unclear, blue light has been shown to influence the locus coeruleus, which in turn releases norephinephrine throughout the cortex, affecting a wide range of functions. We aimed to investigate how 30 minutes of blue light exposure affects functional brain responses during an emotional anticipation task.

Participants and Methods

Thirty-five healthy adults (18 females, mean age = 21.58) were randomized to receive a thirty-minute exposure to either blue (active) or amber (placebo) light, immediately followed by an emotional anticipation task during fMRI. The EAT included conditions during which participants were anticipating certain reward, certain threat and uncertain reward/threat.

Results

In contrast to amber light, participants in the blue light group showed significantly reduced activation within the rostral ACC during uncertain anticipation versus certain anticipation of reward, in comparison to individuals in the amber condition.

Conclusions

A single thirty-minute exposure to blue wavelength light versus exposure to a placebo amber wavelength light was associated with reduced activation within the ACC during a situation involving unpredictability of aversive and reward stimuli versus predictability of reward stimuli. The findings suggest that blue wavelength light has the potential to enhance activation within the ACC during certain reward anticipation, possibly due to an increase in norepinephrine, leading to an increase in the effectiveness of dopaminergic reward prediction-error signals. This increase may partly explain the beneficial effect of blue light as a treatment for individuals with depression.

Presented at the: 71st Annual Scientific Convention of the Society for Biological Psychiatry; May 12-14, 2016; Atlanta, GA.

Exposure to blue wavelength light is associated with increases in bidirectional amygdala-DLPFC connectivity at rest

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This study was supported by a U.S. Army US Army MOMRP Grant (WDSK) as well as by an Arizona Health Education Centers (AHEC) Research Grant (AA). The authors have no other conflict of interest.

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Abstract

Daily exposure to blue wavelength has been used as a treatment method for certain mood disorders, such as seasonal affective disorder as well as non-seasonal depression; however, the underlying mechanisms behind these effects remain not well understood. We investigated the effects of a single dose of 30 minutes of blue wavelength light (n = 17) versus non-blue amber light (n = 12) exposure in a sample of healthy adults on subsequent resting-state functional connectivity and directed connectivity, and associations with changes in affect. Individuals who received blue versus amber wavelength light showed greater positive connectivity between the right amygdala and a cluster of voxels within the left dorsolateral prefrontal cortex (DLPFC). In addition, using granger causality, the findings showed that individuals who received blue wavelength light displayed greater bidirectional information flow between these two regions. Furthermore, the strength of amygdala-DLPFC functional connectivity was associated with greater decreases in negative mood for the blue, but not the amber light group. The results suggest that blue light exposure may positively influence mood by modulating greater information flow between the amygdala and the DLPFC, which may result in greater engagement of cognitive control strategies that are needed to regulate arousal and mood. Future research will be necessary to investigate whether it is possible to enhance these beneficial effects of blue wavelength light exposure on mood further, such as by using blue light during practice of emotion regulation strategies.

Introduction

Light has a powerful effect on mood. A sunny day often seems to enhance positive outlook and helping behavior (Beecher et al., 2016; Guéguen & Lamy, 2013), and it is well established that bright light can be an effective treatment for mood disorders, with effects as potent as some pharmacologic treatments(Maruani & Geoffroy, 2019). Even a single half-hour exposure to bright light seems to improve mood (Aan Het Rot, Miloserdov, Buijze, Meesters, & Gordijn, 2017). Moreover, the wavelength of light also seems to be important to these effects, with considerable evidence now pointing to the importance of blue wavelengths (~460nm) on mood and cognition. Studies have shown that acute exposure to blue wavelength or bright light leads to immediate increases in simple alertness and attention (Cajochen et al., 2005; Phipps-Nelson, Redman, Schlangen, & Rajaratnam, 2009) as well as more complex cognitive functions such as improved working memory performance (Alkozei, Smith, Pisner, et al., 2016) and short-term verbal memory (Alkozei, Smith, Dailey, Bajaj, & Killgore, 2017). Daily morning blue wavelength light exposure over several weeks has also been used as an effective treatment for seasonal and non-seasonal depression (Even, Schröder, Friedman, & Rouillon, 2008; Glickman, Byrne, Pineda, Hauck, & Brainard, 2006; Perera et al., 2016; Strong et al., 2009), certain sleep disorders, such as delayed sleep phase syndrome (Lack, Bramwell, Wright, & Kemp, 2007) and to improve symptoms of fatigue in individuals with neurological conditions, such as acquired brain injury (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014). The exact mechanisms underlying these beneficial effects of blue light on emotion and cognition, however, are not well understood.

Growing evidence suggests that many of these mood and cognitive effects of light may be mediated by the non-image forming pathways of the visual system. It is well documented that bright light, especially within the blue wavelengths, stimulates intrinsically photosensitive retinal ganglion cells (ipRGCs) which transmit signals to several sub-cortical nuclei. These include the suprachiasmatic nucleus (SCN) in the hypothalamus, which has a strong influence on the circadian rhythm of sleep and wake (Berson, Dunn, & Takao, 2002; Dijk & Archer, 2009). Extensive research has shown that exposure to bright light, particularly in the blue wavelengths, leads to activation of the SCN, which in turn sends signals to the pineal gland to stop the production of the hormone melatonin(Cajochen, 2007; Chellappa et al., 2011). Melatonin is released and suppressed daily in accordance with the circadian rhythm, and its release precedes sleep onset (Pandi-Perumal et al., 2007). Consequently, exposure to blue light at times that are out of phase with the normal circadian rhythm can lead to disruptions in the normal sleep-wake schedule. For instance, blue light exposure during the night, when melatonin levels are high, appears to lead to increases in alertness by suppressing the immediate production of melatonin(Cajochen et al., 2005) and phase delaying the circadian onset of sleep. Notably, by targeting light exposure to specific times in the day, daily melatonin release can be shifted to treat certain sleep disorders (e.g., to treat delayed sleep phase syndrome, daily morning bright light exposure over at least 12 days leads to a phase advance of melatonin release and earlier sleep onset) (Chesson et al., 1999). It has been proposed that seasonal depression is associated with a disturbance in the circadian rhythm during the darker winter months, and that among such individuals, daily bright light

treatment may produce its mood-enhancing effect, in part, by “resynchronizing” the biological clock (Pail et al., 2011).

While circadian factors have been suggested for the outcomes mentioned above, they do not appear to account for all of the mood and cognitive enhancing effects of blue light. For example, suppression of melatonin cannot effectively account for the alerting effects of light during the middle of the day, when melatonin levels are already naturally low, or for the effects of light on non-seasonal depression (i.e., during times of year when sunlight is more prevalent). Direct projections from the ipRGCs, as well as indirect projections from the SCN, to other brain regions involved in emotion and cognition, are proposed to explain some of those non-circadian effects(Rautkyä, Puolakka, & Halonen, 2011). For example, the SCN projects to the brainstem, particularly the locus coeruleus (LC), which is a major source of brain norepinephrine (NE) and has multiple cortical projections(Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Florin-Lechner, Druhan, Aston-Jones, & Valentino, 1996; Foote, Berridge, Adams, & Pineda, 1991). Accordingly, the alerting effects of blue wavelength light could be partially explained by swift increases in activity within the LC in direct response to light stimulation and the subsequent release of NE throughout the cortex. In addition to simple alerting effects, NE plays a crucial role in learning, which may explain the recently demonstrated beneficial effects of blue light on verbal memory performance (Alkozei et al., 2017). Thus, exposure to blue light may exert its effects through at least two pathways, one which produces circadian effects through melatonin suppression and another that produces rapid release of NE.

It appears that depression may be characterized, in part, by a dysfunction of the NE system (Delgado & Moreno, 2000). If blue light in fact produces an acute activation of

the NE system, this could explain some of the mood enhancing aspects of direct light exposure. Some research supports this proposed mechanism, as only 50 seconds of blue wavelength light exposure (in comparison to violet light) led to increases in functional brain responses in an area of the brainstem compatible with the LC (Vandewalle et al., 2007), likely leading to increased NE release. Other studies have also shown that a longer duration of light exposure (~30 minutes) leads to increased activation within the prefrontal cortex during a working memory task, as well as increased activation within the ACC during a reward prediction task, potentially as a result of increased NE release throughout the cortex (Alkozei et al., 2017; Alkozei, Smith, & Killgore, 2016; Alkozei, Smith, Pisner, et al., 2016). While it is clear that exposure to blue light can produce immediate increases in brain activation and cognitive changes, it is not known whether these effects are due to altered patterns of intrinsic connectivity between key nodes involved in affect regulation. In addition, individuals with depression show differences in resting-state functional connectivity compared to healthy controls, such as hypoconnectivity between the amygdala and medial prefrontal cortex, which may underlie difficulties with emotion regulation (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Considering that blue wavelength light appears to lead to immediate increases in activation in the amygdala (Vandewalle et al., 2007), potentially as a result of direct projections from ipRGCs and indirect signals from the brainstem, it is possible that exposure to blue wavelength light may lead to changes in functional connectivity between the amygdala and PFC. Because negative mood states are often associated with reduced prefrontal regulation and increased amygdala activation, alterations in the strength of connectivity via light exposure may contribute to its well-established

antidepressant or mood-enhancing effect. Furthermore, investigating the effect of blue wavelength light on the directionality of information flow between brain areas, i.e., directed connectivity, would clarify the underlying mechanism of blue light exposure on brain function and cognition and emotion.

In summary, while a number of studies have shown that blue wavelength light has a beneficial effect on sleep, cognition, and emotion and some research has aimed to understand the neurobiological mechanisms underlying these effects, several questions remain unanswered. In particular, while understanding the role of blue wavelength light on increased alertness and vigilance has been the central focus of most research, the mechanisms by which blue wavelength light may lead to increases in positive affect and a reduction in depressive symptoms remain largely unknown. Here, we investigate how a single, thirty-minute exposure to blue versus non-blue (amber) light would affect subsequent (i) positive and negative affect, (ii) functional and directed brain connectivity of the amygdala with other brain regions, and (iii) how changes in affect would be associated with observed changes in functional brain connectivity. We hypothesized the following:

1. Blue light exposure would increase positive affect and decrease negative affect in comparison to amber light exposure.
2. Blue light exposure would lead to increased functional and directed functional connectivity between the amygdala and the PFC.
3. Connectivity patterns would be associated with more positive and less negative affect.

Methods

Participants

Twenty-nine healthy adults between 18-32 (M = 21.52, SD = 2.82; 16 men, 13 women) years of age took part in the study and provided useable functional and structural MRI data for analysis (out of a total of thirty-five participants). Participants completed an average of 14.1 years of education (SD = 1.95). According to self-report, all were right handed, primary English speaking, free from psychiatric, neurological, and substance use disorders, and reported a regular sleep schedule of going to bed between 10:00 pm and 1:00 am and waking between 6:00 am and 9:00 am. Participants were asked to keep their regular sleep schedule and were asked to consume their normal levels of caffeine on the day of the study. Participants were randomly assigned to the blue (n = 17) or amber light condition (n = 12) (see below). The two groups did not differ on age, sex, number of hours slept the night before the assessment, or number of reported hours slept on weeknights (see Table 1). In addition, four participants in the blue light group and four participants in the amber light group reported having had one caffeinated product on the day of the assessment. Separate data from this same study have been reported elsewhere, but the functional connectivity and mood findings reported here are novel and have not been previously published. This project was approved by the Institutional Review Board at the University of Arizona and the U.S. Army Human Research Protections Office, and all participants provided written informed consent prior to study participation.

Materials

Positive and Negative Affect Scale (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988) was used to measure positive and negative affect. Participants were asked to indicate, on a 5-point scale, the extent to which (from "very slightly to not at all" to "extremely") they were feeling a number of positive (e.g., interested, excited, proud) and negative feelings (e.g., nervous, determined, irritable) at that very moment. Total scores for positive affect (PANAS-P) and negative affect (PANAS-N) were calculated separately and each had a possible range from 10 to 50. The PANAS is a widely used measure of state affect that has shown good internal consistency, reliability and validity (Crawford & Henry, 2004).

Light exposure. The light protocol is described in detail in the Procedure section. The blue light exposure devices were commercially available Philips goLITE BLU® Energy Light devices (Model HF3321/60; Philips Electronics, Stamford, CT). The amber light devices were provided by the manufacturer for research purposes and were virtually identical to the goLITE BLU devices, with the exception of being fit with a different color LED. Each device consisted of a plastic table-mounted chassis with a 10 x 6 array of light emitting diodes (LEDs), encased in 1 x 1 cm cubical projection elements and a translucent plastic window cover. The goLITE BLU Energy Light is commercially available and has a narrow bandwidth (peaking at λ= 469 nm, at 214 Lux, and panel irradiance (mW/cm2) = 1.23 at 20 cm). The amber devices were otherwise identical to the goLITE BLU devices, with the exception that they were fitted with amber LEDs (peaking at λ = 578 nm, at 188 Lux, and total irradiance (mW/cm2) = 0.35).

Procedure

All participants completed the study procedures at the same time of day to control for circadian effects. Specifics of the procedure are detailed in our previous paper (Alkozei, Smith, Pisner, et al., 2016). In brief, at 7:45 am, participants arrived for the study and completed informed consent as well as basic demographic questionnaires and cognitive tasks. Participants completed light exposure, cognitive tests, and mood assessments in a room located next to the magnetic resonance imaging (MRI) scanner. At approximately 8:30am, participants completed the first PANAS. At 9:45am, participants underwent a "blue light washout" period in an otherwise darkened room, with only two amber light devices placed on the table in front of them for 30 minutes. This washout period was completed to ensure residual effects of outdoor and ambient lighting had dissipated before beginning the experimental light exposure manipulation. At 10:15 am, the two Washout Period light devices were replaced with the four Exposure Period devices (see Figure 1B). Specifically, during the Exposure Period, participants were randomized to receive either 30 minutes of blue (n = 17) or amber (n = 12) light exposure. The 30-minute Exposure Period was initiated by illuminating the two pairs of light devices (either blue or amber, depending on condition), with each pair mounted side by side on the desk in front of the participant, centered at the same location as the Washout Period amber lights. During the 30-minute Exposure and Washout Periods, participants maintained a forward gaze and completed several computerized practice tasks to prepare them for their time in the scanner. To minimize blue light from the computer screen, an amber tinted plexiglass shield was placed in front of the laptop screen. Immediately after the light exposure period, at approximately 10:50 am, participants completed the second

PANAS. At 11:00 am, participants were escorted to the MRI scanner, where the resting state scan was initiated at approximately 11:15 am.

Neuroimaging Methods

Neuroimaging scans were collected on Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. High resolution structural images were first acquired using a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.33 ms/ 12°) over 176 sagittal slices (256 x 256) and a slice thickness of 1 mm (voxel size = 1 x 1 x 1 mm^3). For the resting state functional scan, participants were instructed to let their mind wander while keeping their eyes open. Functional scans were acquired over 32 transverse slices (2.5 mm thickness; matrix: 88 x 84). Each volume was collected with an interleaved sequence (TR/TE/flip angle = 2 s/25 ms/90°). The voxel size of the T2* sequence was 2.5 x 2.5 x 2.5 mm^3 (i.e., with a 40% slice gap, allowing collection of 180 volumes within a 6-min acquisition time). The field of view (FOV) was 220 mm.

Resting-state preprocessing

Neuroimaging data were analyzed using the publicly available CONN functional connectivity toolbox (version 16.a; www.nitrc.org/projects/conn, RRID:SCR_009550), in conjunction with SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http:// www.fil.ion.ucl.ac.uk/spm). Raw functional images were realigned (motion corrected) and unwarped, slice-time corrected using the middle slice as the reference, and coregistered to each subject's high-resolution structural image in accordance with standard algorithms. The Artifact Detection Tool (ART; http:// www.nitrc.org/projects/artifact_detect/) was used to regress out scans as nuisance

covariates in the first-level analysis exceeding 3 SD in mean global signal intensity and scan-to-scan motion exceeding 0.5 mm. No participants were excluded for an excessive number of outlier images (i.e. greater than 20% of images flagged as outliers). These were included in addition to covariates for the 6 ridged-body parameters that characterize estimated subject motion, and used to regress out residual movement-related effects. Images were then normalized to Montreal Neurological Institute (MNI) coordinate space, spatially smoothed (8 mm full-width at half maximum), and resliced to a voxel size of 2 x 2 x 2 mm.

Functional connectivity analysis

Using a standard seed-to-voxel approach, functional connectivity analyses were performed using the default functional connectivity processing pipeline in the CONN toolbox (for details, see(Whitfield-Gabrieli & Nieto-Castanon, 2012)). In this processing pipeline, physiological and other spurious sources of noise were estimated with the aCompCor method(Behzadi, Restom, Liau, & Liu, 2007; Chai, Castañón, Öngür, & Whitfield-Gabrieli, 2012) and subsequently removed together with the movement- and artifact-related covariates mentioned above. The residual blood oxygen level dependent (BOLD) time-series was then band-pass filtered (.01 Hz–.1 Hz). Every participant's structural image was segmented into gray matter, white matter, and cerebral spinal fluid using SPM12. Confounding effects of white matter and cerebral spinal fluid were removed through linear regression. Two seed regions of interest (ROIs) were placed corresponding to the left and right amygdala as defined by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). After the removal of confounds, the residual BOLD time-series from the bilateral amygdala seed ROIs were averaged to

generate a mean time-series. Bivariate correlation maps (Fisher-transformed) were then computed with all other voxels in the brain to derive whole-brain connectivity maps. A group-level approach was used to compare differences in connectivity between the blue and amber groups controlling for the effects of age and sex. Reported results were corrected for multiple comparisons (height threshold $p < 0.001$, two-sided; cluster threshold $p < 0.05$, cluster-size FDR-correction).

Directed functional connectivity analysis: Granger causality

In a second step, we investigated the strength of directionality of information flow (i.e., granger causality (GC)) between the amygdala and significant clusters from the functional connectivity analysis, using parametric GC (Dhamala, Rangarajan, & Ding, 2008a, 2008b). Granger causality is a way to investigate causality between two time series, i.e., the extent to which one time series can predict the other. The strength of GC was estimated by quantifying the inter-relationships between their corresponding oscillatory mechanisms as a function of frequency (f) of oscillations. For that, first the raw time-series data were band pass filtered using the Butterworth filter design with a higher cutoff frequency of 0.0028 Hz (f_1) and a lower cutoff frequency of 0.1 Hz (f_2). Next, the time-series for the bilateral amygdala and significant clusters from the functional connectivity analysis was zero-mean corrected in order to remove slow trends and physiological noise. Furthermore, the optimal model order for the parametric approach was calculated by comparing power spectra from the parametric and non-parametric approaches (Dhamala et al., 2008a). Different model orders from 1 to 10 were tested, and the model order that yielded the lowest power difference was selected.

The threshold level for statistically significant GC strength was estimated from surrogated data using permutation tests (Dhamala et al., 2008a, 2008b) (n = 2000) and a gamma function under a null hypothesis of no interdependence at the significance level of p = 0.0025 (p = 0.01/4, corrected for multiple comparisons).

Results

Affect change from pre- to post- light exposure

For PANAS-P scores, there was a significant main effect of time ($F(1, 26) = 25{,}67$, $p < 0.001$), but no time x group interaction ($F(1, 26) = .13$, $p = 0.72$) from pre- to post-light exposure. Overall, both light groups showed a decrease in their PANAS-P scores from pre- to post- light exposure (see Figure 1a).

For PANAS-N scores, there was also a significant main effect of time ($F(1, 26) = 6.15$, $p = 0.02$), but no time x group interaction ($F(1, 26) = 2.32$, $p = 0.14$) from pre- to post- light exposure. Overall, both light groups showed a decrease in their PANAS-N scores from pre- to post light exposure (see Figure 1b).

Strength of Functional Connectivity

Compared to participants in the amber light group, participants in the blue light group showed significantly greater positive connectivity between the amygdala and a cluster of voxels in the left dorsolateral prefrontal cortex (DLPFC) ($x = -28$, $y = 46$, $z = 14$, $k = 71$, volume p-FDR corrected = 0.005). We re-ran the analysis for the right and left amygdala separately and it appears that the effect was driven by the right amygdala alone ($x = -24$, $y = 46$, $z = 18$, $k = 90$, volume p-FDR corrected, $p < 0.001$) (see Figure 2). No effect for

the left amygdala was found. In summary, individuals who received blue light exposure showed significantly greater positive connectivity between the right amygdala and the left DLPFC compared to participants who received amber light.

Strength of Granger Causality

To determine the directionality of the connectivity between the right amygdala and left DLPFC, we employed GC and found that it was bidirectional. In other words, both the strength of the feed-forward (right amygdala (R. AMG) to left DLPFC (L. DLPFC)) (Figure 3a) and feed-backward (L. DLPFC to R. AMG) (Figure 3b) connectivity was significant for the blue-light group, but not the amber-light group. In Figure 3, the dotted line corresponds to a GC value of 0.0422, which represents a significance level at $p < 0.0025$ ($p = 0.01/4$, corrected for multiple comparisons).

The relationship between connectivity patterns and changes in affect

To investigate whether functional and directed connectivity was associated with changes in affect, we ran Spearman's correlations between connectivity values and PANAS change scores. We chose Spearman's correlations due to the small sample sizes and because the PANAS data violated assumptions of normality. For the blue light group, there was a statistically significant moderate negative relationship with PANAS-N change scores and functional connectivity ($\rho = -.55$, $p = 0.03$), indicating that greater functional connectivity between the amygdala and DLPFC was associated with reduced negative mood following light exposure (see Figure 4). This relationship was not present for the amber light group ($\rho = -0.18$, $p = 0.55$). The strength of the relationship for directed connectivity was much smaller and non-significant for the blue light group (feed

forward connectivity: $\rho = -0.26$, $p = 0.33$; feed backward connectivity $\rho = -0.27$, $p = 0.29$) and for the amber light group (feed forward connectivity: $\rho = -0.25$ $p = 0.45$; feed-backwards: $\rho = -0.30$, $p = 0.73$). There were no significant correlations between connectivity patterns and PANAS-P change scores.

Discussion

This study aimed to investigate the effects of exposure to thirty-minutes of blue wavelength light on subsequent functional brain connectivity at rest and associations with mood and changes in affect. The results showed that individuals exposed to blue wavelength light showed greater positive connectivity between the right amygdala and the left DLPFC than individuals exposed to amber light, and that greater functional connectivity between these two areas was associated with greater decreases in negative mood. These findings build upon results from previous studies that have demonstrated that even after 50 seconds of blue light versus green light exposure, there are transient increases in activation within the right amygdala(Vandewalle et al., 2007), suggesting that blue light also enhances the connectivity between this emotionally responsive region and the prefrontal cortex. In line with this, there is evidence to suggest that the amygdala receives direct projections from ipRGCs (Hattar et al., 2006) and that swift modulations of amygdala activation may contribute to the antidepressant effect of blue wavelength light (Vandewalle, Maquet, & Dijk, 2009). It is therefore likely that blue wavelength light exposure leads to immediate amygdala activation and associated increases in arousal via the direct amygdalar projections from the ipRGCs. In order to respond to these increases in arousal, the DLPFC may, in turn, respond by engaging in cognitive control strategies,

such as selectively directing attention to stimuli in the environment, recruiting emotion regulation strategies, and influencing social decision-making.

A growing body of work demonstrates that depression is characterized by impaired cognitive and emotional processing which may reflect increased activation within areas such as the amygdala and decreased activity within areas involved in the effortful regulation of emotional behavior, such as the DLPFC and other frontal regions (Phillips, Drevets, Rauch, & Lane, 2003). A number of studies demonstrate that during active emotion regulation, individuals with depression (compared to healthy control subjects) show less negative connectivity between the amygdala and the PFC and that this reverses when symptom severity decreases to levels no longer considered clinically significant(Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). Functional resting-state studies, however, suggest that individuals with depression show reduced positive connectivity between the amygdala and several prefrontal regions, in comparison with healthy controls (Cheng et al., 2018; Connolly et al., 2017; Ramasubbu et al., 2014). The results from the present study suggest that blue light exposure may have a beneficial effect on functional connectivity between the amygdala and PFC by increasing information flow between these regions at rest. Furthermore, greater amygdala–DLPFC connectivity following blue light exposure was associated with greater decreases in negative affect from pre- to post-treatment. While those findings are notable, future research should consider that light exposure may be even more beneficial when used in conjunction with emotional learning/therapy. For example, blue light exposure while practicing emotional regulation skills might have an even stronger effect than blue light exposure without affective content. As previous studies have proposed that exposure to

blue light may facilitate learning through increased norepinephrine release from the brainstem(Alkozei et al., 2017), using light therapy in conjunction with therapeutic approaches that enable better emotion regulation abilities, such as cognitive reappraisal, should be the focus of future research. Evidence from one study showing that bright light exposure during fear extinction learning in healthy individuals suppressed fear acquisition and enhanced fear extinction also supports this proposal (Yoshiike, Honma, Yamada, Kim, & Kuriyama, 2018).

It should be noted that participants in our sample were free from psychological disorders, making the detection of subtle changes in mood/affect more challenging. The fact that we did observe a moderate to strong association between the strength of functional connectivity and changes in negative affect (($\rho = 0.55$) makes these results notable. However, replication of this study in a clinical sample of depressed individuals would shed additional light onto the immediate effects of blue light on mood and depressive symptoms. Our results raise the possibility that exposure to blue wavelength light for longer durations, perhaps over several weeks, may positively impact the coupling of the amygdala-DLPFC connection for individuals with clinical depression, which in turn may improve effective emotion regulation skills and executive function. There is some evidence for this, as one study in healthy males demonstrated that three weeks of bright light therapy reduced amygdala and prefrontal reactivity to threat (i.e., angry and fearful faces) in a dose-dependent manner; and that amygdala and prefrontal connectivity also increased in a dose-dependent manner (Fisher et al., 2014). However, these changes did not correspond with changes in mood or stress. As participants in this study were not clinically depressed, it is unclear how these neurobiological changes would correspond to

changes in mood in a sample of individuals with psychopathology. Future research is necessary to understand better how bright light, particularly in the blue wavelengths, affects functional brain responses in individuals with depression and how those may be associated with improved mood.

Of note, the effects of blue wavelength light on amygdala-DLPFC functional connectivity at rest may represent just one mechanism by which light effects emotion and cognition. Other lines of work have focused on the effects of light exposure on the influence of serotonin signaling, which may interact with the effects of blue light on cortico-limbic reactivity. For example, individuals with seasonal affective disorder (SAD) display enhanced serotonin transporter signaling during the winter months, which normalizes with successful treatment or during natural summer remission (Willeit et al., 2008). Another study showed that after a bright-light intervention in healthy males, differences in the 5-HTTLPR genotype moderated changes in functional brain responses between the amygdala and PFC towards threat (Fisher et al., 2014). Future research would likely benefit from investigating the potential interplay between serotonin signaling and amygdala-PFC connectivity on emotional functioning and mood after blue light therapy.

It should be pointed out that our results did not support the notion that a single exposure to blue wavelength light during the day would lead to increased positive and decreased negative affect. Both groups showed a decrease in the intensity of emotion for positive *and* negative affect, raising the possibility that the effects of increased amygdala-PFC connectivity following blue light resulted in a global moderating effect on mood. Of course, it is also possible that group differences in mood changes were not detected due to other confounding study effects, such as intense positive and negative feelings at the

beginning of the study, which dissipated towards the end for both groups (e.g., feeling excited, but apprehensive at the beginning of the day because of the novelty of being in a research study and/or the MRI acquisition). Future research would benefit from investigating the immediate changes in affect in response to light exposure in greater detail, including using more precise forms of self-report measures, investigating differences between healthy control populations and populations with depression, as well as the potential effects of time of day of exposure.

The results of this study should be interpreted with several limitations in mind. In this study, we aimed to investigate one potential mechanism through which blue wavelength light might influence affect and chose to study a group of healthy individuals without psychopathology. However, it is unclear how these results apply to individuals with clinically significant levels of depression. For example, it is possible that blue light exposure has a different effect on depressed individuals, and a similar study incorporating a sample of currently depressed individuals is necessary to help elucidate this. In addition, to better understand how light therapy may alter brain function in depressed individuals, future research would benefit from investigating changes in brain function at rest, as well as in response to emotional tasks, before and after light therapy. Finally, while this research contributes to our understanding of the mechanism by which blue wavelength light leads to improved mood, future research is necessary to continue studying the exact pathways through which light influences functional brain responses and how those immediate modulations in functional connections lead to long-term behavioral and emotional changes in mood and wellbeing.

Conclusion

The present findings suggest that a single 30-minute exposure to blue wavelength light during the day has an effect on positive functional connectivity between the right amygdala and the left dorsolateral prefrontal cortex and that this was associated with improvements in affect. These findings suggest a neurobiological mechanism by which light exposure is often associated with improvements in mood.

Figure Legends

Figure 1. PANAS positive affect (PANAS-P) and negative affect (PANAS-N) scores from pre-light and post-light exposure for both groups.

Figure 2. Displayed is the significant cluster of voxels ($x = -24$, $y = 46$, $z = 18$, $k = 90$, volume p-FDR corrected, $p < 0.001$) from the seed-to-voxel analysis using the right amygdala as the seed region.

Figure 3. Granger Causality (GC)-frequency spectra for (A) feed-forward (right amygdala (R. AMG) to left DLPFC (L. DLPFC)) and (B) feed-backward (L. DLPFC to R. AMG) connections for the amber and blue light groups. The green dotted line here represents the threshold chosen for significant GC strength (~.0422 at $p < 0.0025$, permutation test).

Figure 4. Spearman rank-order correlation between amygdala-DLPFC connectivity values and changes in PANAS negative affect (PANAS-N) scores from pre- to post-light exposure.

References

Aan Het Rot, M., Miloserdov, K., Buijze, A. L. F., Meesters, Y., & Gordijn, M. C. M. (2017). Premenstrual mood and empathy after a single light therapy session. *Psychiatry Research, 256*, 212-218. doi:10.1016/j.psychres.2017.06.052

Alkozei, A., Smith, R., Dailey, N. S., Bajaj, S., & Killgore, W. D. S. (2017). Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. *PloS one, 12*(9), e0184884.

Alkozei, A., Smith, R., & Killgore, W. D. (2016). Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. *Neurosci Lett, 616*, 5-10. doi:10.1016/j.neulet.2016.01.034

Alkozei, A., Smith, R., Pisner, D., Vanuk, J. R., Markowski, S. M., Fridman, A., . . . Killgore, W. D. S. (2016). Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. *Sleep*.

Aston-Jones, G., Chen, S., Zhu, Y., & Oshinsky, M. L. (2001). A neural circuit for circadian regulation of arousal. *Nature neuroscience, 4*(7), 732-738.

Beecher, M. E., Eggett, D., Erekson, D., Rees, L. B., Bingham, J., Klundt, J., . . . Gibson, R. (2016). Sunshine on my shoulders: weather, pollution, and emotional distress. *Journal of affective disorders, 205*, 234-238.

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage, 37*(1), 90-101.

Berson, D. M., Dunn, F. A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science, 295*(5557), 1070-1073.

Cajochen, C. (2007). Alerting effects of light. *Sleep medicine reviews, 11*(6), 453-464.

Cajochen, C., Munch, M., Kobialka, S., Kräuchi, K., Steiner, R., Oelhafen, P., . . . Wirz-Justice, A. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *The Journal of Clinical Endocrinology & Metabolism, 90*(3), 1311-1316.

Chai, X. J., Castañón, A. N., Öngür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *Neuroimage, 59*(2), 1420-1428.

Chellappa, S. L., Steiner, R., Blattner, P., Oelhafen, P., Götz, T., & Cajochen, C. (2011). Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert. *PloS one, 6*(1), e16429.

Cheng, W., Rolls, E. T., Qiu, J., Xie, X., Lyu, W., Li, Y., . . . Lyu, F. (2018). Functional connectivity of the human amygdala in health and in depression. *Social cognitive and affective neuroscience, 13*(6), 557-568.

Chesson, A. L., Jr., Littner, M., Davila, D., Anderson, W. M., Grigg-Damberger, M., Hartse, K., . . . Wise, M. (1999). Practice parameters for the use of light therapy in the treatment of sleep disorders. Standards of Practice Committee, American Academy of Sleep Medicine. *Sleep, 22*(5), 641-660. doi:10.1093/sleep/22.5.641

Connolly, C. G., Ho, T. C., Blom, E. H., LeWinn, K. Z., Sacchet, M. D., Tymofiyeva, O., . . . Yang, T. T. (2017). Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression. *Journal of affective disorders, 207*, 86-94.

Crawford, J. R., & Henry, J. D. (2004). The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non‐clinical sample. *British journal of clinical psychology, 43*(3), 245-265.

Delgado, P. L., & Moreno, F. A. (2000). Role of norepinephrine in depression. *J Clin Psychiatry, 61 Suppl 1*, 5-12.

Dhamala, M., Rangarajan, G., & Ding, M. (2008a). Analyzing information flow in brain networks with nonparametric Granger causality. *Neuroimage, 41*(2), 354-362. doi:10.1016/j.neuroimage.2008.02.020

Dhamala, M., Rangarajan, G., & Ding, M. (2008b). Estimating Granger causality from fourier and wavelet transforms of time series data. *Phys Rev Lett, 100*(1), 018701. doi:10.1103/PhysRevLett.100.018701

Dijk, D.-J., & Archer, S. N. (2009). Light, sleep, and circadian rhythms: together again. *PLoS biology, 7*(6), 1221.

Even, C., Schröder, C. M., Friedman, S., & Rouillon, F. (2008). Efficacy of light therapy in nonseasonal depression: a systematic review. *Journal of affective disorders, 108*(1-2), 11-23.

Fisher, P. M., Madsen, M. K., Mc Mahon, B., Holst, K. K., Andersen, S. B., Laursen, H. R., . . . Knudsen, G. M. (2014). Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling. *Biological psychiatry, 76*(4), 332-339.

Florin-Lechner, S. M., Druhan, J. P., Aston-Jones, G., & Valentino, R. J. (1996). Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. *Brain research, 742*(1), 89-97.

Foote, S., Berridge, C., Adams, L., & Pineda, J. (1991). Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. *Progress in brain research, 88*, 521-532.

Glickman, G., Byrne, B., Pineda, C., Hauck, W. W., & Brainard, G. C. (2006). Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). *Biological Psychiatry, 59*(6), 502-507.

Guéguen, N., & Lamy, L. (2013). Weather and helping: additional evidence of the effect of the sunshine Samaritan. *The Journal of social psychology, 153*(2), 123-126.

Hattar, S., Kumar, M., Park, A., Tong, P., Tung, J., Yau, K. W., & Berson, D. M. (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol, 497*(3), 326-349. doi:10.1002/cne.20970

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of Neuroscience, 27*(33), 8877-8884.

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA psychiatry, 72*(6), 603-611.

Lack, L., Bramwell, T., Wright, H., & Kemp, K. (2007). Morning blue light can advance the melatonin rhythm in mild delayed sleep phase syndrome. *Sleep and Biological Rhythms, 5*(1), 78-80.

Maruani, J., & Geoffroy, P. A. (2019). Bright Light as a Personalized Precision Treatment of Mood Disorders. *Front Psychiatry, 10*, 85. doi:10.3389/fpsyt.2019.00085

Pail, G., Huf, W., Pjrek, E., Winkler, D., Willeit, M., Praschak-Rieder, N., & Kasper, S. (2011). Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology, 64*(3), 152-162. doi:10.1159/000328950

Pandi-Perumal, S. R., Smits, M., Spence, W., Srinivasan, V., Cardinali, D. P., Lowe, A. D., & Kayumov, L. (2007). Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(1), 1-11.

Perera, S., Eisen, R., Bhatt, M., Bhatnagar, N., de Souza, R., Thabane, L., & Samaan, Z. (2016). Light therapy for non-seasonal depression: systematic review and meta-analysis. *British Journal of Psychiatry Open, 2*(2), 116-126.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biological psychiatry, 54*(5), 515-528.

Phipps-Nelson, J., Redman, J. R., Schlangen, L. J., & Rajaratnam, S. M. (2009). Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing. *Chronobiology international, 26*(5), 891-912.

Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola, I., & Goodyear, B. (2014). Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. *Frontiers in psychiatry, 5*, 17.

Rautkyä, E., Puolakka, M., & Halonen, L. (2011). Alerting effects of daytime light exposure-a proposed link between light exposure and brain mechanisms. *Lighting Research and Technology*, 1477153511409294.

Sinclair, K. L., Ponsford, J. L., Taffe, J., Lockley, S. W., & Rajaratnam, S. M. (2014). Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabilitation and neural repair, 28*(4), 303-313.

Strong, R. E., Marchant, B. K., Reimherr, F. W., Williams, E., Soni, P., & Mestas, R. (2009). Narrow‐band blue‐light treatment of seasonal affective disorder in adults and the influence of additional nonseasonal symptoms. *Depression and anxiety, 26*(3), 273-278.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.

Vandewalle, G., Maquet, P., & Dijk, D.-J. (2009). Light as a modulator of cognitive brain function. *Trends in cognitive sciences, 13*(10), 429-438.

Vandewalle, G., Schmidt, C., Albouy, G., Sterpenich, V., Darsaud, A., Rauchs, G., . . . Luxen, A. (2007). Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. *PloS one, 2*(11), e1247.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology, 54*(6), 1063.

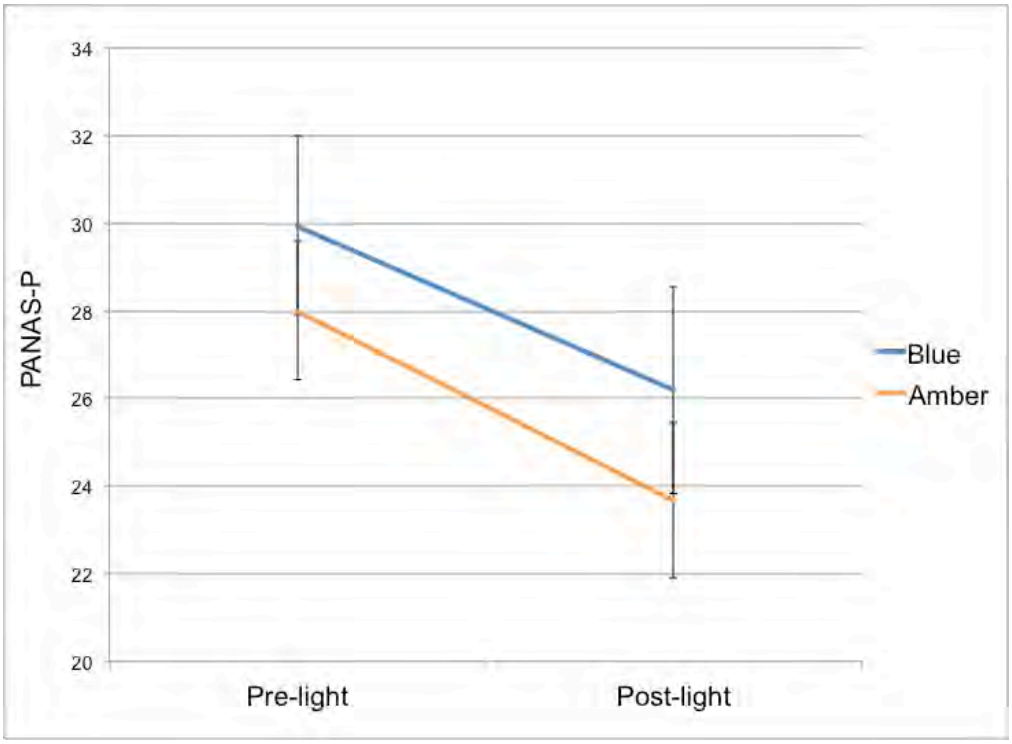
Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141.

Willeit, M., Sitte, H. H., Thierry, N., Michalek, K., Praschak-Rieder, N., Zill, P., . . . Bondy, B. (2008). Enhanced serotonin transporter function during depression in seasonal affective disorder. *Neuropsychopharmacology, 33*(7), 1503.

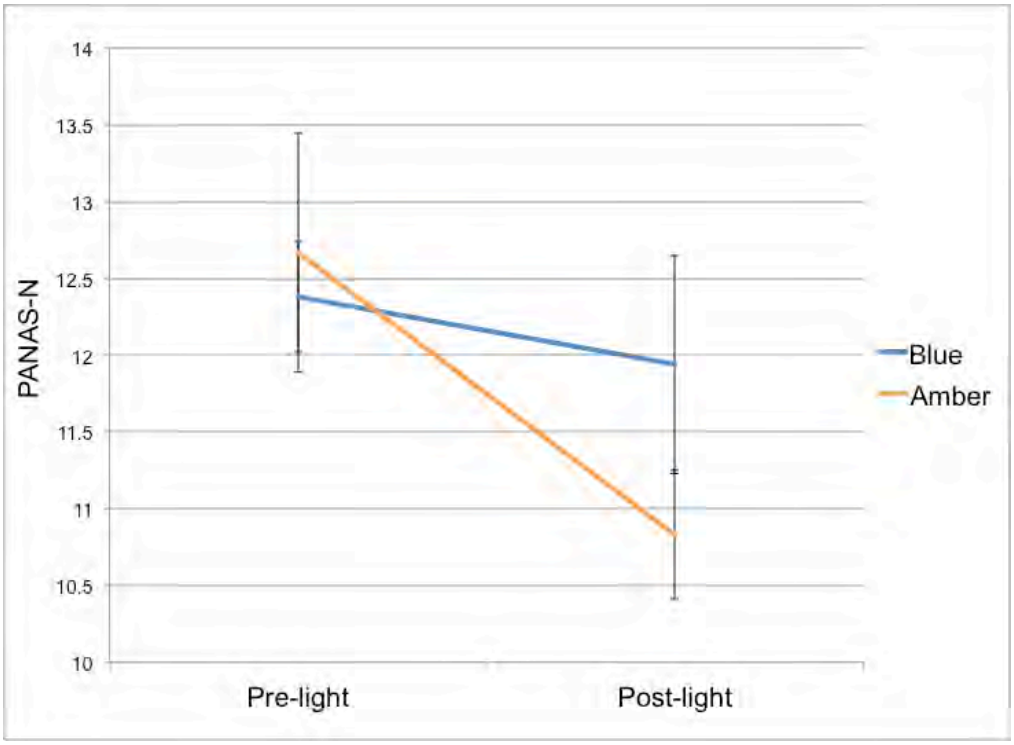
Yoshiike, T., Honma, M., Yamada, N., Kim, Y., & Kuriyama, K. (2018). Effects of bright light exposure on human fear conditioning, extinction, and associated prefrontal activation. *Physiology & Behavior, 194*, 268-276.

Figure 1.

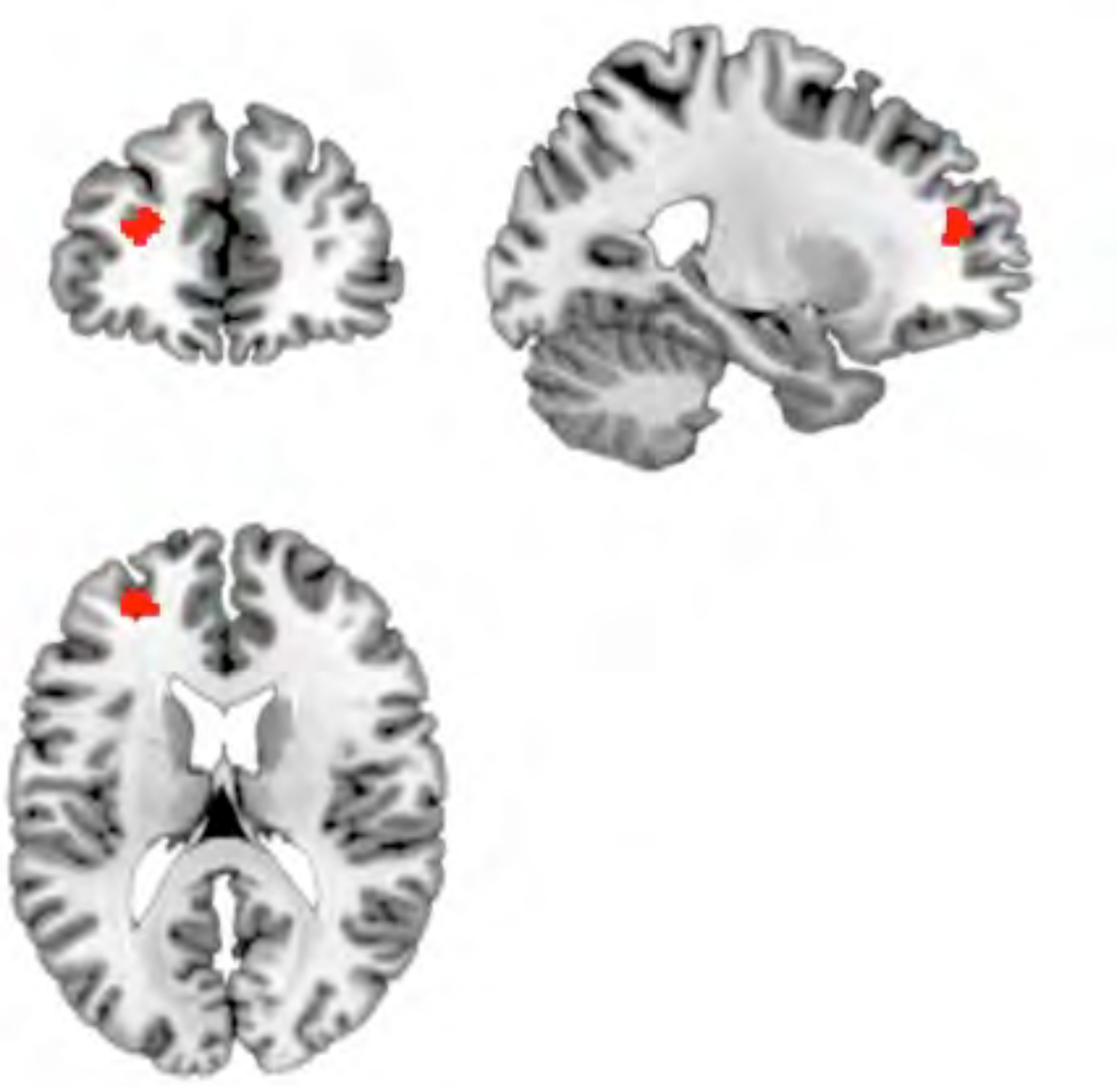
(a) PANAS_positive (PANAS-P)

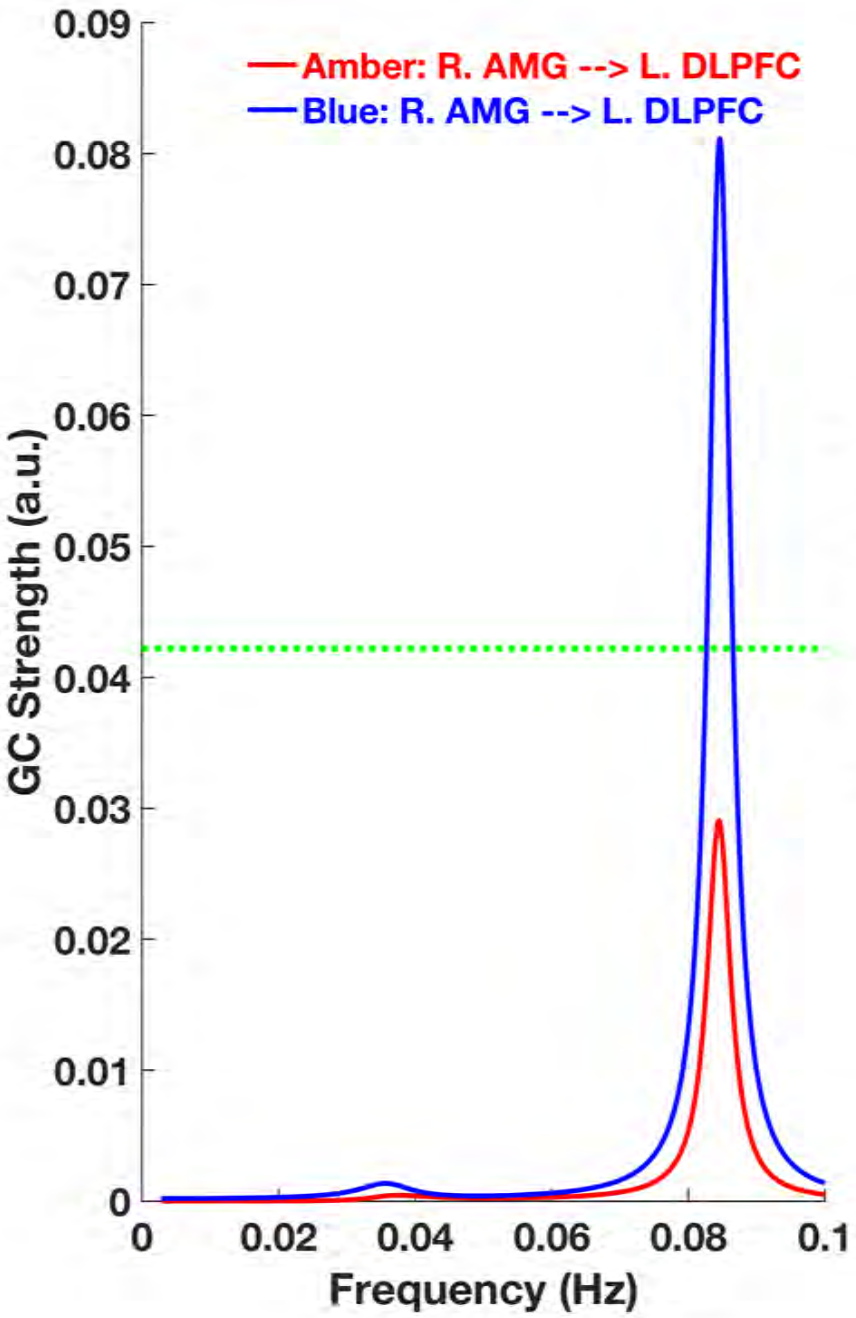


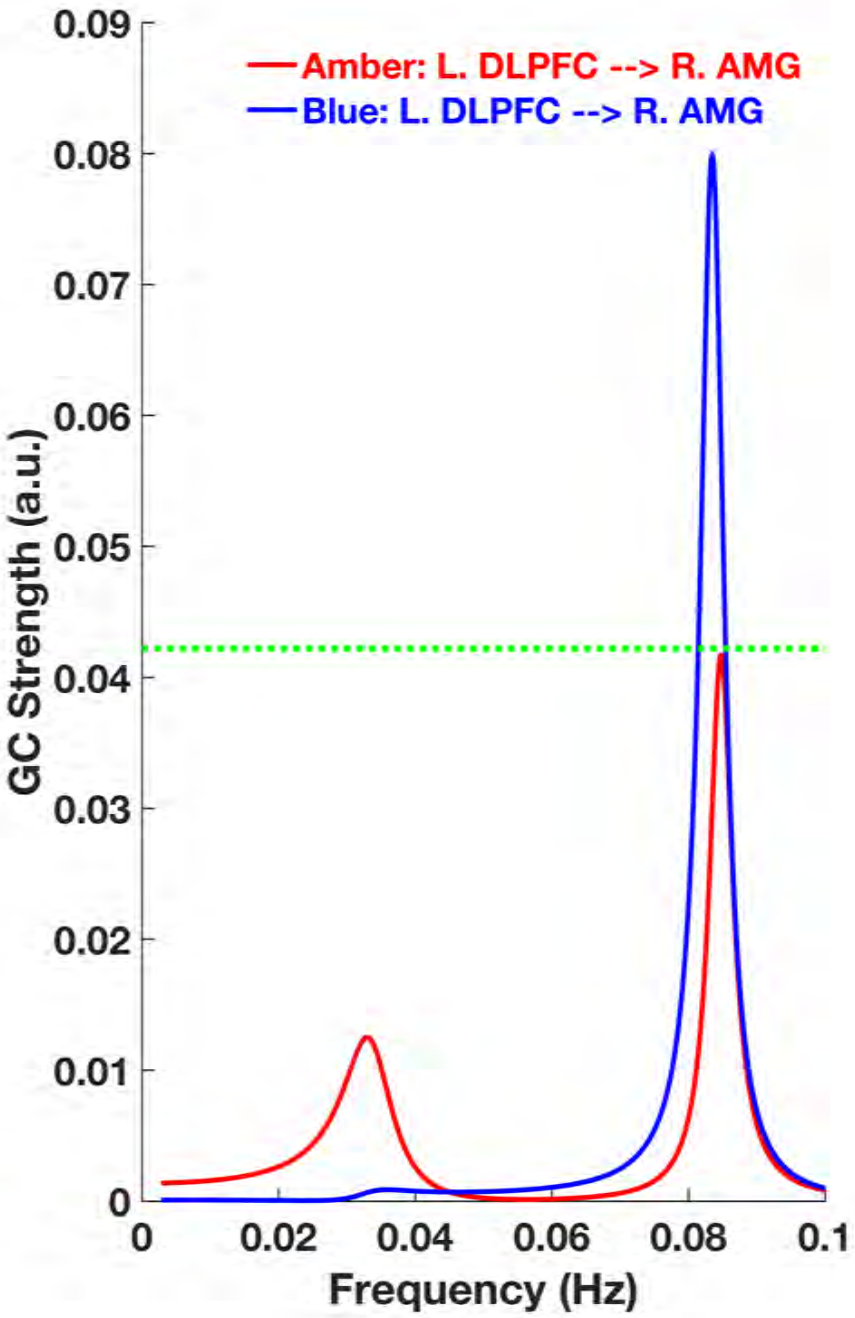
(b) PANAS_negative (PANAS-N)

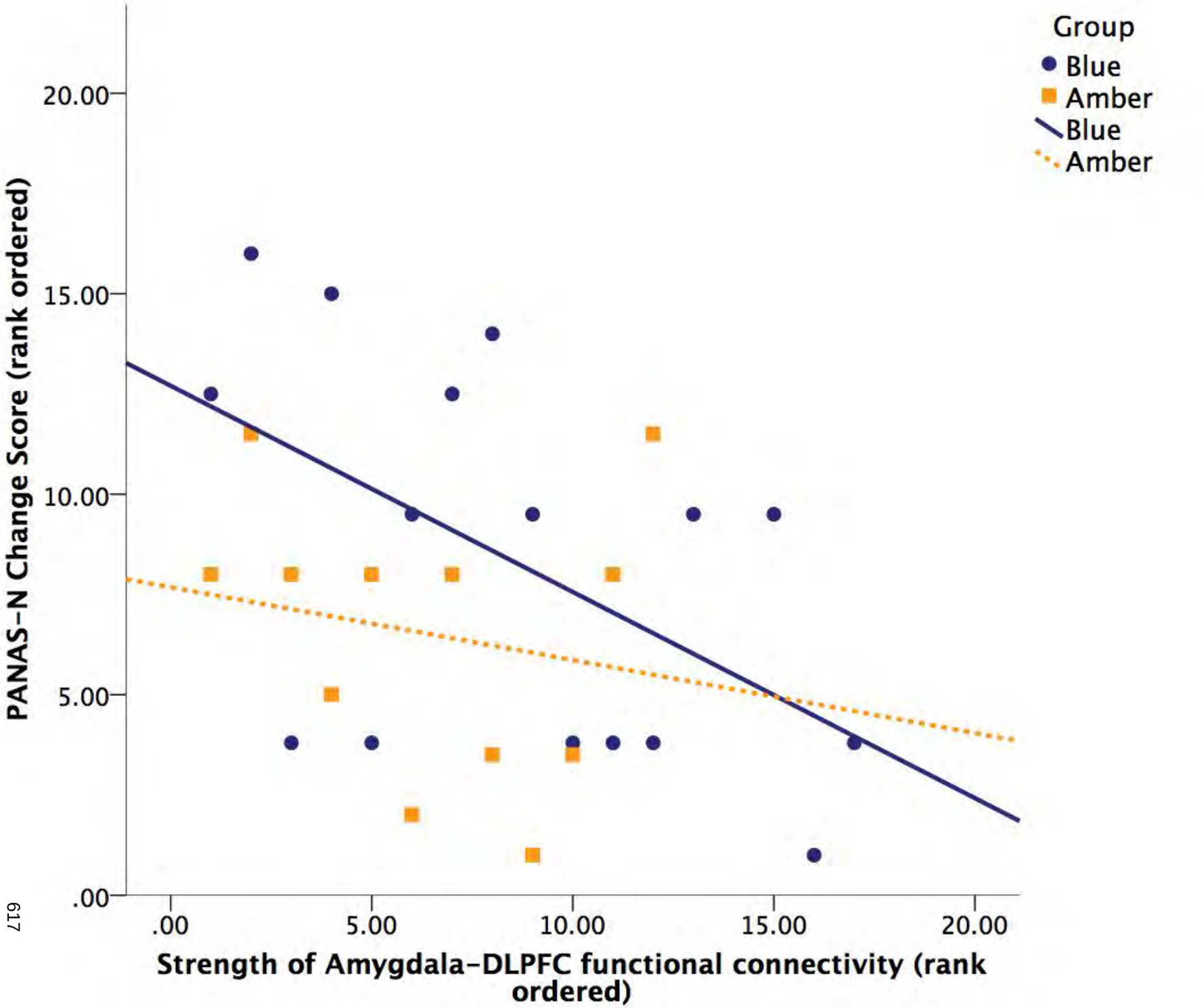


Error bars represent standard error.




Amber: R. AMG --> L. DLPFC
Blue: R. AMG --> L. DLPFC
GC Strength (a.u.)
Frequency (Hz)
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.02
0.04
0.06
0.08
0.1


Amber: L. DLPFC --> R. AMG
Blue: L. DLPFC --> R. AMG
GC Strength (a.u.)
Frequency (Hz)
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.02
0.04
0.06
0.08
0.1


Group
Blue
Amber
Blue
Amber
20.00
15.00
10.00
5.00
.00
PANAS-N Change Score (rank ordered)
.00
5.00
10.00
15.00
20.00
Strength of Amygdala-DLPFC functional connectivity (rank ordered)

TITLE: Blue Light Exposure Enhances Neural Efficiency of the Task Positive Network During a Cognitive Interference Task

RUNNING HEAD: Blue Light & Neural Efficiency

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Conflicts of interests: None declared.

Funding: This research was supported by a USAMRAA grant (W81XWH-14-1-0571).

ABSTRACT

Exposure to light, particularly blue-wavelength light has been shown to acutely increase brain activation, alertness, and some elementary aspects of cognitive performance such as working memory and emotional anticipation. Whether blue light exposure can have effects on brain activation and performance during more complex cognitive control tasks up to 30-minutes after light cessation is unknown. Here, in a sample of 30 healthy adults, we examined the effects of a 30-minute exposure to either blue (n = 14) or amber placebo (n = 16) light on subsequent brain activation and performance during the Multi-Source Interference Task (MSIT) measured a half-hour after light exposure. Performance metrics for the MSIT, including accuracy, response time, and cognitive throughput, did not differ between the blue and amber conditions. However, brain activation within the task positive network (TPN) to the interference condition was significantly lower in the blue relative to the amber condition, while no group differences were observed for suppression of the default mode network (DMN). These findings suggest that, compared to placebo, a single pulse of blue light was associated with enhanced neural efficiency as demonstrated by reduced TPN activation to achieve the same level of performance. Blue light may be an effective method for optimizing neurocognitive performance under some conditions.

KEYWORDS: fMRI; neuroimaging; multi-source interference task; MSIT; blue light exposure; neural efficiency; task positive network; default mode network

SUPPORT: This work was supported by a grant from the US Army Medical Research and Materiel Command to WDSK (W81XWH-14-0571).

INTRODUCTION

Light is one of the most vital environmental influences on human life and it has powerful effects on our health, daily rhythms, sleep, mood, and cognitive performance [23]. Many natural rhythms, including neurohormonal secretion (e.g., melatonin, cortisol) and daily sleep-wake cycles are entrained and regulated by daily exposure to the blue wavelengths of light via the non-image-forming visual system. When stimulated by blue-wavelength light, intrinsically photosensitive retinal ganglion cells (ipRGCs) located on the outer surface of the retina send signals to the suprachiasmatic nucleus of the hypothalamus and other brainstem nuclei to regulate circadian rhythms and modulate general alertness [10]. While the circadian-related effects of light on sleep and alertness are well-documented [9, 19], less is known about the direct (i.e., non-circadian) stimulating effects of light on immediate brain functioning and cognition. Studies have shown that light can acutely enhance alertness [14], psychomotor vigilance [16], and sleepiness [17].

Most brain imaging studies have examined the acute effects of light either during light stimulation or immediately after its cessation [21, 22, 24]. In particular, light exposure acutely increases activation of the locus coeruleus (LC), the primary brain region responsible for norepinephrine release and a major regulator of alertness and cognition [24]. Recently, our team showed that some effects of blue light on brain activation and performance may extend longer than previously realized after termination of exposure. First, we found that a single 30-minute dose of blue light reduced brain activation within the rostral anterior cingulate cortex (rACC) during an emotional anticipation task more than 40 minutes after the end of light exposure [2]. Second, we also showed that the same dose

of blue light exposure can enhance activation within the dorsolateral and ventrolateral prefrontal cortex during an n-back working memory task about 35 minutes after exposure, a finding that was associated with improved performance [3]. These findings suggest that a brief single exposure to blue-wavelength light can sustain emotional and working memory performance for at least a half-a-hour after the light pulse ends, if not longer. However, the potential of blue light exposure to subsequently affect the efficiency of higher-level cognitive processing, such as minimizing the effects of cognitive interference on task performance, has not been explored. Therefore, we presently examined the effects of a 30-minute dose of blue-wavelength light on subsequent functional brain activation and performance during the Multi-Source Interference Test (MSIT)[5, 6], a popular and well-validated neuroimaging task designed to assess cognitive interference resolution. The MSIT produces robust and reliable activation within a network of regions comprising the dorsal anterior cingulate cortex (dACC)/supplementary motor area/medial prefrontal cortex [8]. We hypothesized that exposure to blue light would enhance the efficiency of cortical systems involved in resolving cognitive interference on the MSIT. Therefore, based on the predictions of the neural efficiency hypothesis [15], we expected that blue light would thus reduce task positive activation to the MSIT interference condition while also reducing suppression of default mode activation compared to a matched placebo light exposure.

METHODS

Participants

Thirty (16 male; 14 female) right-handed, primary English speaking, healthy adults ranging in age from 18 to 32 years ($\underline{M}$ = 22.3, $\underline{SD}$ = 3.6) were randomly assigned to either a blue light ($\underline{n}$ = 14; 8 male; 6 female) or amber placebo light ($\underline{n}$ = 16; 8 male; 8 female) condition.

Participants had obtained an average of 14.2 years (SD = 2.0) of formal education, and self-reported normal typical sleep patterns, averaging 7.2 hrs (SD = 1.0) on weeknights, and 8.2 hrs (SD = 0.7) on weekend nights. Participants self-reported obtaining an average of 6.9 hrs (SD = 0.6) of sleep the night before participation. All were recruited via posted flyers and Internet advertisements within the Tucson, AZ metropolitan area, and were screened to exclude known history of severe medical, neurological, psychiatric conditions, head injury, drug or alcohol treatment, or current use of illicit substances. Although other data from this sample have been published previously [1, 3], the present fMRI data on the MSIT are novel and have not been previously reported. This project was reviewed and approved by the University of Arizona College of Medicine Institutional Review Board and the US Army Human Research Protections Office.

Materials and Procedure

The study methods have been described in detail elsewhere [3]. In brief, participants arrived at the laboratory at 0745 to complete informed consent and baseline assessments. At 0830, participants completed a two-subtest version of the Wechsler Abbreviated Scale of Intelligence-2 (WASI-II). To ensure that any acute effects of prior environmental blue light exposure had been minimized before randomized light treatment, participants then completed a light "washout" period where they sat quietly in a dimly lit room for 30-minutes starting at 0945, with ambient lighting provided by two amber light exposure devices that were situated 80 cm from the participant's nasion at 45º to the left and right of center (see Figure 1). The two amber washout light devices consisted of a plastic table-mounted chassis with a 10 x 6 array of light emitting diodes (LEDs) peaking at λ = 578 nm,

at 188 Lux, and total irradiance (mW/cm^2) = 0.35). LEDs were housed in 1 x 1 cm cubical projection elements covered with a translucent plastic window cover. During the light washout period, from 0955 to 1000, participants were familiarized with the MSIT (described below) and completed a practice trial of task for approximately 5 minutes. During MSIT practice, Blue light emissions from the desktop computer screen were minimized by an amber screen cover in front of the screen.

INSERT FIGURE 1 ABOUT HERE

At 1015, while seated in same location, participants completed the 30-minute "bright light" exposure treatment period with either blue or amber light (see Figure 1). Participants were randomly assigned (using block randomization) to undergo exposure to an array of 4 light devices fitted with *either* amber (n = 16), or 4 identical appearing devices fitted with blue wavelength LEDs (peaking at λ = 469 nm, at 214 Lux, and panel irradiance (mW/cm^2) = 1.23 at 20 cm; n = 14) (i.e., Philips goLITE BLU® Energy Light devices, Model HF3321/60; Philips Electronics, Stamford, CT). All 4 lights emitted the same color wavelength (i.e., *either* blue or amber). At 1045, participants were escorted to the MRI scanner room next door while wearing amber colored glasses to block ambient blue light. From 1100 to 1230, participants completed a series of structural and functional MRI scans, including the MSIT (described below) from approximately 1115 to 1125. Participants were released at 1245.

Neuroimaging

Multi-Source Interference Task (MSIT). While undergoing fMRI, participants completed the MSIT, a well-validated cognitive interference task that produces consistent and robust activation patterns within the cingulo-frontal-parietal attention network during fMRI [5, 6, 12]. The MSIT consists of an alternating series of two conditions that are performed within the MRI scanner. During each trial, the participant is presented with a row of three digits on a video screen. On each presentation, two of the digits are always the same and one digit differs from the others, and participants are required to indicate the location of the inconsistent digit by making a key press on a button box in their right hand. For the "control" trials, the two distractor digits are always "0" and the inconsistent digit was always congruent with its physical position in the series and therefore matches its location on the button box (e.g., "100" = press button "1"; "020" = press button "2"; "003" = press button "3"). For the "interference" trials, the distractor digits were numbers other than zero and the inconsistent digit was never in the same spatial position as the required button press (e.g., "331" = press button "1"; "211" = press button "2"; "232" = press button "3"). During each trial, the digit sets were presented for 1750 ms, with a prerelease of 500 ms, yielding a stimulus presentation of 1250 ms and an interstimulus interval of 500 ms. Four blocks of control trials were alternated with four blocks of interference trials, with each block consisting of 24 digit set presentations, yielding a total of 192 sets presented over a total run time of 6 min and 36 s. The task was generated in E-Prime software and presented from a laptop computer via a high-resolution, rear projection system to a translucent screen viewed through the mirror mounted to the head coil.

Neuroimaging Parameters. Structural and functional neuroimaging data were acquired on a Skyra 3T scanner (Siemens, Erlangen, Germany) using a 32-channel head coil. For structural imaging, a T1-weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.33 ms/ 12 degree) over 176 sagittal slices (256 x 256) and a slice thickness of 1.00 mm (voxel size = 1 x 1 x 1 mm) was acquired. For the functional MSIT scans, T2*-weighted echoplanar MRI scans were collected over 32 transverse slices and a slice thickness of 2.5 mm (voxel size 2.5 x 2.5 x 2.5 mm) using an interleaved sequence (TR/TE/flip angle = 2.0 s/ 25.0 ms/ 90 degree) with 198 images collected per slice. Data were collected with a 22.0 cm field of view and a 64 x 64 acquisition matrix.

Image Processing and Statistical Analysis. Image processing and statistical analysis were undertaken in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; *http://www.fil.ion.ucl.ac.uk/spm*) following a standard pipeline [3] that involved image realignment, unwarping, co-registration, normalization to Montreal Neurological Institute (MNI) coordinate space, spatial smoothing (6 mm full-width at half maximum), and reslicing to 2 x 2 x 2 mm voxels. A high pass filter (128 second cut-off period) was implemented to remove low frequency confounds, and the Artifact Detection Tool (*http://www.nitrc.org/projects/artifact_detect/*) was used to remove motion artifacts. At the individual level, a general linear models (GLM) was specified to contrast activation between the interference trials and the control trials for each participant (i.e., interference > control).

At the group level, individual contrast maps (interference > control) were entered into a one-sample t-test in SPM12. From this analysis, the positive contrast identified regions that showed increased activation during the interference task (vs control), while the negative contrast indicated regions that showed reduced activation (vs control) during the interference task. A highly conservative threshold was used for this initial analysis, employing a whole-brain family-wise error (FWE) correction of $p < .001$ (corrected) and a minimum cluster size of 8 (i.e., twice the cluster-wise False Discovery Rate threshold, FDR = 4 as indicated by SPM12). The first eigenvariate representing total combined activation from the full set of surviving clusters was extracted as a whole-brain network from the positive and negative contrasts respectively and entered into IBM SPSS version 26 for further analysis. The extracted whole brain activation of each of these networks was then compared between the blue and the amber conditions using one-way analysis of variance and zero-order correlations.

RESULTS

The MSIT produced activation in expected brain networks even at highly stringent thresholds (see Figure 2). Specifically, the interference > control contrast led to significant positive task-related activation throughout a network of regions including bilateral occipital, parietal, and middle cingulate cortex (see Table 1). Collectively we identify this pattern of activation as the *task positive network* (TPN) for the MSIT interference condition. Significant deactivations during the interference condition were observed within the angular gyri bilaterally, as well as medial cortical structures including the middle/posterior cingulate gyrus, and anterior cingulate gyrus/medial orbitofrontal gyrus

(see Table 1). We identify this collective pattern of activation as the *default mode network* (DMN). The total activation (i.e., first eigenvariate across all regions combined) was extracted for the TPN and DMN separately.

INSERT FIGURE 2 ABOUT HERE

INSERT TABLE 1 ABOUT HERE

As shown in Figure 3a, total activation of the TPN was significantly lower among participants completing the blue light condition relative to the amber placebo light condition ($F(1, 28) = 5.70$, $p = .024$, partial $\eta^2 = .169$), showing a large effect size. In contrast, the two groups did not differ in total suppression of the DMN ($F(1,28) = 0.01$, $p = .910$, partial $\eta^2 = .000$). These analyses were repeated after controlling for WASI-II full-scale intelligence, but the results remained virtually unchanged.

Behavioral task data from the MSIT were scored in three ways. First, accuracy was the percent of correct responses for all trials for a particular condition. Second, response time was the mean time taken to press one of the three response keys. Third, a metric of "cognitive throughput" (i.e., (% correct/mean response time) x 600)), which indicates the number of correct responses per working minute. Behavioral data showed that the blue and amber groups did not differ in terms of accuracy ($F(1, 28) = 0.26$, $p = .615$, partial $\eta^2 = .009$), response time ($F(1, 28) = 0.86$, $p = .363$, partial $\eta^2 = .030$), or throughput ($F(1, 28)$

= 0.75, p = .394, partial η^2 = .026) for the control task (see Figure 3b). Similarly, the groups did not differ in terms of accuracy ($F(1, 28) = 0.27$, p = .609, partial η^2 = .009), response time ($F(1, 28) = 0.03$, p = .864, partial η^2 = .001), or throughput ($F(1, 28) = 0.16$, p = .688, partial η^2 = .006) for the interference task (see Figure 3c).

Finally, we examined the correlations between brain network activation and behavioral performance (i.e., MSIT throughput) within each group. There was no association between TPN activation and control or interference throughput for either the blue or amber groups. In contrast, for the DMN, the correlation between network deactivation and performance was significant within the blue group for both the control task (r = -.54, p = .046) and the interference task (r = -.54, p = .046), but not for the amber group (see Figure 3d).

INSERT FIGURE 3 ABOUT HERE

DISCUSSION

We compared the effects of a single 30-minute exposure of blue light versus amber placebo light on neural efficiency during the MSIT. While task performance was equivalent between groups with regard to accuracy, response time, and cognitive throughput, the blue light condition showed significantly lower activation of the TPN relative to the amber placebo condition. Consistent with the neural efficiency hypothesis [15], this suggest that a single half-hour exposure to blue light reduced metabolic demands on task-related cortical resources without compromising task performance. However, contrary to our hypothesis, we did not find any difference between conditions in global suppression of the DMN.

The neural efficiency hypothesis posits that individuals with greater cognitive capacity require less brain activation (i.e., fewer neural resources) to complete the same cognitive tasks when such tasks are of low to moderate difficulty [15]. The MSIT conditions used here are consistent with this difficulty requirement, as the accuracy level for the control task was 99.6% blue and 99.7% for amber, and the accuracy for the interference task was 96.7% for blue and 96.2% for amber, with no differences observed between groups in performance (see Figure 3b and 3c). Similar outcomes were found for MSIT response time and throughput. Thus, both tasks were completed nearly perfectly by all participants, but those in the blue group required significantly less brain activation to complete the more demanding (yet relatively easy) interference task than those in the amber placebo group. Furthermore, this difference was not accounted for by differences in measured intelligence. Apparently, exposure to blue-wavelength light for 30-minutes allowed the task to be completed equally well with less demand on TPN neural resources, regardless of baseline intelligence. Of course, this begs the question: by what mechanism does light exposure produce this enhanced efficiency?

While there have been many proposed neurobiological mechanisms underlying neural efficiency [18], we posit that the most likely mechanism here is optimized allocation of attentional resources due to the effects of light on norepinephrine regulation by the locus coeruleus (LC). The LC is crucial for promoting wakefulness, arousal, attention, and efficiency of cognitive processing [11, 25]. Further, the LC appears to amplify neural gain to focus cognition on prioritized cognitive tasks [7], and has been shown to be particularly

responsive to light exposure [20, 24]. Blue light has been shown to acutely activate the LC and downstream cortical regions when task performance coincides with light exposure [23]. While speculative, we propose that these stimulating effects may continue to prime cognitive networks for efficient functioning for at least a half an hour after the cessation of light exposure. Analogous to the way a "warm up" before athletic activity allows more efficient and precise muscle movement, this pre-activation of cortical attention systems would potentially allow fewer redundant or unnecessary cognitive resources to be engaged to carry out a simple cognitive task (i.e., greater neural efficiency). Of course, these suggestions are speculative and will require further research before they can be accepted.

These findings build upon prior work showing that acute exposure to blue light can enhance cognitive performance and brain functioning [1-3, 21-24]. These acute effects of light likely involve different mechanisms than longer-term treatment with blue light for recovery from traumatic injury or mood dysfunction. For instance, we have recently shown that six-weeks of blue light exposure leads to neuroplastic changes in gray and white matter and concomitant cognitive improvements among individuals recovering from mild traumatic brain injury [4, 13]. However, these changes likely reflect the effects of daily morning blue light on circadian and sleep patterns, which in turn, may have contributed to structural and functional recovery. Thus, blue light exposure may have differential effects on the brain across several timeframes, ranging from acute effects on brain activation over the course of seconds to minutes, to slightly longer effects on cortical neural efficiency on the time scale of at least half an hour, as seen here, and finally longer term neuroplastic changes and

associated functional outcomes due to sleep and circadian entrainment that may emerge over the course of weeks or months.

Although the present findings suggest that blue light may enhance neural efficiency for a simple cognitive interference task, several limitations should be considered. First, the sample size was modest, and further work will need to be done to replicate these findings. Second, we contrasted the blue light outcomes with that of a matched amber placebo light. However, at this early stage in research, it is not possible to say with certainty whether amber light is without effects on the brain. It is possible that amber light may be producing its own effects that obscure those produced by the blue light. Third, we expected that improved neural efficiency from the blue light would also be associated with diminished deactivation within the DMN relative to the placebo, but this was not observed. Instead, we found that greater deactivation of the DMN was associated with better performance, but only for the blue condition, and for both the control and interference conditions. As suppression of the DMN often contributes to cognitive performance, the role of the DMN in response to blue light and its effect on cognition will need to be explored further.

CONCLUSION

A single 30-minute exposure to blue-wavelength light was associated with greater neural efficiency than an equal duration exposure to amber placebo light, as evidenced by reduced activation of the TPN and sustained performance during a task requiring ongoing resolution of cognitive interference. These findings provide further evidence that blue-wavelength light has acute enhancing effects on some aspects of cognition.

REFERENCES

[1] A. Alkozei, R. Smith, N.S. Dailey, S. Bajaj, W.D.S. Killgore, Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance, PLoS ONE 12 (2017) e0184884.

[2] A. Alkozei, R. Smith, W.D. Killgore, Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli, Neurosci. Lett. 616 (2016) 5-10.

[3] A. Alkozei, R. Smith, D.A. Pisner, J.R. Vanuk, S.M. Berryhill, A. Fridman, B.R. Shane, S.A. Knight, W.D. Killgore, Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task, Sleep 39 (2016) 1671-1680.

[4] S. Bajaj, J.R. Vanuk, R. Smith, N.S. Dailey, W.D.S. Killgore, Blue-Light Therapy following Mild Traumatic Brain Injury: Effects on White Matter Water Diffusion in the Brain, Front Neurol 8 (2017) 616.

[5] G. Bush, L.M. Shin, The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network, Nat. Protoc. 1 (2006) 308-313.

[6] G. Bush, L.M. Shin, J. Holmes, B.R. Rosen, B.A. Vogt, The Multi-Source Interference Task: validation study with fMRI in individual subjects, Mol. Psychiatry 8 (2003) 60-70.

[7] D.V. Clewett, R. Huang, R. Velasco, T.H. Lee, M. Mather, Locus Coeruleus Activity Strengthens Prioritized Memories Under Arousal, J. Neurosci. 38 (2018) 1558-1574.

[8] Y. Deng, X. Wang, Y. Wang, C. Zhou, Neural correlates of interference resolution in the multi-source interference task: a meta-analysis of functional neuroimaging studies, Behav. Brain Funct. 14 (2018) 8.

[9] A.S. Fisk, S.K.E. Tam, L.A. Brown, V.V. Vyazovskiy, D.M. Bannerman, S.N. Peirson, Light and Cognition: Roles for Circadian Rhythms, Sleep, and Arousal, Front Neurol 9 (2018) 56.

[10] R.G. Foster, Neurobiology: bright blue times, Nature 433 (2005) 698-699.

[11] E. Glennon, I. Carcea, A.R.O. Martins, J. Multani, I. Shehu, M.A. Svirsky, R.C. Froemke, Locus coeruleus activation accelerates perceptual learning, Brain Res. 1709 (2019) 39-49.

[12] S.A. Gruber, M.K. Dahlgren, K.A. Sagar, A. Gonenc, W.D.S. Killgore, Age of onset of marijuana use impacts inhibitory processing, Neurosci. Lett. 511 (2012) 89-94.

[13] W.D.S. Killgore, J.R. Vanuk, B.R. Shane, M. Weber, S. Bajaj, A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury, Neurobiol. Dis. 134 (2019) 104679.

[14] S.W. Lockley, E.E. Evans, F.A. Scheer, G.C. Brainard, C.A. Czeisler, D. Aeschbach, Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans, Sleep 29 (2006) 161-168.

[15] A.C. Neubauer, A. Fink, Intelligence and neural efficiency, Neurosci. Biobehav. Rev. 33 (2009) 1004-1023.

[16] J. Phipps-Nelson, J.R. Redman, D.J. Dijk, S.M. Rajaratnam, Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance, Sleep 26 (2003) 695-700.

[17] J. Phipps-Nelson, J.R. Redman, L.J. Schlangen, S.M. Rajaratnam, Blue light exposure reduces objective measures of sleepiness during prolonged nighttime performance testing, Chronobiol. Int. 26 (2009) 891-912.

[18] R.A. Poldrack, Is "efficiency" a useful concept in cognitive neuroscience?, Dev Cogn Neurosci 11 (2015) 12-17.

[19] C. Schmidt, F. Collette, C. Cajochen, P. Peigneux, A time to think: circadian rhythms in human cognition, Cogn Neuropsychol 24 (2007) 755-789.

[20] E. Szabadi, Functional neuroanatomy of the central noradrenergic system, J Psychopharmacol 27 (2013) 659-693.

[21] G. Vandewalle, E. Balteau, C. Phillips, C. Degueldre, V. Moreau, V. Sterpenich, G. Albouy, A. Darsaud, M. Desseilles, T.T. Dang-Vu, P. Peigneux, A. Luxen, D.J. Dijk, P. Maquet, Daytime light exposure dynamically enhances brain responses, Curr. Biol. 16 (2006) 1616-1621.

[22] G. Vandewalle, S. Gais, M. Schabus, E. Balteau, J. Carrier, A. Darsaud, V. Sterpenich, G. Albouy, D.J. Dijk, P. Maquet, Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure, Cereb. Cortex 17 (2007) 2788-2795.

[23] G. Vandewalle, P. Maquet, D.J. Dijk, Light as a modulator of cognitive brain function, Trends Cogn Sci 13 (2009) 429-438.

[24] G. Vandewalle, C. Schmidt, G. Albouy, V. Sterpenich, A. Darsaud, G. Rauchs, P.Y. Berken, E. Balteau, C. Degueldre, A. Luxen, P. Maquet, D.J. Dijk, Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem, PLoS ONE 2 (2007) e1247.

[25] E.M. Vazey, D.E. Moorman, G. Aston-Jones, Phasic locus coeruleus activity regulates cortical encoding of salience information, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E9439-E9448.

Table 1: Brain Activation During the MSIT.

Target Region	Cluster Size	MNI coordinates			*T*
		x	y	z	
Task Positive Network					
Left Middle Occipital Gyrus	748	-30	-88	4	14.83
Right Inferior Occipital Gyrus	656	38	-84	-2	13.76
Left Superior Parietal Lobule	300	-24	-60	48	13.48
Left Middle Frontal Gyrus	174	-28	-4	54	11.62
Left Supplementary Motor Area/Middle Cingulate Gyrus	129	-2	10	50	10.88
Left Inferior Parietal Lobule	361	-44	-34	42	10.32
Left Precentral Gyrus	62	-42	4	30	9.80
Right Middle Cingulate Gyrus	19	12	14	44	9.19
Right Superior Occipital Gyrus	75	26	-62	38	9.03
Right Cerebellum	27	32	-60	-26	8.71
Right Cerebellum	8	28	-68	-22	8.62
Left Insula	8	-28	26	6	8.29
Default Mode Network					
Left Angular Gyrus/Middle Occipital Gyrus	124	-42	-78	36	12.09

Left Middle/Posterior Cingulate Gyrus	350	-4	-44	36	10.13
Left Medial Obitofrontal/Anterior Cingulate Gyrus	64	-4	36	-10	9.06
Right Angular Gyrus	21	48	-70	36	8.52

All voxels significant at $p < .001$ (height) for Family Wise Error (FWE), and extent corrected at $p < .05$ (FDR).

Figure Legends

Figure 1. Experimental conditions and schedule. All participants began the study session by completing a 30-minute "light washout" period from 9:45 a.m. to 10:15 a.m. to minimize prior exposure to ambient blue light. During that time, participants sat in a darkened room facing two amber light devices at 45-degree angles from the center of fixation. During this time, participants completed a 5-minute practice session with the Multi-Source Interference Task (MSIT) on a laptop computer. Beginning at 10:15 a.m., participants were randomly assigned to receive 30-minutes of blue or amber bright light exposure. Bright light exposure was provided by four light devices (either all blue or all amber) in the same location as the previous amber light washout devices. After the bright light exposure period, participants were escorted to the neuroimaging scanner to undergo functional magnetic resonance imaging. The MSIT task began at ~11:17 a.m. and ended at ~11:25 a.m.

Figure 2. Group brain activation patterns for the Multi-Source Interference Task (MSIT). Data are shown for the contrast "interference > control" in multiple axial slices (top), midline sagittal slice (bottom left), and "glass brain" maximum intensity projection (bottom right). Warm colors represent activation of the task positive network (TPN) for the interference > control contrast, while cool colors represent task-related deactivations, which conform roughly to the default mode network (DMN). All data are whole brain corrected

for family-wise error (FWE) at $p < .001$, and a cluster threshold of 8 voxels (twice the cluster-wise false discovery rate (FDR) threshold).

Figure 3. Group mean comparisons between primary variables during the Multi-Source Interference Task (MSIT). a) Mean activation within the task positive network (TPN) was significantly (p = .024) lower for the blue group than the amber group (left), but did not differ between groups for the default mode network (right); b) Mean performance variables for the MSIT Control condition showed no between-groups difference for accuracy (left) response time (RT; middle), or cognitive throughput (i.e., number of correct responses per working minute; right); c) Mean performance variables for the MSIT Interference condition showed no between-groups difference for accuracy (left) response time (RT; middle), or cognitive throughput (i.e., number of correct responses per working minute; right); d) Scatterplots showing the association between default mode activation and Cognitive Throughput, which was significant for the blue group in the Control (left) and Interference conditions but not the amber group. a.u. = arbitrary units; ns = nonsignificant; *p < .05.

Figure 1

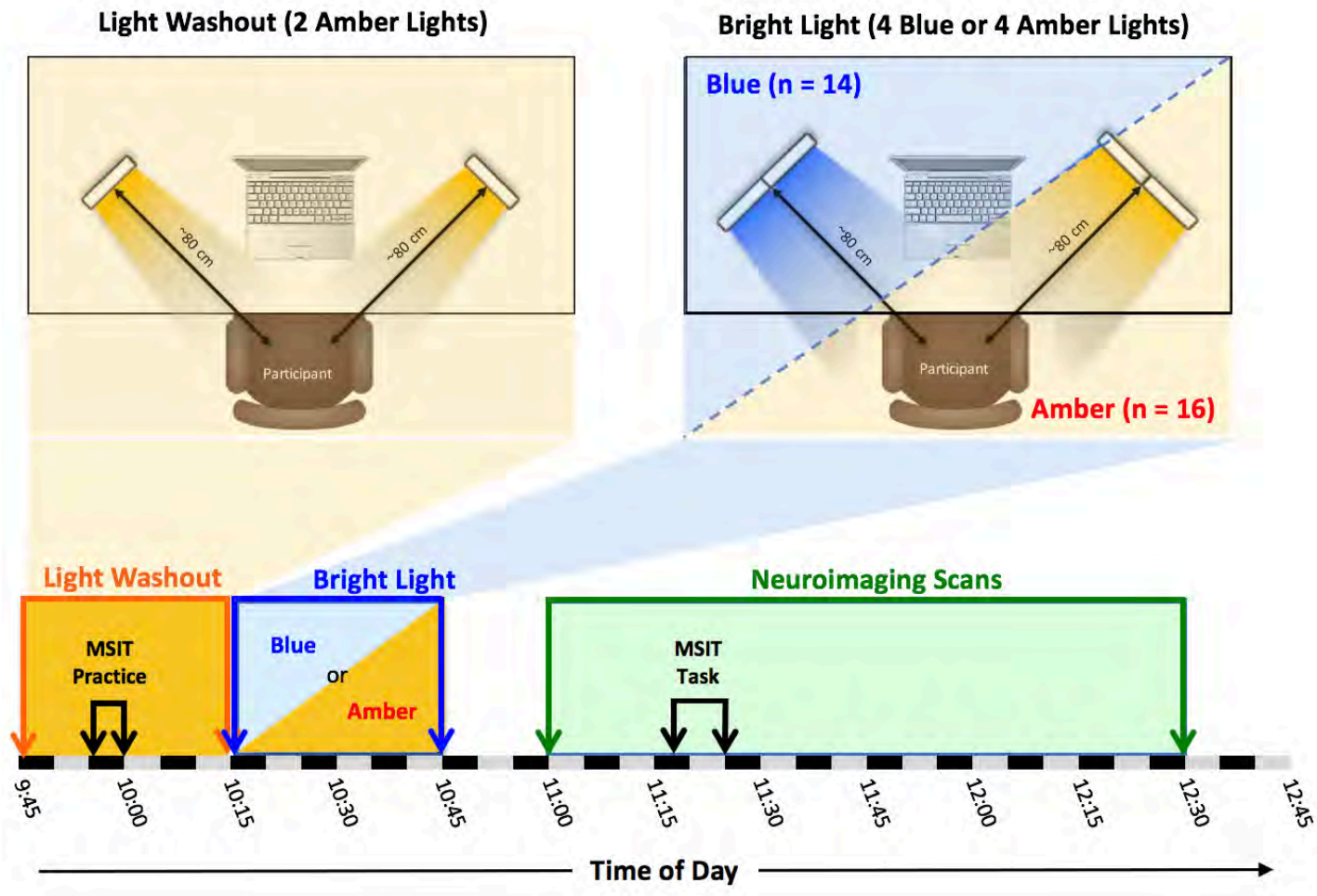

Light Washout (2 Amber Lights)
~80 cm
~80 cm
Participant
Bright Light (4 Blue or 4 Amber Lights)
Blue (n = 14)
~80 cm
~80 cm
Participant
Amber (n = 16)
Light Washout
MSIT Practice
Bright Light
Blue
or
Amber
Neuroimaging Scans
MSIT Task
9:45
10:00
10:15
10:30
10:45
11:00
11:15
11:30
11:45
12:00
12:15
12:30
12:45
Time of Day

Figure 2

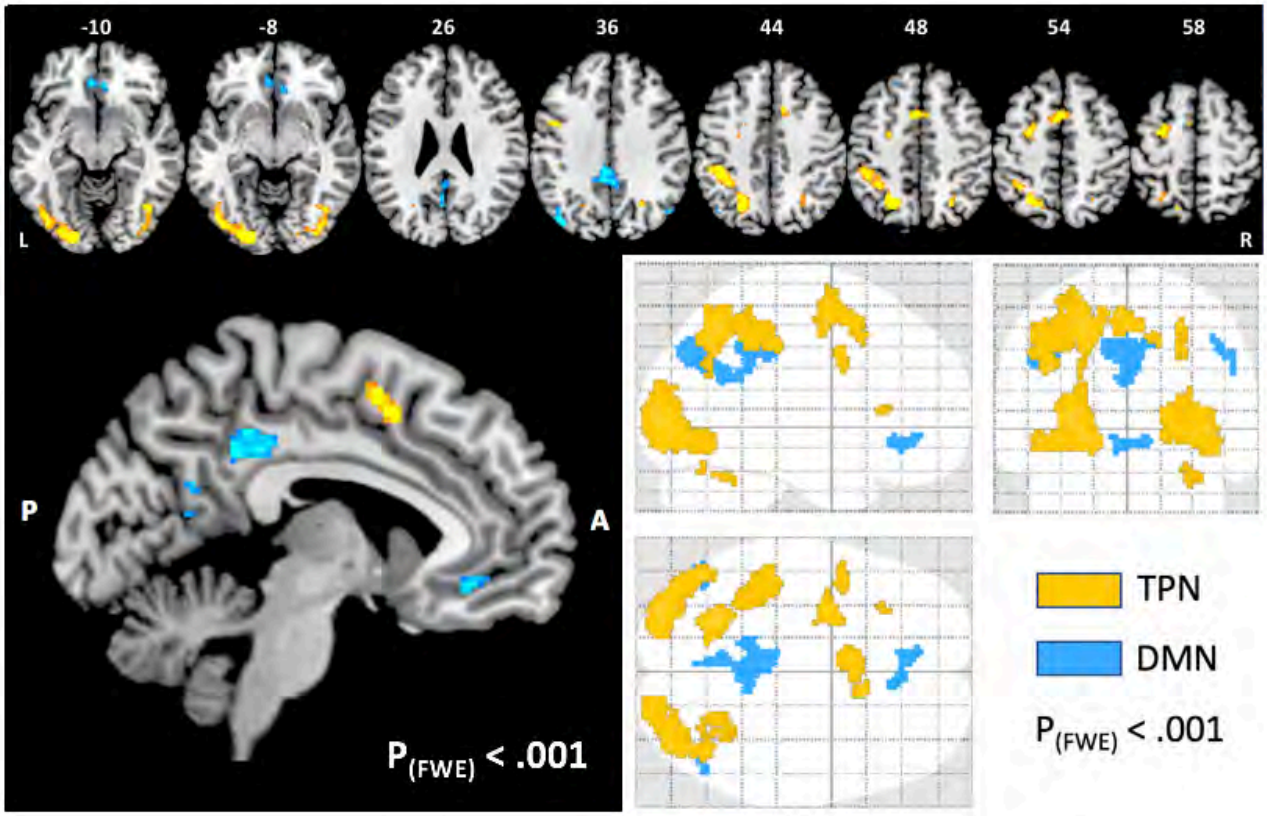
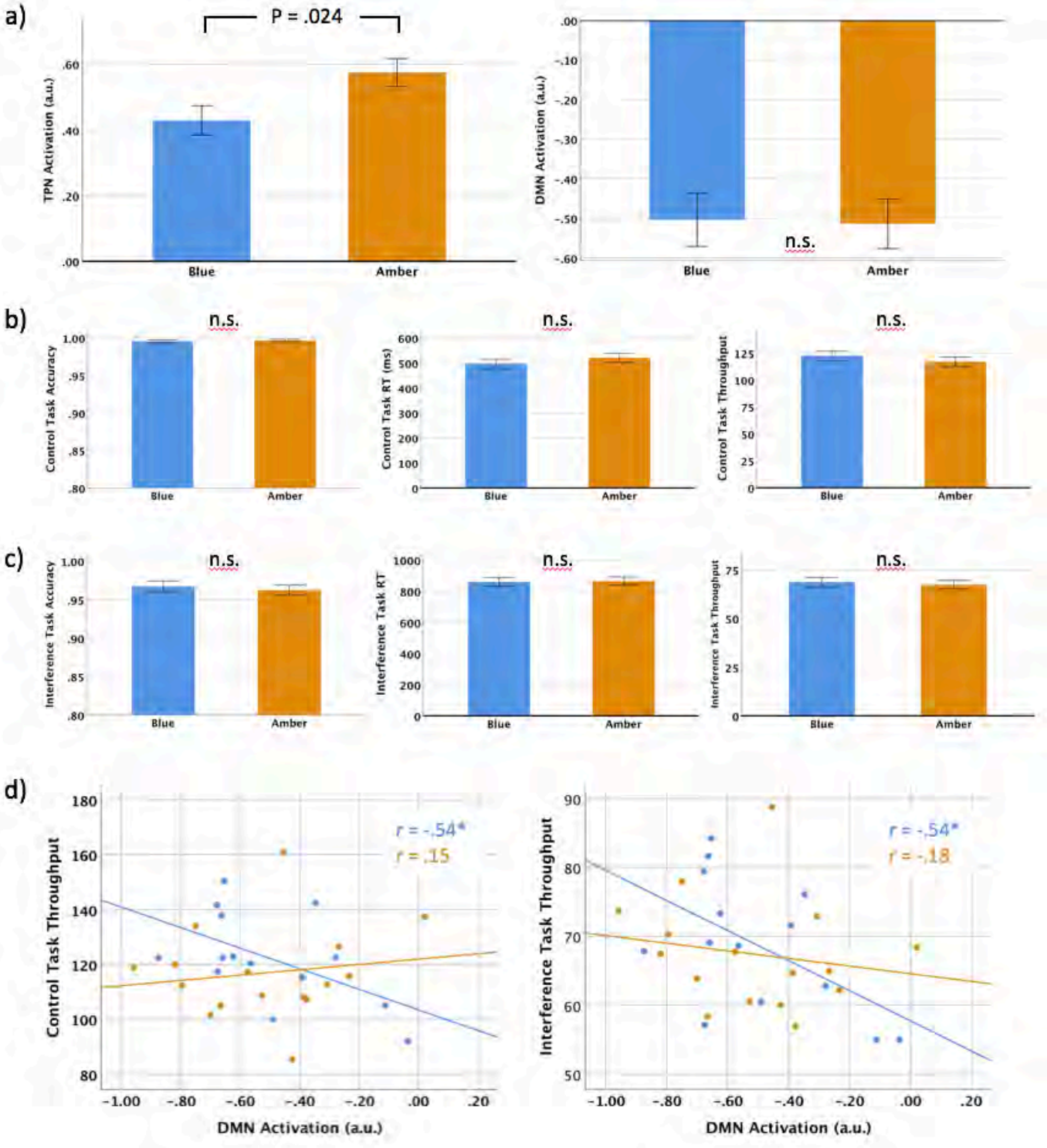


Figure 3


a)
P = .024
TPN Activation (a.u.)
.60
.40
.20
.00
Blue
Amber
DMN Activation (a.u.)
.00
-.10
-.20
-.30
-.40
-.50
-.60
n.s.
Blue
Amber
b)
n.s.
Control Task Accuracy
1.00
.95
.90
.85
.80
Blue
Amber
n.s.
Control Task RT (ms)
600
500
400
300
200
100
0
Blue
Amber
n.s.
Control Task Throughput
125
100
75
50
25
0
Blue
Amber
c)
n.s.
Interference Task Accuracy
1.00
.95
.90
.85
.80
Blue
Amber
n.s.
Interference Task RT
1000
800
600
400
200
0
Blue
Amber
n.s.
Interference Task Throughput
75
50
25
0
Blue
Amber
d)
Control Task Throughput
180
160
140
120
100
80
r = -.54*
r = .15
-1.00
-.80
-.60
-.40
-.20
.00
.20
DMN Activation (a.u.)
Interference Task Throughput
90
80
70
60
50
r = -.54*
r = -.18
-1.00
-.80
-.60
-.40
-.20
.00
.20
DMN Activation (a.u.)

Bright Light Therapy for Treatment of Sleep Problems Following Mild Traumatic Brain Injury

Log Number: PT130230; Award Number: W81XWH-14-1-0571

PI: William D. Killgore, Ph.D. **Org:** University of Arizona **Award Amount:** $1,853,909

Study Aims

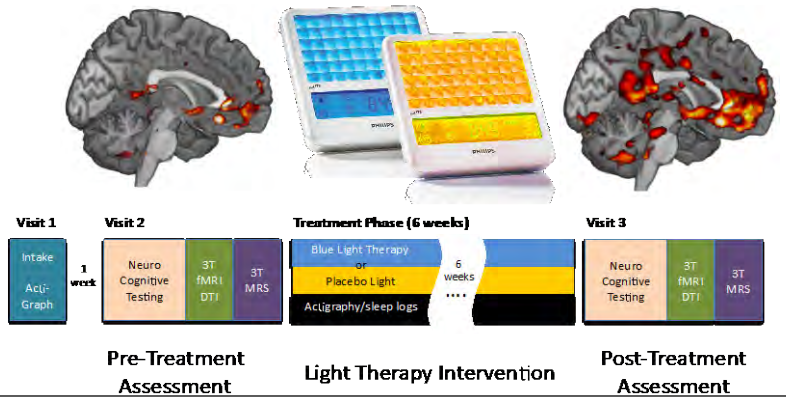
•**Aim 1**: Identify brain regions that are responsive to Blue Light and its association with melatonin changes (localization of effect—Study 1).

•**Aim 2**: Double the pilot study sample size by running an additional 30 participants through a randomized placebo-controlled trial to determine whether 6 weeks of treatment with Blue Light will improve self-reported and objective measures of sleep, brain function, brain structure, and cognitive performance in mTBI patients relative to Amber Light placebo.

Approach

Study 1 : Healthy participants will be exposed to 30 minutes of Blue or Amber light followed by functional MRI scanning and melatonin sampling. **Study 2**: Following MRI scanning and neurocognitive testing, 30 persons with mTBI will be randomly assigned to receive either 6-weeks of morning Blue Light or Amber Placebo light treatment, followed by post-tx scans and assessments. Data will be combined with the data collected from the pilot study to yield a more powerful study (n ≈ 60).

6-week Treatment (n = 15 per group)



Accomplishments: Study 1 (MRI Effect Localization Study) data collection is 100% complete. 13 manuscripts have been published, 54 conference abstracts published, and one thesis completed. Study 2 (main treatment study) is 100% complete. All aspects of the project have been completed and the final report submitted.

Timeline and Cost

Activities	CY14	CY15	CY16	CY17	CY18	CY19
Regulatory/IRB/HRPO						
Equipment Procurement						
Hiring/Training						
Data Collection: Study 1						
Data Collection: Study 2						
Analysis/Publication						
Estimated Total Budget ($K)	$154	$615	$617	$468	$0	$0

Updated: 25 DEC 2019

Goals/Milestones

CY14 Goal – Study Preparation

☑Obtain all Regulatory/IRB/HRPO approvals and start study

CY15-17 Goal – Recruitment and Data Collection

☑Collect All Data for Study 1 (currently **100% completed**)

☑Begin Data collection for Study 2 (Main Treatment Study)

☑Complete at least 67% of data collection for Study 2

CY18 Goal – No Cost Extension: Complete Data Collection and Analysis

☑Complete 100% of data collection (currently **100% completed**)

☑Analyze and Publish findings (will continue after study end date)

Goals/Milestones Accomplished

- 13 published papers & 54 abstracts accepted/published; 1 thesis.
- Treatment is effective for sleep timing, daytime sleepiness, specific neurocognitive recovery, and changes in brain structure/function

Budget Expenditure to Date

Projected Expenditure: $1,854K

Actual Expenditure: $1,854K

Curriculum Vitae

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PLACE AND DATE OF BIRTH	Anchorage Alaska, September 2, 1965
CITIZENSHIP	USA

CHRONOLOGY OF EDUCATION

8/83 - 5/85	A.A. (Liberal Arts), San Antonio College
8/83 - 5/85	A.A.S (Radio-TV-Film), San Antonio College
8/85 - 5/90	B.A. (Psychology), *Summa cum laude* with Distinction, University of New Mexico
8/90 - 5/92	M.A. (Clinical Psychology), Texas Tech University
8/92 - 8/96	Ph.D. (Clinical Psychology), Texas Tech University Dissertation Title: *Development and validation of a new instrument for the measurement of transient mood states: The facial analogue mood scale (FAMS)*. Lubbock, TX: Texas Tech University;1995. Advisor: Bill Locke, Ph.D.

POST-DOCTORAL TRAINING

8/95 - 7/96	Predoctoral Fellow, Clinical Psychology, Yale School of Medicine
8/96 - 7/97	Postdoctoral Fellow, Clinical Neuropsychology, University of OK Health Sciences Center
8/97 - 7/99	Postdoctoral Fellow, Clinical Neuropsychology, University of Pennsylvania Medical School
7/99 - 9/00	Research Fellow, Neuroimaging, McLean Hospital/ Harvard Medical School
9/13 - 5/14	Certificate in Applied Biostatistics, Harvard Medical School

LICENSURE/CERTIFICATION

2001 -	Licensed Psychologist, #966, State of New Hampshire

CHRONOLOGY OF EMPLOYMENT

Academic Appointments

10/00 - 8/02	Instructor in Psychology in the Department of Psychiatry Harvard Medical School, Boston, MA
9/02 - 7/07	Clinical Instructor in Psychology in the Department of Psychiatry Harvard Medical School, Boston, MA
8/07 - 10/10	Instructor in Psychology in the Department of Psychiatry Harvard Medical School, Boston, MA
4/08-	Faculty Affiliate, Division of Sleep Medicine Harvard Medical School, Boston, MA
10/10 - 10/12	Assistant Professor of Psychology in the Department of Psychiatry Harvard Medical School, Boston, MA
10/12 - 6/14	Associate Professor of Psychology in the Department of Psychiatry Harvard Medical School, Boston, MA
7/14-	Associate Professor of Psychology in the Department of Psychiatry (part-time) Harvard Medical School, Boston, MA
7/14-	Professor of Psychiatry—Tenured University of Arizona College of Medicine, Tucson, AZ
7/14-	Professor of Medical Imaging University of Arizona College of Medicine, Tucson, AZ
9/14-	Professor of Psychology University of Arizona College of Science, Tucson, AZ

Hospital/Clinical/Institutional Appointments

10/00 - 8/02	Assistant Research Psychologist, McLean Hospital, Belmont, MA
8/02 - 7/04	Research Psychologist, Department of Behavioral Biology, Walter Reed Army Institute of Research, Silver Spring, MD
7/04 - 10/07	Chief, Neurocognitive Performance Branch, Walter Reed Army Institute of Research, Silver Spring, MD
10/07 - 3/10	DoD Contractor, Chief Psychologist, GovSource, Inc., U.S. Department of Defense (DoD)
8/08	Consulting Psychologist, The Brain Institute, University of Utah
9/02 - 4/05	Special Volunteer, National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH), Bethesda, MD
9/02 - 7/07	Research Consultant, McLean Hospital, Belmont, MA
8/05 - 5/06	Neuropsychology Postdocotoral Research Program Training Supervisor, Walter Reed Hospital, Washington, DC
8/07 -	Research Psychologist, McLean Hospital, Belmont, MA
7/10 - 6-11	DoD Contractor, Consulting Psychologist, Clinical Research Management (CRM)
7/11 - 6/14	Director, Social Cognitive, and Affective Neuroscience (SCAN) Laboratory, McLean Hospital, Belmont, MA
7/14-	Director, Social, Cognitive, and Affective Neuroscience (SCAN) Laboratory, University of Arizona, Tucson, AZ
3/16 -12/18	ORISE Knowledge Preservation Fellow; Walter Reed Army Institute of Research, Silver Spring, MD

Military Positions

11/01 - 8/02	First Lieutenant, Medical Service Corps, United States Army Reserve (USAR)
8/02 - 7/05	Captain, Medical Service Corps, United States Army-Active Regular Army (RA)
8/05 - 10/07	Major, Medical Service Corps, United States Army-Active Regular Army (RA)
10/07 - 7/12	Major, Medical Service Corps, United States Army Reserve (USAR)
7/12 – 9/19	Lieutenant Colonel, Medical Service Corps, United States Army Reserve (USAR)
3/16 -	Deputy Consultant to the Surgeon General of the Army (SGA) for 71F Research Psychology, US Army Reserves
9/19-	Colonel, Medical Service Corps, United States Army Reserve (USAR)

HONORS AND AWARDS

1990	Outstanding Senior Honors Thesis in Psychology, University of New Mexico
1990-1995	Maxey Scholarship in Psychology, Texas Tech University
2001	Rennick Research Award, Co-Author, International Neuropsychological Society
2002	Honor Graduate, AMEDD Officer Basic Course, U.S. Army Medical Department Center and School
2002	Lynch Leadership Award Nominee, AMEDD Officer Basic Course, U.S. Army Medical Department Center and School
2003	Outstanding Research Presentation Award, 2003 Force Health Protection Conference, U.S. Army Center for Health Promotion and Preventive Medicine
2003	Who's Who in America
2004	Who's Who in Medicine and Healthcare
2005	Edward L. Buescher Award for Excellence in Research by a Young Scientist, Walter Reed Army Institute of Research (WRAIR) Association
2009	Merit Poster Award, International Neuropsychological Society
2009	Outstanding Research Presentation Award, 2009 Force Health Protection Conference, U.S. Army Center for Health Promotion and Preventive Medicine
2010	Best Paper Award, Neuroscience, 27th U.S. Army Science Conference
2011	Published paper included in *Best of Sleep Medicine 2011*
2011	Blue Ribbon Finalist, 2011 Top Poster Award in Clinical and Translational Research, Society of Biological Psychiatry
2012	Defense Advanced Research Projects Agency (DARPA) Young Faculty Award in Neuroscience
2014	Blue Ribbon Finalist, 2014 Top Poster Award in Basic Neuroscience, Society of Biological Psychiatry
2014	Harvard Medical School Excellence in Mentoring Award Nominee
2014	AASM Young Investigator Award (co-author), Honorable Mention, American Academy of Sleep Medicine
2017	Trainee Abstract Merit Award (mentor/co-author), Sleep Research Society
2018	Trainee Abstract Merit Award (mentor/co-author), Sleep Research Society.
2020	Nelson Butters Award for Best Paper by a Postdoctoral Fellow (mentor/co-author), International Neuropsychological Society

SERVICE/OUTREACH

Local/State Service/Outreach

2003	Scientific Review Committee, Walter Reed Army Institute of Research (WRAIR), Silver Spring, MD
2005	Scientific Review Committee, Walter Reed Army Institute of Research (WRAIR), Silver Spring, MD
2012-14	McLean Hospital Research Committee, McLean Hospital, Belmont, MA
2016	House Ad Hoc Committee on Treatment of Traumatic Brain Injuries and Benefits of Hyperbaric Oxygen Therapy, Arizona House of Representatives

National/International Service/Outreach

2004	University of Alabama, Clinical Nutrition Research Center (UAB CNRC) Pilot/Feasibility Study Program Review Committee
2006	U.S. Small Business Administration, Small Business Technology Transfer (STTR) Program Review Committee
2006	Cognitive Performance Assessment Program Area Steering Committee, U.S. Army Military Operational Medicine Research Program Funding Panel
2006	External Member, Doctoral Thesis Committee, Belinda J. Liddle, Ph.D., University of Sydney, Australia
2007	Cognitive Performance Assessment Program Area Steering Committee, U.S. Army Military Operational Medicine Research Program Funding Panel
2008	United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Extramural Grant Review Panel
2008-2011	Long-Distance High School Research Mentor, Christina Song, NY
2009	NIH-CSR Brain Disorders and Clinical Neuroscience N02 Member Study Conflict Section Review Panel
2009	Sleep Physiology and Fatigue Interventions Program Area Steering Committee, U.S. Army Military Operational Medicine Research Program
2009	Scotland, UK, Biomedical and Therapeutic Research Committee, Grant Reviewer
2010	Canada, Social Sciences and Humanities Research Council of Canada, Grant Reviewer
2011	National Science Foundation (NSF) Grant Reviewer
2011-	National Network of Depression Centers (NNDC), Military Task Group
2011	Israel, Israel Science Foundation (ISF), Grant Reviewer
2011	Scientific Review Committee, US Army Institute of Environmental Medicine (USARIEM)
2012	National Science Foundation (NSF) Grant Reviewer
2012-	American Academy of Sleep Medicine, Member
2013	Israel, Israel Science Foundation (ISF), Grant Reviewer
2014-	Organization for Human Brain Mapping, Member
2015-	Human Affectome Project Advisory Board Member
2016-	Sleep Research Society Member
2017-2018	External Reviewer, Doctoral Thesis Reviewer, Kalina R. Rossa, Queensland University of Technology, Australia.
2018	Marsden Fund Council Grant Proposal Referee, Royal Society Te Aparangi, New Zealand.
2018	External Faculty Promotion Dossier Reviewer, Oregon Health & Science University
2018-2019	Long-Distance High School Research Mentor, Taleen Postian, Byram Hills HS, NY
2019	External Reviewer, Doctoral Thesis Reviewer, William Ryan McMahon, Monash University, Australia.

Departmental Committees

2006	Chair, Undergraduate Honors Thesis Committee, Jessica Richards, Department of Psychology, University of Maryland, Baltimore County, MD
2012-	Member, Research Committee, McLean Hospital, Belmont, MA
2014	Psychiatry Senior Research Manager Candidate Search Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2014-2015	Member, Faculty Search Committee, Department of Psychology, University of Arizona, Tucson, AZ.
2014-2016	Member, Comprehensive Examination Committee, Natalie Bryant, Department of Psychology, University of Arizona, Tucson, AZ
2014-2015	Chair/Research Faculty Mentor, Undergraduate Honors Thesis Committee, Haley Kent, Department of Biochemistry, University of Arizona, Tucson, AZ
2014-	Member, Psychiatry Research Investigator Committee, Department of Psychiatry, University of Arizona, Tucson, AZ.
2015	Member, Dissertation Committee, Ryan S. Smith, Ph.D., Department of Psychology, University of Arizona, Tucson AZ.
2015	Imaging Excellence Cluster Hire Search Committee, Department of Medical Imaging, University of Arizona, Tucson, AZ
2015-	Member, Mentoring Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2016	Member, Chief of Neuroradiology Faculty Search Committee, Department of Medical Imaging, University of Arizona, Tucson, AZ
2016-2017	Member, Dissertation Committee, Brian Arizmendi, Department of Psychology, University of Arizona, Tucson, AZ
2016-2017	Member, Masters Thesis Committee, Saren Seeley, Department of Psychology, University of Arizona, Tucson, AZ
2016-2017	Member, Masters Thesis Committee, Mairead McConnell, Department of Psychology, University of Arizona, Tucson, AZ
2016-2018	Member, Masters Thesis Committee, John Vanuk, Department of Psychology, University of Arizona, Tucson, AZ
2016-2017	Faculty Advisor, Undergraduate Honor Thesis Committee, Matthew Nettles, Neuroscience/Cognitive Science, University of Arizona, Tucson, AZ
2016-	Scientific Review Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2017-2018	Faculty Advisor, Undergraduate Honors Thesis Committee, Debby Waugaman, Psychology, University of Arizona, Tucson, AZ
2017-2018	Faculty Advisor, Undergraduate Honors Thesis Committee, Jun Lee, Department of Psychology, University of Arizona, Tucson, AZ
2017-	Chair, Psychiatry Research Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2017-	Member, Promotion and Tenure Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2017-	Member, Mentoring Committee, Department of Psychiatry, University of Arizona, Tucson, AZ
2019	Member, Comprehensive Examination Committee, Ji-Soo Kim, Department of Psychology, University of Arizona, Tucson, AZ

2019 Member, Comprehensive Examination Committee, John Vanuk, Department of Psychology, University of Arizona, Tucson, AZ
2019- Member, Masters Thesis Committee, Veronica Kraft, Department of Psychology, University of Arizona, Tucson, AZ

University Committees/Service

2014 Ad Hoc Member, Interview Committee for Defense and Security Research Institute Director Position, University of Arizona, Tucson, AZ.
2014-2018 Member, Mechanisms of Emotion, Social Relationships, and Health Interdisciplinary Developing Research Program, Clinical and Translational Science Institute, BIO5, University of Arizona, Tucson, AZ
2015 Vice President's Executive Committee for Defense and Security Strategic Planning, University of Arizona, Tucson, AZ
2015- MRI Operations Committee, University of Arizona, Tucson, AZ
2016 Faculty Mentor, Undergraduate Biology Research Program (UBRP), University of Arizona, Tucson, AZ
2016 Faculty Mentor, Border Latino & American Indian Summer Exposure to Research (BLAISER) Program, University of Arizona, Tucson, AZ
2016 Faculty Mentor, Medical Student Research Committee (MSRC) Program, University of Arizona College of Medicine, Tucson, AZ
2018 Administrative Review Committee: Psychiatry Department Chair
2019 Reviewer, Psychology Department Faculty Pilot Grant Program
2019 Reviewer, Arizona Alzheimer's Consortium
2019- 3T Faculty Advisory Committee, University of Arizona, Tucson, AZ
2019 Faculty Mentor, Steps 2 STEM High School Research Internship Program, Tucson, AZ

Editorial Board Membership

2009-2018 Editorial Board Member, International Journal of Eating Disorders
2012- Editorial Board Member, Dataset Papers in Neuroscience
2012- Editorial Board Member, Dataset Papers in Psychiatry
2012- Editor, Journal of Sleep Disorders: Treatment and Care

Ad Hoc Journal Reviewer (102 Journals)

2001-2012 Reviewer, Psychological Reports
2001-2012 Reviewer, Perceptual and Motor Skills
2002 Reviewer, American Journal of Psychiatry
2002-2013 Reviewer, Biological Psychiatry
2003 Reviewer, Clinical Neurology and Neurosurgery
2004-2016 Reviewer, NeuroImage
2004-2006 Reviewer, Neuropsychologia
2004-2016 Reviewer, Journal of Neuroscience
2004 Reviewer, Consciousness and Cognition
2005 Reviewer, Experimental Brain Research

2005	Reviewer, Schizophrenia Research
2005-2012	Reviewer, Archives of General Psychiatry
2005	Reviewer, Behavioral Brain Research
2005-2009	Reviewer, Human Brain Mapping
2005-2013	Reviewer, Psychiatry Research: Neuroimaging
2006	Reviewer, Journal of Abnormal Psychology
2006	Reviewer, Psychopharmacology
2006	Reviewer, Developmental Science
2006	Reviewer, Acta Psychologica
2006, 2015	Reviewer, Neuroscience Letters
2006-2019	Reviewer, Journal of Sleep Research
2006-2016	Reviewer, Physiology and Behavior
2006-2019	Reviewer, SLEEP
2007	Reviewer, Journal of Clinical and Experimental Neuropsychology
2008	Reviewer, European Journal of Child and Adolescent Psychiatry
2008	Reviewer, Judgment and Decision Making
2008-2010	Reviewer, Aviation, Space, & Environmental Medicine
2008	Reviewer, Journal of Psychophysiology
2008	Reviewer, Brazilian Journal of Medical and Biological Research
2008	Reviewer, The Harvard Undergraduate Research Journal
2008	Reviewer, Bipolar Disorders
2008-2013	Reviewer, Chronobiology International
2008	Reviewer, International Journal of Obesity
2009	Reviewer, European Journal of Neuroscience
2009-2018	Reviewer, International Journal of Eating Disorders
2009	Reviewer, Psychophysiology
2009	Reviewer, Traumatology
2009	Reviewer, Clinical Medicine: Therapeutics
2009	Reviewer, Acta Pharmacologica Sinica
2009	Reviewer, Collegium Antropologicum
2009	Reviewer, Journal of Psychopharmacology
2009-2014	Reviewer, Obesity
2009	Reviewer, Scientific Research and Essays
2009	Reviewer, Child Development Perspectives
2009-2010	Reviewer, Personality and Individual Differences
2009-2010	Reviewer, Noise and Health
2009-2010	Reviewer, Sleep Medicine
2010	Reviewer, Nature and Science of Sleep
2010	Reviewer, Psychiatry and Clinical Neurosciences
2010	Reviewer, Learning and Individual Differences
2010	Reviewer, Cognitive, Affective, and Behavioral Neuroscience
2010	Reviewer, BMC Medical Research Methodology
2010-2011	Reviewer, Journal of Adolescence
2010-2012	Reviewer, Brain Research
2011	Reviewer, Brain
2011-2019	Reviewer, Social Cognitive and Affective Neuroscience
2011	Reviewer, Journal of Traumatic Stress
2011	Reviewer, Social Neuroscience

2011-2014	Reviewer, Brain and Cognition
2011	Reviewer, Frontiers in Neuroscience
2011-2012	Reviewer, Sleep Medicine Reviews
2012	Reviewer, Journal of Experimental Psychology: General
2012	Reviewer, Ergonomics
2012-2017	Reviewer, Behavioral Sleep Medicine
2012	Reviewer, Neuropsychology
2012	Reviewer, Emotion
2012	Reviewer, JAMA
2012	Reviewer, BMC Neuroscience
2012-2015	Reviewer, Cognition and Emotion
2012	Reviewer, Journal of Behavioral Decision Making
2012	Reviewer, Psychosomatic Medicine
2012-2014	Reviewer, PLoS One
2012	Reviewer, American Journal of Critical Care
2012-2014	Reviewer, Journal of Sleep Disorders: Treatment and Care
2013	Reviewer, Experimental Psychology
2013	Reviewer, Clinical Interventions in Aging
2013	Reviewer, Frontiers in Psychology
2013	Reviewer, Brain Structure and Function
2013	Reviewer, Appetite
2013-2018	Reviewer, JAMA Psychiatry
2014	Reviewer, Acta Psychologica
2014	Reviewer, Neurology
2014	Reviewer, Applied Neuropsychology: Child
2014-2016	Reviewer, Journal of Applied Psychology
2015	Reviewer, Early Childhood Research Quarterly
2015	Reviewer, Behavioral Neuroscience
2015-2019	Reviewer, Scientific Reports
2016-2018	Reviewer, Neuroscience & Biobehavioral Reviews
2016	Reviewer, Psychological Science
2016	Reviewer, Medicine & Science in Sports and Exercise
2016	Reviewer, Archives of Clinical Neuropsychology
2016	Reviewer, Advances in Cognitive Psychology
2017	Reviewer, Data in Brief
2017	Reviewer, Neuroscience
2017-2018	Reviewer, Sleep Health
2017	Reviewer, Journal of Experimental Social Psychology
2017-2018	Reviewer, Neural Plasticity
2018	Reviewer, NeuroImage: Clinical
2018	Reviewer, Journal of Psychiatric Research
2018	Reviewer, Journal of Clinical Sleep Medicine
2019	Reviewer, Harvard Review of Psychiatry
2019	Reviewer, Progress in Brain Research

PUBLICATIONS/CREATIVE ACTIVITY

Refereed Journal Articles

1. **Killgore WD**. The Affect Grid: a moderately valid, nonspecific measure of pleasure and arousal. Psychol Rep. 83(2):639-42, 1998.

2. **Killgore WD**. Empirically derived factor indices for the Beck Depression Inventory. Psychol Rep. 84(3 Pt 1):1005-13, 1999.

3. **Killgore WD**. Affective valence and arousal in self-rated depression and anxiety. Percept Mot Skills. 89(1):301-4, 1999.

4. **Killgore WD**, Adams RL. Prediction of Boston Naming Test performance from vocabulary scores: preliminary guidelines for interpretation. Percept Mot Skills. 89(1):327-37, 1999.

5. **Killgore WD**, Gangestad SW. Sex differences in asymmetrically perceiving the intensity of facial expressions. Percept Mot Skills. 89(1):311-4, 1999.

6. **Killgore WD**. The visual analogue mood scale: can a single-item scale accurately classify depressive mood state? Psychol Rep. 85(3 Pt 2):1238-43, 1999.

7. **Killgore WD**, DellaPietra L, Casasanto DJ. Hemispheric laterality and self-rated personality traits. Percept Mot Skills. 89(3 Pt 1):994-6, 1999.

8. **Killgore WD**, Glosser G, Casasanto DJ, French JA, Alsop DC, Detre JA. Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control. Seizure. 8(8):450-5, 1999.

9. **Killgore WD**. Evidence for a third factor on the Positive and Negative Affect Schedule in a college student sample. Percept Mot Skills. 90(1):147-52, 2000.

10. **Killgore WD**, Dellapietra L. Item response biases on the logical memory delayed recognition subtest of the Wechsler Memory Scale-III. Psychol Rep. 86(3 Pt 1):851-7, 2000.

11. **Killgore WD**, Casasanto DJ, Yurgelun-Todd DA, Maldjian JA, Detre JA. Functional activation of the left amygdala and hippocampus during associative encoding. Neuroreport. 11(10):2259-63, 2000.

12. Yurgelun-Todd DA, Gruber SA, Kanayama G, **Killgore WD**, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord. 2(3 Pt 2):237-48, 2000.

13. **Killgore WD**. Sex differences in identifying the facial affect of normal and mirror-reversed faces. Percept Mot Skills. 91(2):525-30, 2000.

14. **Killgore WD**, DellaPietra L. Using the WMS-III to detect malingering: empirical validation of the rarely missed index (RMI). J Clin Exp Neuropsychol. 22(6):761-71, 2000.

15. **Killgore WD**. Academic and research interest in several approaches to psychotherapy: a computerized search of literature in the past 16 years. Psychol Rep. 87(3 Pt 1):717-20, 2000.

16. Maldjian JA, Detre JA, **Killgore WD**, Judy K, Alsop D, Grossman M, Glosser G. Neuropsychologic performance after resection of an activation cluster involved in cognitive memory function. AJR Am J Roentgenol. 176(2):541-4, 2001.

17. **Killgore WD**, Oki M, Yurgelun-Todd DA. Sex-specific developmental changes in amygdala responses to affective faces. Neuroreport. 12(2):427-33, 2001.

18. **Killgore WD**, Yurgelun-Todd DA. Sex differences in amygdala activation during the perception of facial affect. Neuroreport. 12(11):2543-7, 2001.

19. Casasanto DJ, **Killgore WD**, Maldjian JA, Glosser G, Alsop DC, Cooke AM, Grossman M, Detre JA. Neural correlates of successful and unsuccessful verbal memory encoding. Brain Lang. 80(3):287-95, 2002.

20. **Killgore WD**. Laterality of lesions and trait-anxiety on working memory performance. Percept Mot Skills. 94(2):551-8, 2002.

21. **Killgore WD**, Cupp DW. Mood and sex of participant in perception of happy faces. Percept Mot Skills. 95(1):279-88, 2002.

22. Yurgelun-Todd DA, **Killgore WD**, Young AD. Sex differences in cerebral tissue volume and cognitive performance during adolescence. Psychol Rep. 91(3 Pt 1):743-57, 2002.

23. Yurgelun-Todd DA, **Killgore WD**, Cintron CB. Cognitive correlates of medial temporal lobe development across adolescence: a magnetic resonance imaging study. Percept Mot Skills. 96(1):3-17, 2003.

24. **Killgore WD**, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage. 19(4):1381-94, 2003.

25. **Killgore WD**, Yurgelun-Todd DA. Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. Neuroimage. 21(4):1215-23, 2004.

26. **Killgore WD**, Yurgelun-Todd DA. Sex-related developmental differences in the lateralized activation of the prefrontal cortex and amygdala during perception of facial affect. Percept Mot Skills. 99(2):371-91, 2004.

27. **Killgore WD**, Glahn DC, Casasanto DJ. Development and Validation of the Design Organization Test (DOT): a rapid screening instrument for assessing visuospatial ability. J Clin Exp Neuropsychol. 27(4):449-59, 2005.

28. **Killgore WD**, Yurgelun-Todd DA. Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods. Neuroreport. 16(8):859-63, 2005.

29. Wesensten NJ, **Killgore WD**, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J Sleep Res. 14(3):255-66, 2005.

30. **Killgore WD**, Yurgelun-Todd DA. Social anxiety predicts amygdala activation in adolescents viewing fearful faces. Neuroreport. 16(15):1671-5, 2005.

31. **Killgore WD**, Yurgelun-Todd DA. Developmental changes in the functional brain responses of adolescents to images of high and low-calorie foods. Dev Psychobiol. 47(4):377-97, 2005.

32. Kahn-Greene ET, Lipizzi EL, Conrad AK, Kamimori GH, **Killgore WD**. Sleep deprivation adversely affects interpersonal responses to frustration. Pers Individ Dif. 41(8):1433-1443, 2006.

33. McBride SA, Balkin TJ, Kamimori GH, **Killgore WD**. Olfactory decrements as a function of two nights of sleep deprivation. J Sens Stud. 24(4):456-63, 2006.

34. **Killgore WD**, Yurgelun-Todd DA. Ventromedial prefrontal activity correlates with depressed mood in adolescent children. Neuroreport. 17(2):167-71, 2006.

35. **Killgore WD**, Vo AH, Castro CA, Hoge CW. Assessing risk propensity in American soldiers: preliminary reliability and validity of the Evaluation of Risks (EVAR) scale--English version. Mil Med. 171(3):233-9, 2006.

36. **Killgore WD**, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. J Sleep Res. 15(1):7-13, 2006.

37. **Killgore WD**, Stetz MC, Castro CA, Hoge CW. The effects of prior combat experience on the expression of somatic and affective symptoms in deploying soldiers. J Psychosom Res. 60(4):379-85, 2006.

38. **Killgore WD**, McBride SA, Killgore DB, Balkin TJ. The effects of caffeine, dextroamphetamine, and modafinil on humor appreciation during sleep deprivation. Sleep. 29(6):841-7, 2006.

39. **Killgore WD**, McBride SA. Odor identification accuracy declines following 24 h of sleep deprivation. J Sleep Res. 15(2):111-6, 2006.

40. **Killgore WD**, Yurgelun-Todd DA. Affect modulates appetite-related brain activity to images of food. Int J Eat Disord. 39(5):357-63, 2006.

41. Kendall AP, Kautz MA, Russo MB, **Killgore WD**. Effects of sleep deprivation on lateral visual attention. Int J Neurosci. 116(10):1125-38, 2006.

42. Yurgelun-Todd DA, **Killgore WD**. Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study. Neurosci Lett. 406(3):194-9, 2006.

43. **Killgore WD**, Killgore DB, Ganesan G, Krugler AL, Kamimori GH. Trait-anger enhances effects of caffeine on psychomotor vigilance performance. Percept Mot Skills. 103(3):883-6, 2006.

44. **Killgore WD**, Yurgelun-Todd DA. Unconscious processing of facial affect in children and adolescents. Soc Neurosci. 2(1):28-47, 2007.

45. **Killgore WD**, Yurgelun-Todd DA. The right-hemisphere and valence hypotheses: could they both be right (and sometimes left)?. Soc Cogn Affect Neurosci. 2(3):240-50, 2007.

46. **Killgore WD**, Killgore DB. Morningness-eveningness correlates with verbal ability in women but not men. Percept Mot Skills. 104(1):335-8, 2007.

47. **Killgore WD**, Killgore DB, Day LM, Li C, Kamimori GH, Balkin TJ. The effects of 53 hours of sleep deprivation on moral judgment. Sleep. 30(3):345-52, 2007.

48. Rosso IM, **Killgore WD**, Cintron CM, Gruber SA, Tohen M, Yurgelun-Todd DA. Reduced amygdala volumes in first-episode bipolar disorder and correlation with cerebral white matter. Biol Psychiatry. 61(6):743-9, 2007.

49. Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, **Killgore WD**. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. Sleep Med. 8(3):215-21, 2007.

50. **Killgore WD**. Effects of sleep deprivation and morningness-eveningness traits on risk-taking. Psychol Rep. 100(2):613-26, 2007.

51. **Killgore WD**, Gruber SA, Yurgelun-Todd DA. Depressed mood and lateralized prefrontal activity during a Stroop task in adolescent children. Neurosci Lett. 416(1):43-8, 2007.

52. **Killgore WD**, Yurgelun-Todd DA. Positive affect modulates activity in the visual cortex to images of high calorie foods. Int J Neurosci. 117(5):643-53, 2007.

53. Vo AH, Satori R, Jabbari B, Green J, **Killgore WD**, Labutta R, Campbell WW. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med. 78(5 Suppl):B113-8, 2007.

54. **Killgore WD**, Yurgelun-Todd DA. Neural correlates of emotional intelligence in adolescent children. Cogn Affect Behav Neurosci. 7(2):140-51, 2007.

55. **Killgore WD**, Kendall AP, Richards JM, McBride SA. Lack of degradation in visuospatial perception of line orientation after one night of sleep loss. Percept Mot Skills. 105(1):276-86, 2007.

56. **Killgore WD**, Lipizzi EL, Kamimori GH, Balkin TJ. Caffeine effects on risky decision making after 75 hours of sleep deprivation. Aviat Space Environ Med. 78(10):957-62, 2007.

57. **Killgore WD**, Richards JM, Killgore DB, Kamimori GH, Balkin TJ. The trait of Introversion-Extraversion predicts vulnerability to sleep deprivation. J Sleep Res. 16(4):354-63, 2007.

58. **Killgore WD**, Kahn-Green ET, Killgore DB, Kamimori GH, Balkin TJ. Effects of acute caffeine withdrawal on Short Category Test performance in sleep-deprived individuals. Percept Mot Skills. 105(3 pt.2):1265-74, 2007.

59. **Killgore WD**, Killgore DB, McBride SA, Kamimori GH, Balkin TJ. Odor identification ability predicts changes in symptoms of psychopathology following 56 hours of sleep deprivation. J Sensory Stud. 23(1):35-51, 2008.

60. **Killgore WD**, Rupp TL, Grugle NL, Reichardt RM, Lipizzi EL, Balkin TJ. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. J Sleep Res. 17(3):309-21, 2008.

61. Huck NO, McBride SA, Kendall AP, Grugle NL, **Killgore WD**. The effects of modafinil, caffeine, and dextroamphetamine on judgments of simple versus complex emotional expressions following sleep deprivation. Int. J Neuroscience. 118(4):487-502, 2008.

62. **Killgore WD**, Kahn-Greene ET, Lipizzi EL, Newman RA, Kamimori GH, Balkin TJ. Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. Sleep Med. 9(5):517-26, 2008.

63. **Killgore WD**, Grugle NL, Killgore DB, Leavitt BP, Watlington GI, McNair S, Balkin TJ. Restoration of risk-propensity during sleep deprivation: caffeine, dextroamphetamine, and modafinil. Aviat Space Environ Med. 79(9):867-74, 2008.

64. **Killgore WD**, Muckle AE, Grugle NL, Killgore DB, Balkin TJ. Sex differences in cognitive estimation during sleep deprivation: effects of stimulant countermeasures. Int J Neurosci. 118(11):1547-57, 2008.

65. **Killgore WD**, Cotting DI, Thomas JL, Cox AL, McGurk D, Vo AH, Castro CA, Hoge CW. Post-combat invincibility: violent combat experiences are associated with increased risk-taking propensity following deployment. J Psychiatr Res. 42(13):1112-21, 2008.

66. **Killgore WD**, Gruber SA, Yurgelun-Todd DA. Abnormal corticostriatal activity during fear perception in bipolar disorder. Neuroreport. 19(15):1523-7, 2008.

67. **Killgore WD**, McBride SA, Killgore DB, Balkin TJ, Kamimori GH. Baseline odor identification ability predicts degradation of psychomotor vigilance during 77 hours of sleep deprivation. Int. J Neurosci. 118(9):1207-1225, 2008.

68. **Killgore WD**, Rosso HM, Gruber SA, Yurgelun-Todd DA. Amygdala volume and verbal memory performance in schizophrenia and bipolar disorder. Cogn Behav Neur. 22(1):28-37, 2009.

69. **Killgore WD**, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ. Sustaining executive functions during sleep deprivation: A comparison of caffeine, dextroamphetamine, and modafinil. Sleep. 32(2):205-16, 2009.

70. **Killgore WD**, Grugle NL, Reichardt RM, Killgore DB, Balkin TJ. Executive functions and the ability to sustain vigilance during sleep loss. Aviat Space Environ Med. 80(2):81-7, 2009.

71. Picchioni, D, **Killgore, WD,** Braun, AR, & Balkin, TJ. Positron emission tomography correlates of EEG microarchitecture waveforms during non-REM sleep. Int J Neurosci. 119: 2074-2099, 2009.

72. **Killgore, WD**, Lipizzi, EL, Grugle, NL, Killgore, DB, & Balkin, TJ. Handedness correlates with actigraphically measured sleep in a controlled environment. Percept Mot Skills. 109: 395-400, 2009.

73. **Killgore, WD**, Killgore, DB, Grugle, NL, & Balkin, TJ. Odor identification predicts executive function deficits during sleep deprivation. Int J Neurosci, 120: 328-334, 2010.

74. **Killgore, WD**, Ross, AJ, Kamiya, T, Kawada, Y, Renshaw, PF, & Yurgelun-Todd, DA. Citicoline affects appetite and cortico-limbic responses to images of high calorie foods. Int J Eat Disord. 43: 6-13, 2010.

75. **Killgore, WD,** & Yurgelun-Todd, DA. Cerebral correlates of amygdala responses during non-conscious perception of facial affect in adolescent and pre-adolescent children. Cogn Neurosci, 1: 33-43, 2010.

76. **Killgore, WD**, & Yurgelun-Todd, DA. Sex differences in cerebral responses to images of high vs low calorie food. Neuroreport, 21: 354-358, 2010.

77. **Killgore, WD**, Grugle, NL, Killgore, DB, & Balkin, TJ. Sex differences in self-reported risk-taking propensity on the Evaluation of Risks scale. Percept Mot Skills, 106: 693-700, 2010.

78. **Killgore, WD**, Kelley, AM, & Balkin, TJ. So you think you're bulletproof: Development and validation of the Invincibility Belief Index. Mil Med, 175: 499-508, 2010.

79. **Killgore, WD**, Castro, CA, & Hoge, CW. Preliminary Normative Data for the Evaluation of Risks Scale—Bubble Sheet Version (EVAR-B) for Large Scale Surveys of Returning Combat Veterans. Mil Med, 175: 725-731, 2010.

80. Britton, JC, Rauch, SL, Rosso, IM, **Killgore, WD**, Price, LM, Ragan, J, Chosak, A, Hezel, D, Pine, DS, Leibenluft, E, Pauls, DL, Jenike, MA, Stewart, SE. Cognitive inflexibility and frontal cortical activation in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry, 49: 944-953, 2010.

81. Britton, JC, Stewart, SE, **Killgore, WD**, Rosso, IM, Price, LM, Gold, AL, Pine, DS, Wilhelm, S, Jenike, MA, & Rauch, SL. Amygdala activation in response to facial expressions in pediatric obsessive-compulsive disorder. Depress Anxiety, 27: 643-651, 2010.

82. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Socializing by day may affect performance by night: Vulnerability to sleep deprivation is differentially mediated by social exposure in extraverts vs. introverts. Sleep, 33: 1475-1485, 2010.

83. Rosso, IM, Makris, N, Britton, JC, Price, LM, Gold, AL, Zai, D, Bruyere, J, Deckersbach, T, **Killgore, WD**, & Rauch, SL. Anxiety sensitivity correlates with two indices of right anterior

insula structure in specific animal phobia. Depress Anxiety, 27: 1104-1110, 2010.

84. **Killgore, WD**, Britton, JC, Price, LM, Gold, AL, Deckersbach, T, & Rauch, SL. Neural correlates of anxiety sensitivity during masked presentation of affective faces. Depress Anxiety, 28: 243-249, 2011.

85. **Killgore, WD**, Kamimori, GH, & Balkin, TJ. Caffeine protects against increased risk-taking propensity during severe sleep deprivation. J Sleep Res 20: 395-403, 2011.

86. Capaldi, VF, Guerrero, ML, & **Killgore, WD**. Sleep disruption among returning combat veterans from Iraq and Afghanistan. Mil Med, 176: 879-888, 2011.

87. **Killgore, WD**, Grugle, NL, & Balkin, TJ. Gambling when sleep deprived: Don't bet on stimulants. Chronobiol Int, 29: 43-54, 2012.

88. Gruber, SA, Dahlgren, MK, Sagar, KA, Gonenc, A, & **Killgore, WD.** Age of onset of marijuana use impacts inhibitory processing. Neurosci Lett 511(2):89-94, 2012.

89. **Killgore, WD**, Capaldi, VF, & Guerrero, ML. Nocturnal polysomnographic correlates of daytime sleepiness. Psychol Rep, 110(10), 63-72, 2012.

90. **Killgore, WD**, Weber, M, Schwab, ZJ, DelDonno, SR, Kipman, M, Weiner, MR, & Rauch, SL. Grey matter correlates of trait and ability models of emotional intelligence. Neuroreport 23, 551-555, 2012.

91. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, Weber, M. Voxel-based morphometric grey matter correlates of daytime sleepiness. Neurosci Lett, 518(1), 10-13, 2012.

92. **Killgore, WD**, Schwab, ZJ, & Weiner, MR. Self-reported nocturnal sleep duration is associated with next-day resting state functional connectivity. Neuroreport, 23, 741-745, 2012.

93. **Killgore, WD**, & Schwab, ZJ. Sex differences in the association between physical exercise and cognitive ability. Perceptual and Motor Skills, 115, 605-617, 2012.

94. Kipman, M, Weber, M, Schwab, ZJ, DelDonno, SR, & **Killgore, WD**. A funny thing happened on the way to the scanner: Humor detection correlates with gray matter volume. Neuroreport, 23, 1059-1064, 2012.

95. **Killgore, WD**, Schwab, ZJ, Weber, M, Kipman, M, DelDonno, SR, Weiner, MR, & Rauch, SL. Daytime sleepiness affects prefrontal regulation of food intake. NeuroImage, 71, 216-223, 2013.

96. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, & Weber, M. Insomnia-related complaints correlate with functional connectivity between sensory-motor regions. Neuroreport, 24, 233-240, 2013.

97. Weber, M, Webb, CA, DelDonno, SR, Kipman, M, Schwab, ZJ, Weiner, MR, & **Killgore, WD**. Habitual 'Sleep Credit' is associated with greater gray matter volume of the medial prefrontal

cortex, higher emotional intelligence, and better mental health. Journal of Sleep Research, 22, 527-534, 2013.

98. Weber, M., **Killgore, WD**, Rosso, IM, Britton, JC, Schwab, ZJ, Weiner, MR, Simon, NM, Pollack, MH, & Rauch, SL. Voxel-based morphometric gray matter correlates of posttraumatic stress disorder. Journal of Anxiety Disorders, 27, 413-419, 2013.

99. **Killgore, WD**, Schwab, ZJ, Tkachenko, O, Webb, CA, DelDonno, SR, Kipman M, Rauch SL, and Weber M. Emotional intelligence correlates with functional responses to dynamic changes in facial trustworthiness. Social Neuroscience, 8, 334-346, 2013.

100. **Killgore, WD**. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. Sleep, 36, 1597-1608, 2013.

101. **Killgore, WD**, Kipman, M, Schwab, ZJ, Tkachenko, O, Preer, L, Gogel, H, Bark, JS, Mundy, EA, Olson, EA, & Weber, M. Physical exercise and brain responses to images of high calorie food. Neuroreport, 24, 962-967, 2013.

102. **Killgore, WD**, Weber, M, Schwab, ZJ, Kipman, M, DelDonno, SR, Webb, CA, & Rauch, SL. Cortico-limbic responsiveness to high-calorie food images predicts weight status among women. International Journal of Obesity, 37, 1435-1442, 2013.

103. Thomas, JJ, Hartman, AS, & **Killgore, WD**. Non-fat-phobic eating disorders: Why we need to investigate implicit associations and neural correlates. International Journal of Eating Disorders, 46, 416-419, 2013.

104. Webb, CA, Schwab, ZJ, Weber, M, DelDonno, SR, Kipman M, Weiner, MR, & **Killgore WD**. Convergent and divergent validity of integrative versus mixed model measures of emotional intelligence. Intelligence, 41, 149-156, 2013.

105. Weber, M, Webb, CA, & **Killgore, WD**. A brief and selective review of treatment approaches for sleep disturbance following traumatic brain injury. Journal of Sleep Disorders and Therapy, 2 (2), 1-5, 2013 (electronic publication).

106. **Killgore, WD,** Olson, EA, & Weber, M. Physical exercise habits correlate with gray matter volume of the hippocampus in healthy humans. Scientific Reports, 3, 3457, doi: 10.1038/srep0347, 2013.

107. **Killgore, WD**, Britton, JC, Schwab, ZJ, Price, LM, Weiner, MR, Gold, AL, Rosso, IM, Simon, NM, Pollack, MH, & Rauch, SL. Cortico-Limbic Responses to Masked Affective Faces Across PTSD, Panic Disorder, and Specific Phobia. Depression & Anxiety, 31, 150-159, 2014.

108. Cohen-Gilbert, JE, **Killgore, WD**, White, CN, Schwab, ZJ, Crowley, DJ, Covell, MJ, Sneider, JT, & Silveri, MM. Differential influence of safe versus threatening facial expressions on decision-making during an inhibitory control task in adolescence and adulthood. Developmental Science, 17, 212-223, 2014.

109. Dillon, DG, Rosso, IM, Pechtel, P, **Killgore, WD**, Rauch, SL, & Pizzagalli, DA. Peril and pleasure: An RDoC-inspired examination of threat responses and reward processing in anxiety and depression. Depression and Anxiety, 31, 233-249, 2014.

110. Preer, L, Tkachenko, O, Gogel, H., Bark, JS, & **Killgore, WD**. Personality traits associated with sleep initiation problems. Journal of Sleep Disorders: Treatment and Care, 3, 1-5, doi:10.4172/2325-9639.1000127, 2014.

111. Tkachenko, O, Olson, EA, Weber, M, Preer, LA, Gogel, H, & **Killgore, WD.** Sleep difficulties are associated with elevated symptoms of psychopathology. Experimental Brain Research, 232, 1567-1574, 2014.

112. Cui, J., Olson, EA, Weber, M, Schwab, ZJ, Rosso, IM, Rauch, SL, & **Killgore, WD**. Trait emotional suppression is associated with increased activation of the rostral anterior cingulate cortex in response to masked angry faces. NeuroReport, 25, 771-776, 2014.

113. Webb, CA, DelDonno, S, & **Killgore, WD**. The role of cognitive versus emotional intelligence in Iowa Gambling Task performance: What's emotion got to do with it? Intelligence, 44, 112-119, 2014.

114. **Killgore WD**, & Gogel, H. The Design Organization Test (DOT): Further Demonstration of Reliability and Validity as a Brief Measure of Visuospatial Ability. Applied Neuropsychology: Adult, 21, 297-309, 2014.

115. Webb, CA, Weber, M, Mundy, EA, & **Killgore, WD**. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: A voxel-based morphometric analysis. Psychological Medicine, 44, 2833-2843, 2014.

116. **Killgore, WD**, Kamimori, GH, & Balkin, TJ. Caffeine improves the efficiency of planning and sequencing abilities during sleep deprivation. Journal of Clinical Psychopharmacology, 34, 660-662, 2014.

117. Rosso, IM, Olson, EA, Britton, JC, Steward, SE, Papadimitriou, G, **Killgore, WD**, Makris, N, Wilhelm, S, Jenike, MA, & Rauch SL. Brain white matter integrity and association with age at onset in pediatric obsessive-compulsive disorder. Biology of Mood & Anxiety Disorders, 4:13, 1-10, 2014.

118. Cui, J, Tkachenko, O, Gogel, H, Kipman, M, Preer, LA, Weber, M, Divatia, SC, Demers, LA, Olson, EA, Buchholz, JL, Bark, JS, Rosso, IM, Rauch, SL, & **Killgore, WD**. Microstructure of frontoparietal connections predicts individual resistance to sleep deprivation. NeuroImage, 106, 123-133, 2015.

119. Brennan, BP, Tkachenko, O, Schwab, ZJ, Juelich, RJ, Ryan, EM, Athey, AJ, Pope, HG, Jenike, MA, Baker, JT, **Killgore, WD**, Hudson, JI, Jensen, JE, & Rauch, SL. An examination of rostral anterior cingulate cortex function and neurochemistry in obsessive-compulsive disorder. Neuropsychopharmacology, 40, 1866-1876, 2015.

120. Alkozei, A, & **Killgore WD**. Emotional intelligence is associated with reduced insula responses to angry faces. NeuroReport, 26, 567-571, 2015.

121. Mundy, EA, Weber, M, Rauch, SL, **Killgore, WD**, Simon, NM, Pollack, MH, & Rosso, IM. Adult anxiety disorders in relation to trait anxiety and perceived stress in childhood. Psychological Reports, 117, 1-17, 2015.

122. **Killgore, WD**, Vanuk, JR, Knight, SA, Markowski, SM, Pisner, D, Shane B, Fridman, A, & Alkozei, A. Daytime sleepiness is associated with altered resting thalamocortical connectivity. NeuroReport, 26, 779-784, 2015.

123. Olson, EA, Rosso, IM, Demers, LA, Divatia, S., & **Killgore, WD**. Sex differences in psychological factors associated with social discounting. Journal of Behavioral Decision Making, 29, 60-66, 2016.

124. Alkozei, A, Schwab, ZJ, & **Killgore, WD**. The role of emotional intelligence during an emotionally difficult decision-making task. Journal of Nonverbal Behavior, 40, 39-54, 2016.

125. **Killgore, WD**, Singh, P, Kipman, M, Pisner, D, Fridman, A, and Weber, M. Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury. Neuroscience Letters, 612, 238-244, 2016.

126. Alkozei, A, Smith, R, & **Killgore, WD**. Exposure to blue wavelength light modulates anterior cingulate cortex activation in response to 'uncertain' versus 'certain' anticipation of positive stimuli. Neuroscience Letters, 616, 5-10, 2016.

127. Olson, EA, Weber, M, Rauch, SL, & **Killgore, WD**. Daytime sleepiness is associated with reduced integration of temporally distant outcomes on the Iowa Gambling Task. Behavioral Sleep Medicine, 14, 200-211, 2016.

128. **Killgore, WD**, Sonis, LA, Rosso, IM, & Rauch, SL. Emotional intelligence partially mediates the association between anxiety sensitivity and anxiety symptoms. Psychological Reports, 118, 23-40, 2016.

129. Freed, MC, Novak, LA, **Killgore, WD**, Rauch, S, Koehlmoos, TP, Ginsberg, JP, Krupnick, J, Rizzo, AS, Andrews, A, & Engle, CC. IRB and research regulatory delays within the military healthcare setting: Do they really matter? And if so, why and for whom? American Journal of Bioethics, 16, 30-37, 2016.

130. Alkozei, A, Smith, R, Pisner, D, Vanuk, JR, Markowski, SM, Fridman, A, Shane, BR, Knight, SA, & **Killgore, WD**. Exposure to blue light increases later functional activation of the prefrontal cortex during working memory. SLEEP, 39, 1671-1680, 2016.

131. Smith, R, Alkozei, A, Lane, RD, & **Killgore, WD**. Unwanted reminders: The effects of emotional memory suppression on subsequent neuro-cognitive processing. Consciousness and Cognition, 44, 103-113, 2016.

132. Kelly, MR, **Killgore, WD**, Haynes, PL. Understanding recent insights in sleep and posttraumatic stress disorder from a research domain criteria (RDoC) framework. Current Sleep Medicine Reports, 2, 223-232, 2016.

133. Rosso, IM, **Killgore, WD**, Olson, EA, Webb, CA, Fukunaga, R, Auerbach, RP, Gogel, H, Buchholz, JL, & Rauch, SL. Internet-based cognitive behavior therapy for major depressive disorder: A randomized controlled trial. Depression and Anxiety, 34, 236-245, 2017.

134. Alkozei, A, Smith, R, Kotzin, MD, Waugaman, DL, & **Killgore, WD**. The association between trait gratitude and self-reported sleep quality is mediated by depressive mood state. Behavioral Sleep Medicine, 1-9, 2017.

135. Smith, R, Alkozei, A, & **Killgore, WD**. Contributions of self-report and performance-based individual differences measures of social cognitive ability on large-scale network functioning. Brain Imaging and Behavior, 11, 685-697, 2017.

136. Pisner, DA, Smith, R, Alkozei, A, Klimova, A, & **Killgore, WD**. Highways of the emotional intellect: White matter microstructural correlates of an ability-based measure of emotional intelligence. Social Neuroscience, 12, 253-267, 2017.

137. **Killgore, WD**, Balkin, TJ, Yarnell, AM, & Capaldi, VF. Sleep deprivation impairs recognition of specific emotions. Neurobiology of Sleep and Circadian Rhythms, 3, 10-16, 2017.

138. Smith, R, Lane, R, Alkozei, A, Bao, J, Smith, C, Sanova, A, Nettles, M, & **Killgore, WD**. Maintaining the feelings of others in working memory is associated with activation of the left anterior insula and left frontal-parietal control networks. Social, Cognitive, and Affective Neuroscience, 12, 848-860, 2017.

139. Marin, MF, Zsido, RG, Song, H, Lasko, NB, **Killgore, WD**, Rauch SL, Simon, NM, & Milad, MR. Skin conductance responses and neural activations during fear conditioning and extinction recall across anxiety disorders. JAMA Psychiatry, 74, 622-631, 2017.

140. Alkozei, A*, **Killgore, WD***, Smith, R, Dailey, NS, Bajaj, S, & Haack M. Chronic sleep restriction increases negative implicit attitudes toward Arab Muslims. Scientific Reports, 7: 4285, 1-6, 2017. (*authors contributed equally).

141. **Killgore, WD**, Smith, R, Olson EA, Weber, M, Rauch, SL, & Nickerson, LD. Emotional intelligence is associated with connectivity within and between resting state networks. Social Cognitive and Affective Neuroscience, 12, 1624-1636, 2017.

142. Smith, R, Alkozei, A, Bao, J, Lane, RD, & **Killgore, WD**. Resting state functional connectivity correlates of emotional awareness. NeuroImage, 159, 99-106, 2017.

143. Alkozei, A, Smith, R, Dailey, NS, Bajaj, S, & **Killgore, WD**. Acute exposure to blue wavelength light during memory consolidation improves verbal memory performance. PLoS One, 12, e0184884, 2017.

144. Bajaj, S, Vanuk, JR, Smith, R, Sailey, NS, & **Killgore, WD**. Blue light therapy following mild traumatic brain injury: Effects on white mater water diffusion in the brain. Frontiers in Neurology, 8, 616, 2017.

145. Bajaj, S, Alkozei, A, Dailey, NS, & **Killgore, WD**. Brain aging: Uncovering cortical characteristics of healthy aging in you adults. Frontiers in Aging Neuroscience, 9, 412, 2017.

146. Smith, R, Alkozei, A, Bao, J, & **Killgore WD**. Successful goal-directed memory suppression is associated with increased inter-hemispheric coordination between right and left fronto-parietal control networks. Psychological Reports, 121, 93-111, 2018.

147. Alkozei, A, Smith, R, & **Killgore, WD**. Gratitude and subjective wellbeing: A Proposal of two causal frameworks. Journal of Happiness Studies, 5, 1519-1542, 2018.

148. Smith, R, Alkozei, A, & **Killgore, WD**. Conflict-Related Dorsomedial Frontal Cortex Activation During Healthy Food Decisions is Associated with Increased Cravings for High-Fat Foods. Brain Imaging and Behavior, 12, 685-696, 2018.

149. Webb, CA, Olson, EA, **Killgore, WD**, Pizzagalli, DA, Rauch, SL, & Rosso, IM. Rostral anterior cingulate cortex morphology predicts treatment response to internet-based CBT for depression. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3, 255-262, 2018.

150. Smith, R, **Killgore, WD**, & Lane, RD. The structure of emotional experience and its relation to trait emotional awareness: A theoretical review. Emotion, 18, 670-692, 2018.

151. Smith, R, Alkozei, A, **Killgore, WD**, & Lane, RD. Nested positive feedback loops in the maintenance of major depression: An integration and extension of previous models. Brain, Behavior, and Immunity, 67, 374-397, 2018.

152. Alkozei, A, **Killgore, WD**, Smith, R, Dailey, N.S., Bajaj, S, Raikes, A, & Haack, M. Chronic sleep restriction differentially affects implicit biased toward food among men and women: Preliminary evidence. Journal of Sleep Research, 27, e12629, 2018.

153. Smith, R, Bajaj, S, Dailey, NS, Alkozei, A, Smith, C, Sanova, A, Lane, RD, & **Killgore, WD**. Greater cortical thickness within the limbic visceromotor network predicts higher levels of trait emotional awareness. Consciousness and Cognition, 57, 54-61, 2018.

154. Bajaj, S, Dailey, NS, Rosso, IM, Rauch, SL, & **Killgore, WD**. Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury. Human Brain Mapping, 39, 1886-1897, 2018.

155. Smith, R, Lane, RD, Alkozei, A, Bao, J, Smith, C, Sanova, A, Nettles, M, & **Killgore, WD**. The role of medial prefrontal cortex in the working memory maintenance of one's own emotional responses. Scientific Reports, 8, 3460, 2018.

156. **Killgore, WD**, Kent, HC, Knight, SA, & Alkozei, A. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. NeuroReport, 29,

488-494, 2018.

157. Alkozei, A, Smith, R, Demers, LA, Divatia, S, Weber, M, Berryhill, SM, & **Killgore, WD**. Increases in emotional intelligence after an online training program are associated with better decision-making in the Iowa Gambling Task. Psychological Reports, 33294118771705, 2018.

158. Dailey, NS, Smith, R, Bajaj, S, Alkozei, A, Gottschlisch, MK, Raikes, AC, Satterfield, BC, & **Killgore, WD**. Elevated aggression and reduced white matter integrity in mild traumatic brain injury: A DTI study. Frontiers in Behavioral Neuroscience, 12, 118, 2018.

159. Raikes, AC, Bajaj, S, Dailey, NS, Smith, R, Alkozei, A, Satterfield, BC, & **Killgore, WD**. Diffusion tensor imaging (DTI) correlates of self-reported sleep quality and depression following mild traumatic brain injury. Frontiers in Neurology, 9, 468, 2018.

160. Smith, R, Sanova, A, Alkozei, A, Lane, RD, & **Killgore, WD**. Higher levels of trait emotional awareness are associated with more efficient global information integration throughout the brain: A graph-theoretic analysis of resting state functional connectivity. Social Cognitive and Affective Neuroscience,13, 665-675, 2018.

161. Alkozei, A, Smith, R, & **Killgore, WD**. Implicit self-esteem is associated with higher levels of trait gratitude in women but not men. Journal of Positive Psychology, DOI: 10.1080/17439760.2018.1497691, 2018.

162. Bajaj, S, Raikes, A, Smith, R, Dailey, NS, Alkozei, A, Vanuk, JR, & **Killgore, WD**. The relationship between general intelligence and cortical structure in healthy individuals. Neuroscience, 388, 36-44, 2018.

163. Alkozei, A, Haack, M, Skalamera, J, Smith, R, Satterfield, BC, Raikes, A, & **Killgore, WD**. Chronic sleep restriction affects the associations between implicit bias and explicit social decision-making. Sleep Health, 4, 456-462, 2018.

164. Raikes, A, & **Killgore, WD**. Potential for the development of light therapies in mild traumatic brain injury. Concussion, 3, CNC57, 2018.

165. Smith, R, Lane, RD, Sanova, A, Smith, C, & **Killgore, WD**. Common and unique neural systems underlying the working memory maintenance of emotional vs. bodily reactions to affective stimuli: The moderating role of trait emotional awareness. Frontiers in Human Neuroscience, 12, 370, 2018.

166. Dailey, NS, Smith, R, Vanuk, JR, Raikes, AC, & **Killgore, WD**. Resting-state functional connectivity as a biomarker of aggression in mild traumatic brain injury. NeuroReport, 29, 1413-1417, 2018.

167. McConnell, MH, **Killgore, WD**, & O'Connor, MF. Yearning predicts subgenual anterior cingulate activity in bereaved individuals. Heliyon, 4, e00852, 2018.

168. Smith, R, **Killgore, WD**, Alkozei, A, & Lane, RD. A neuro-cognitive process model of emotional intelligence. Biological Psychology, 139, 131-151, 2018.

169. Raikes, AC, Satterfield, BC, & **Killgore, WD**. Evidence of actigraphic and subjective sleep disruption following mild traumatic brain injury. Sleep Medicine, 54, 62-69, 2019.

170. Smith, R, Weihs, KL, Alkozei, A, **Killgore, WD**, & Lane RD. An embodied neurocomputational framework for organically integrating biopsychosocial processes: An application to the role of social support in health and disease. Psychosomatic Medicine, 81, 125-145, 2019.

171. Satterfield, BC, Raikes, AC, & **Killgore, WD**. Rested-baseline responsivity of the ventral striatum is associated with caloric and macronutrient intake during one night of sleep deprivation. Frontiers in Psychiatry, 9, 749, 2019.

172. Raikes, AC, Athey, A, Alfonso-Miller, P, **Killgore, WD**, & Grandner, MA. Insomnia and daytime sleepiness: Risk factors for sports-related concussion. Sleep Medicine, 58, 66-74 (2019).

173. Smith, R, Alkozei, A, & **Killgore, WD**. Parameters as trait indicators: Exploring a complementary neurocomputational approach to conceptualizing and measuring trait differences in emotional intelligence. Frontiers in Psychology, 10, 848 (2019).

174. Vanuk, JR, Alkozei, A, Raikes, AC, Allen, JJB, & **Killgore, WD**. Ability-based emotional intelligence is associated with greater cardiac vagal control and reactivity. Frontiers in Human Neuroscience, 11, 181 (2019).

175. Bajaj, S, Raikes, AC, Smith RS, Vanuk, JR, & **Killgore WD**. The role of prefrontal cortical surface area and volume in preclinical suicidal ideation in a non-clinical sample. Frontiers in Psychiatry, 21, 445 (2019).

176. Bajaj, S, & **Killgore, WD**. Sex differences in limbic network and risk-taking propensity in healthy individuals. Journal of Neuroscience Research (in press).

177. Satterfield, BC & **Killgore, WD**. Habitual sleep duration predicts caloric and macronutrient intake during sleep deprivation. Sleep Health (in press).

178. Bajaj, S, & **Killgore, WD**. Vulnerability to mood degradation during sleep deprivation is influenced by white-matter compactness of the triple-network model. NeuroImage (in press).

179. Alkozei, A, Smith, R, Waugaman, D, Kotzin, M, Bajaj, S, & **Killgore, WD**. The mediating role of interpretation bias on the relationship between trait gratitude and depressive symptoms. International Journal of Applied Positive Psychology (in press).

180. **Killgore, WD**, Vanuk, JR, Shane, BR, Weber, M, & Bajaj, S. A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function and cognition following mild traumatic brain injury. Neurobiology of Disease (in press).

181. Li, Huanjie, Smith, SM, Gruber, S, Lukas, SE, Silveri, MM, Hill, KP, **Killgore, WD**, & Nickerson, LD. Denoising scanner effects from multimodal MRI data using linked independent component analysis. NeuroImage (in press).

Book Chapters/Editorials/Other Published Articles

1. **Killgore, WD.** Cortical and limbic activation during visual perception of food. In Dube, L, Bechara, A, Dagher, A, Drewnowski, A, Lebel, J, James, P, & Yada, R. (Eds), Obesity Prevention: The Role of Brain and Society on Individual Behavior. Elsevier, Boston, 2010, pp. 57-71.

2. **Killgore, WD.** Asleep at the trigger: Warfighter judgment and decision-making during prolonged wakefulness. In Bartone, P. (Ed), Applying Research Psychology to Improve Performance and Policy. 2010, pp. 59-77.

3. **Killgore, WD.** Effects of Sleep Deprivation on Cognition. In Kerkhof, G. & Van Dongen, H. Progress in Brain Research: Sleep and Cognition. Elsevier, B.V. New York, 2010, pp. 105-129.

4. **Killgore, WD.** Caffeine and other alerting agents. In Thorpy, M. & Billiard, M. (Eds), Sleepiness: Causes, Consequences, Disorders and Treatment. Cambridge University Press, UK, 2011, pp. 430-443.

5. **Killgore WD.** Priorities and challenges for caffeine research: Energy drinks, PTSD, and withdrawal reversal. The Experts Speak Column, J Caffeine Res, 1, 11-12, 2011.

6. **Killgore, WD.** Odor identification ability predicts executive function deficits following sleep deprivation. In Lee-Chiong, T (Ed), Best of Sleep Medicine 2011. National Jewish Health, Denver CO, 2011, pp. 31-33.

7. **Killgore, WD.** Socio-emotional and neurocognitive effects of sleep loss. In Matthews, G. (Ed), Handbook of Operator Fatigue. Ashgate, London UK, 2012, pp. 227-243.

8. **Killgore, WD.** Sleepless nights and bulging waistlines (Editorial). Journal of Sleep Disorders: Treatment and Care, 1(1), doi: 10.4172/jsdtc.1000e101, 2012.

9. **Killgore, WD**, & Penetar, DM. Sleep and Military Operational Effectiveness. In Kushida, CA (Ed), The Encyclopedia of Sleep, 2013, vol. 1, pp. 311-319. Academic Press, Waltham, MA.

10. **Killgore, WD**, Weiner, MR, & Schwab, ZJ. Sleep deprivation, personality, and psychopathic changes. In Kushida, CA (Ed), The Encyclopedia of Sleep, 2013, vol. 1, pp. 264-271. Academic Press, Waltham, MA.

11. Schoenberg, MR, & **Killgore, WD**. Psychologic and Psychiatric Assessment. In Kushida, CA (Ed), The Encyclopedia of Sleep, 2013, vol. 2, pp. 23-26. Academic Press, Waltham, MA.

12. **Killgore, WD.** Sleep loss and performance. In Moore, BA, & Barnett, JE (Eds), Military Psychologists' Desk Reference, 2013, pp. 241-246. Oxford University Press, New York.

13. Weber, M., & **Killgore, WD**. What are the emerging therapeutic uses of bright light therapy for neurological disorders? (Editorial). Future Neurology, 8, 495-497, 2013.

14. **Killgore WD** & Weber, M. Sleep deprivation and cognitive performance. In Bianchi, M (Ed), Sleep Deprivation and Disease: Effects on the Body, Brain and Behavior, 2014, pp. 209-229. Springer, New York.

15. **Killgore, WD**. Sleep deprivation and behavioral risk taking. In Watson, RR, Sleep Modulation by Obesity, Diabetes, Age and Diet, 2015, pp. 279-287. Elsevier, San Diego, CA.

16. **Killgore, WD**. Lighting the way to better sleep and health (Editorial). Journal of Sleep Disorders: Treatment and Care, 5:1, 2016.

17. Singh, P, & **Killgore WD**. Time dependent differences in gray matter volume post mild traumatic brain injury. Neural Regeneration Research, 11, 920-921, 2016.

18. Klimova, A, Singh, P, & **Killgore WD**. White matter abnormalities in MS: Advances in diffusion tensor imaging/tractography. In Watson, RR & Killgore, WD (Eds), Nutrition and Lifestyle in Neurological Autoimmune Diseases: Multiple Sclerosis. Elsevier, San Diego, CA, pp. 21-28, 2017.

19. Alkozei, A, Smith, R, & **Killgore, WD**. Grateful people are happy and healthy—But why? Frontiers for Young Minds (in press).

20. Smith, R, Alkozei, A, & **Killgore WD**. How do emotions work? Frontiers for Young Minds (in press).

21. Satterfield, BC, & **Killgore, WD**. Sleep loss, executive function, and decision-making. In Grandner, MG (Ed), Sleep and Health. Elsevier, San Diego (in press).

22. Satterfield, BC, Raikes, AC, & **Killgore, WD**. Sleep in social cognition and judgment. In Krizan, Z. (Ed), Sleep, Personality, and Social Behavior. Springer Nature (in press).

Books

1. Watson, RR, **& Killgore, WD** (Eds.). Nutrition and lifestyle in neurological autoimmune diseases: Multiple Sclerosis. Elsevier, San Diego, CA, 2017.

Published U.S. Government Technical Reports

1. **Killgore, WD**, Estrada, A, Rouse, T, Wildzunas, RM, Balkin, TJ. Sleep and performance measures in soldiers undergoing military relevant training. USAARL Report No. 2009-13. June, 2009.

2. Kelley, AM, **Killgore, WD**, Athy, JR, Dretsch, M. Risk propensity, risk perception, and sensation seeking in U.S. Army Soldiers: A preliminary study of a risk assessment battery. USAARL Report No. 2010-02. DTIC #: ADA511524. October, 2009.

CONFERENCES/SCHOLARLY PRESENTATIONS

Colloquia

2000 *The Neurobiology of Emotion in Children*, McLean Hospital, Belmont, MA *[Invited Lecture]*

2001 *The Neurobiology of Emotion in Children and Adolescents*, McLean Hospital, Belmont, MA *[Invited Lecture]*

2002 Cortico-Limbic Activation in Adolescence and Adulthood, Youth Advocacy Project, Cape Cod, MA [Invited Lecture]

2008 Lecture on *Sleep Deprivation, Executive Function, and Resilience to Sleep Loss*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2008 Lecture on *The Role of Research Psychology in the Army*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2008 Lecture on *Combat Stress Control: Basic Battlemind Training*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2009 Lecture entitled *Evaluate a Casualty, Prevent Shock, and Prevent Cold Weather injuries*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA*[Invited Lecture]*

2009 Lecture on *Combat Exposure and Sleep Deprivation Effects on Risky Decision-Making*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2009 Lecture on the *Sleep History and Readiness Predictor (SHARP)*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2009 Lecture on *The Use of Actigraphy for Measuring Sleep in Combat and Military Training*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2010 Lecture entitled *Casualty Evaluation*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2010 Lecture entitled *Combat Stress and Risk-Taking Behavior Following Deployment*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2010 Lecture entitled *Historical Perspectives on Combat Medicine at the Battle of Gettysburg*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2010 Lecture entitled *Sleep Loss, Stimulants, and Decision-Making*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2010 Lecture entitled *PTSD: New Insights from Brain Imaging*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2011 Lecture entitled *Effects of bright light therapy on sleep, cognition and brain function after mild traumatic brain injury*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2011 Lecture entitled *Laboratory Sciences and Research Psychology in the Army*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2011 Lecture entitled *Tools for Assessing Sleep in Military Settings*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2011 Lecture entitled *The Brain Basis of Emotional Trauma and Practical Issues in Supporting Victims of Trauma*, U.S. Department of Justice, United States Attorneys Office, Serving Victims of Crime Training Program, Holyoke, MA *[Invited Lecture]*

2011 Lecture entitled *The Brain Altering Effects of Traumatic Experiences*; 105th Reinforcement Training Unit (RTU), U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2012 Lecture entitled *Sleep Loss, Caffeine, and Military Performance*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2012 Lecture entitled *Using Light Therapy to Treat Sleep Disturbance Following Concussion*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2013 Lecture entitled *Brain Responses to Food: What you See Could Make you Fat*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2013 Lecture entitled *Predicting Resilience Against Sleep Loss*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2014 Lecture entitled *Get Some Shut-Eye or Get Fat: Sleep Loss Affects Brain Responses to Food*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2014 Lecture entitled *Emotional Intelligence: Developing a Training Program*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2014 Lecture entitled *Supporting Cognitive and Emotional Health in Warfighters*. Presented to the Senior Vice President for the Senior Vice President for Health Sciences and Dean of the Medical School, University of Arizona, Tucson, AZ *[Invited Lecture]*

2015 Lecture entitled *Understanding the Effects of Mild TBI (Concussion) on the Brain*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2015 Presentation entitled Superhuman Brains: The Neurocircuitry that Underlies the Ability to Resist Sleep Deprivation. Presented at the Neuroscience Datablitz, University of Arizona, Tucson, AZ *[Invited Lecture]*

2015 Presentation entitled: SCAN Lab Traumatic Stress Study. Presented at the Tucson Veteran Center, Tucson AZ *[Invited Lecture]*

2016 Presentation entitled: SCAN Lab Overview. Presented at the University of Arizona 2016 Sleep workshop, Tucson, AZ *[Invited Lecture]*

2016 Lecture entitled *Trauma Exposure and the Brain*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2016 Presentation entitled *Supporting Cognitive and Emotional Health in Warfighters*. UAHS Development Team, University of Arizona Health Sciences Center, Tucson, AZ *[Invited Lecture]*

2016 Lecture entitled Novel Approaches for Reducing Depression in the Military; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2016 Presentation entitled: SCAN Lab Traumatic Stress and TBI Studies. Presented at the Tucson Veteran Center, Tucson AZ *[Invited Lecture]*

2016 Lecture entitled The Battle for Mosul: An S2 Brief; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2017 Lecture entitled *A New Experimental Treatment for Sleep Problems Following Mild TBI*; 105th IMA Detachment, U.S. Army Reserve Center, Boston, MA *[Invited Lecture]*

2017 Lecture entitled *Basics of Neuroimaging Research*; UA Psychiatry Resident Neuroscience Course, University of Arizona Department of Psychiatry, Tucson, AZ *[Invited Lecture]*

2019 Presentation entitled Physiology Student Opportunities in the Social Cognitive and Affective Neuroscience Lab. Presented at the University of Arizona Physiology Honors Academy, Tucson, AZ *[Invited Discussant]*

2019 Presentation entitled Morning Blue Light Exposure Improves Sleep and Fear Extinction Recall in PTSD. Presented at the University of Arizona Sleep Lecture Series, Tucson, AZ *[Invited Lecture]*

2019 Presentation entitled Morning Blue Light Exposure Improves Sleep and Fear Extinction Recall in PTSD. Presented at the Annual Club Hypnos Meeting Datablitz, San Antonio, TX *[Invited Lecture]*

Seminars

2001 *Using Functional MRI to Study the Developing Brain*, Judge Baker Children's Center, Harvard Medical School, Boston, MA *[Invited Lecture]*

2002 Lecture on the *Changes in the Lateralized Structure and Function of the Brain during Adolescent Development*, Walter Reed Army Institute of Research, Washington, DC *[Invited Lecture]*

2005 Lecture on *Functional Neuroimaging, Cognitive Assessment, and the Enhancement of Soldier Performance*, Walter Reed Army Institute of Research, Washington, DC *[Invited Lecture]*

2005 Lecture on *The Sleep History and Readiness Predictor*: Presented to the Medical Research and Materiel Command, Ft. Detrick, MD *[Invited Lecture]*

2006 Lecture on *Optimization of Judgment and Decision Making Capacities in Soldiers Following Sleep Deprivation*, Brain Imaging Center, McLean Hospital, Belmont MA *[Invited Lecture]*

2006 Briefing to the Chairman of the Cognitive Performance Assessment Program Area Steering Committee, U.S. Army Military Operational Medicine Research Program, entitled *Optimization of Judgment and Decision Making Capacities in Soldiers Following Sleep Deprivation*, Walter Reed Army Institute of Research *[Invited Lecture]*

2005 Briefing to the Chairman of the National Research Council (NRC) Committee on Strategies to Protect the Health of Deployed U.S. Forces, John H. Moxley III, on the *Optimization of Judgment and Decision Making Capacities in Soldiers Following Sleep Deprivation*, Walter Reed Army Institute of Research, Washington, DC *[Invited Lecture]*

2006 Lecture on *Norming a Battery of Tasks to Measure the Cognitive Effects of Operationally Relevant Stressors*, Cognitive Performance Assessment Program Area Steering Committee, U.S. Army Military Operational Medicine Research Program, Washington, DC *[Invited Lecture]*

2007 Lecture on *Cerebral Responses During Visual Processing of Food*, U.S. Army Institute of Environmental Medicine, Natick, MA *[Invited Lecture]*

2007 Briefing on the *Measurement of Sleep-Wake Cycles and Cognitive Performance in Combat Aviators*, U.S. Department of Defense, Defense Advanced Research Projects Agency (DARPA), Washington, DC *[Invited Lecture]*

2007 Lecture on *The Effects of Fatigue and Pharmacological Countermeasures on Judgment and Decision-Making*, U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL *[Invited Lecture]*

2008 Lecture on the *Validation of Actigraphy and the SHARP as Methods of Measuring Sleep and Performance in Soldiers*, U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL *[Seminar]*

2009 Lecture on Sleep Deprivation, *Executive Function, and Resilience to Sleep Loss*: Walter Reed Army Institute of Research AIBS Review, Washington DC *[Invited Lecture]*

2009 Lecture Entitled *Influences of Combat Exposure and Sleep Deprivation on Risky Decision-Making*, Evans U.S. Army Hospital, Fort Carson, CO *[Invited Lecture]*

2009 Lecture on *Making Bad Choices: The Effects of Combat Exposure and Sleep Deprivation on Risky Decision-Making*, 4th Army, Division West, Quarterly Safety Briefing to the Commanding General and Staff, Fort Carson, CO*[Invited Lecture]*

2010 Lecture on *Patterns of Cortico-Limbic Activation Across Anxiety Disorders*, Center for Anxiety, Depression, and Stress, McLean Hospital, Belmont, MA *[Invited Lecture]*

2010 Lecture on *Cortico-Limbic Activation Among Anxiety Disorders*, Neuroimaging Center, McLean Hospital, Belmont, MA *[Invited Lecture]*

2011 Lecture on *Shared and Differential Patterns of Cortico-Limbic Activation Across Anxiety Disorders*, McLean Research Day Brief Communications, McLean Hospital, Belmont, MA *[Invited Lecture]*

2011 Lecture Entitled *The effects of emotional intelligence on judgment and decision making, Military Operational Medicine Research Program Task Area C*, R & A Briefing, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2011 Lecture Entitled *Effects of bright light therapy on sleep, cognition, brain function, and neurochemistry following mild traumatic brain injury*, Military Operational Medicine Research Program Task Area C, R & A Briefing, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2012 Briefing to GEN (Ret) George Casey Jr., former Chief of Staff of the U.S. Army, entitled *Research for the Soldier*. McLean Hospital, Belmont, MA. *[Invited Lecture]*

2012 Lecture Entitled *Effects of bright light therapy on sleep, cognition, brain function, and neurochemistry following mild traumatic brain injury*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2013 Lecture Entitled *Update on the Effects of Bright light therapy on sleep, cognition, brain function, and neurochemistry following mild traumatic brain injury*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2013 Lecture Entitled *Internet Based Cognitive Behavioral Therapy: Effects on Depressive Cognitions and Brain Function*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD [*Invited Lecture*]

2013 Seminar Entitled *Predicting Resilience Against Sleep Loss*, United States Military Academy at West Point, West Point, NY [*Invited Symposium*].

2014 Lecture entitled *Sleep Loss, Brain Function, and Cognitive Performance*, presented to the Psychiatric Genetics and Translational Research Seminar, Massachusetts General Hospital/Harvard Medical School, Boston, MA *[Invited Lecture]*

2014 Grand Rounds Lecture entitled *Sleep Loss, Brain Function, and Performance of the Emotional-Executive System*. University of Arizona Psychiatry Grand Rounds, Tucson, AZ *[Invited Lecture]*

2014 Psychology Department Colloquium entitled *Sleep Loss, Brain Function, and Performance of the Emotional-Executive System*. University of Arizona Department of Psychology, Tucson, AZ *[Invited Lecture]*

2014 Lecture Entitled *Internet Based Cognitive Behavioral Therapy: Effects on Depressive Cognitions and Brain Function*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2014 Lecture Entitled *The Neurobiological Basis and Potential Modification of Emotional Intelligence Through Affective/Behavioral Training*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2014 Lecture entitled *Supporting Cognitive and Emotional Health in Warfighters*. Presented to the Senior Vice President for t for Health Sciences and Dean of the Medical School, University of Arizona, Tucson, AZ *[Invited Lecture]*

2015 Lecture entitled *Sleep Loss and Brain Responses to Food*. Presented for the Sleep Medicine Lecture Series, University of Arizona Medical Center, Tucson, AZ *[Invited Lecture]*

2015 Presentation entitled *Superhuman Brains: The Neurocircuitry that Underlies the Ability to Resist Sleep Deprivation*. Presented at the Neuroscience Datablitz, University of Arizona, Tucson, AZ *[Invited Lecture]*

2015 Lecture entitled *Sleep Deprivation Selectively Impairs Emotional Aspects of Cognition*. Presented at the Pamela Turbeville Speaker Series, McClelland Institute for Children, Youth, and Families, Tucson, AZ, *[Invited Lecture]*

2015 Lecture Entitled Multimodal Neuroimaging to Predict Resistance to Sleep Deprivation, presented at the Pulmonary Research Conference, Department of Medicine, Sleep

Medicine Sleep Lecture Series, University of Arizona College of Medicine, Tucson, AZ *[Invited Lecture]*.

2015 Lecture entitled Sleep Deprivation Selectively Impairs Emotional Aspects of Cognition. Presented at the Pamela Turbeville Speaker Series, McClelland Institute for Children, Youth, and Families, Tucson, AZ, *[Invited Lecture]*

2015 Lecture Entitled *Effects of bright light therapy on sleep, cognition, brain function, and neurochemistry following mild traumatic brain injury*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2015 Lecture Entitled *A Non-Pharmacologic Method for Enhancing Sleep in PTSD*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2015 Lecture Entitled *Internet Based Cognitive Behavioral Therapy: Effects on Depressive Cognitions and Brain Function*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2015 Lecture Entitled *Operating Under the Influence: The Effects of Sleep Loss and Stimulants on Decision-Making and Performance.* Presented at the annual SAFER training for interns and residents, University of Arizona Department of Psychiatry, Tucson AZ *[Invited Lecture]*

2016 Lecture entitled *Translational Neuroimaging: Using MRI Techniques to Promote Recovery and Resilience*. Functional Neuroimaging Course, Spring 2016, Psychology Department, University of Arizona, Tucson, AZ *[Invited Lecture]*

2016 Lecture entitled *Supporting Cognitive and Emotional Health in Warfighters*. Presented at the Department of Behavioral Biology, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2016 Lecture Entitled *Internet Based Cognitive Behavioral Therapy: Effects on Depressive Cognitions and Brain Function*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2016 Lecture Entitled *A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry following TBI*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2016 Lecture Entitled *Refinement and Validation of a Military Emotional Intelligence Training Program*, Military Operational Medicine Research Program 2016

Resilience In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2017 Lecture Entitled *Bright Light Therapy for Treatment of Sleep Problems following Mild TBI*, Military Operational Medicine Research Program Combat Casualty Care In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2017 Lecture Entitled *Refinement and Validation of a Military Emotional Intelligence Training Program*, Military Operational Medicine Research Program 2017 Resilience In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2018 Lecture Entitled *Introduction to Chronobiology (Part 1)*, Sleep Research Seminar Series, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2018 Lecture Entitled *Introduction to Chronobiology (Part 2)*, Sleep Research Seminar Series, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2018 Lecture Entitled *A Non-Pharmacologic Method for Enhancing Sleep in PTSD*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2018 Lecture Entitled *Refinement and Validation of a Military Emotional Intelligence Training Program*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2019 Lecture Entitled *Update: A Non-Pharmacologic Method for Enhancing Sleep in PTSD*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2019 Lecture Entitled *Update: Refinement and Validation of a Military Emotional Intelligence Training Program*, Military Operational Medicine Research Program In Progress Review (IPR) Briefing, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD *[Invited Lecture]*

2019 Grand Rounds Lecture entitled *Light Therapy: Implications for Recovery Following PTSD and mTBI*. University of Arizona Psychiatry Grand Rounds, Tucson, AZ *[Invited Lecture]*

Symposia/Conferences

1999 Oral Platform Presentation entitled *Functional MRI lateralization during memory encoding predicts seizure outcome following anterior temporal lobectomy*, 27th Annual

Meeting of the International Neuropsychological Society, Boston, MA. *[Submitted Presentation]*

2000 Lecture on the *Neurobiology of Emotional Development in Children*, 9th Annual Parents as Teachers Born to Learn Conference, St. Louis, MO *[Invited Lecture]*

2001 Oral Platform Presentation entitled *Sex differences in functional activation of the amygdala during the perception of happy faces*, 29th Annual Meeting of the International Neuropsychological Society, Chicago, IL. *[Submitted Presentation]*

2002 Oral Platform Presentation entitled *Developmental changes in the lateralized activation of the prefrontal cortex and amygdala during the processing of facial affect*, 30th Annual Meeting of the International Neuropsychological Society, Toronto, Ontario, Canada. *[Submitted Presentation]*

2002 Oral Platform Presentation *Gray and white matter volume during adolescence correlates with cognitive performance: A morphometric MRI study*, 30th Annual Meeting of the International Neuropsychological Society, Toronto, Ontario, Canada. *[Submitted Presentation]*

2004 Lecture on *Sleep Deprivation, Cognition, and Stimulant Countermeasures*: Seminar Presented at the Bi-Annual 71F Research Psychology Short Course, Ft. Detrick, MD, U.S. Army Medical Research and Materiel Command *[Invited Lecture]*

2004 Lecture on the *Regional Cerebral Blood Flow Correlates of Electroencephalographic Activity During Stage 2 and Slow Wave Sleep: An H215O PET Study*: Presented at the Bi-Annual 71F Research Psychology Short Course, Ft. Detrick, MD, U.S. Army Medical Research and Materiel Command *[Invited Lecture]*

2004 Oral Platform Presentation entitled *Regional cerebral metabolic correlates of electroencephalographic activity during stage-2 and slow-wave sleep: An H215O PET Study*, 18th Associated Professional Sleep Societies Annual Meeting, Philadelphia, PA. *[Submitted Presentation]*

2006 Lecture on *The Sleep History and Readiness Predictor*: Presented at the Bi-Annual 71F Research Psychology Short Course, Ft. Rucker, AL, U.S. Army Medical Research and Materiel Command *[Invited Lecture]*

2007 Symposium on *Cortical and Limbic Activation in Response to Visual Images of Low and High-Caloric Foods*, 6th Annual Meeting of the International Society for Behavioral Nutrition and Physical Activity (ISBNPA), Oslo, Norway *[Invited Lecture]*

2008 Lecture on *Sleep Deprivation, Executive Function, & Resilience to Sleep Loss*, First Franco-American Workshop on War Traumatism, IMNSSA, Toulon, France *[Invited Lecture]*

2009 Symposium Entitled *Sleep Deprivation, Judgment, and Decision-Making*, 23rd Annual Meeting of the Associated Professional Sleep Societies, Seattle, WA *[Invited Symposium]*

2009 Symposium Session Moderator for *Workshop on Components of Cognition and Fatigue: From Laboratory Experiments to Mathematical Modeling and Operational Applications*, Washington State University, Spokane, WA *[Invited Speaker]*

2009 Lecture on *Comparative Studies of Stimulant Action as Countermeasures for Higher Order Cognition and Executive Function Impairment that Results from Disrupted Sleep Patterns*, Presented at the NIDA-ODS Symposium entitled: Caffeine: Is the Next Problem Already Brewing, Rockville, MD *[Invited Lecture]*

2010 Oral Platform Presentation entitled *Sleep deprivation selectively impairs emotional aspects of cognitive functioning*, 27th Army Science Conference, Orlando, FL. *[Submitted Presentation]*

2010 Oral Platform Presentation entitled *Exaggerated amygdala responses to masked fearful faces are specific to PTSD versus simple phobia*, 27th Army Science Conference, Orlando, FL. *[Submitted Presentation]*

2012 Oral Symposium Presentation entitled *Shared and distinctive patterns of cortico-limbic activation across anxiety disorders*, 32nd Annual Conference of the Anxiety Disorders Association of America, Arlington, VA. *[Invited Symposium]*

2012 Oral Platform Presentation entitled *Shared and unique patterns of cortico-limbic activation across anxiety disorders*. 40th Meeting of the International Neuropsychological Society, Montreal, Canada. *[Submitted Presentation]*

2013 Lecture entitled *Brain responses to visual images of food: Could your eyes be the gateway to excess?* Presented to the NIH Nutrition Coordinating Committee and the Assistant Surgeon General of the United States, Bethesda, MD *[Invited Lecture]*

2014 Symposium Entitled *Operating Under the Influence: The Effects of Sleep Loss and Stimulants on Decision-Making and Performance*, Invited Faculty Presenter at the 34th Annual Cardiothoracic Surgery Symposium (CREF), San Diego, CA [*Invited Symposium*].

2014 Symposium Entitled *The Effects of Sleep Loss on Food Preference*, SLEEP 2014, Minneapolis, MN *[Invited Symposium]*

2015 Symposium Entitled *The Neurobiological Basis and Potential Modification of Emotional Intelligence in Military Personnel*. Invited presentation at the Yale Center for Emotional Intelligence, New Haven, CT *[Invited Lecture]*

2015 Lecture Entitled *Predicting Resilience to Sleep Loss with Multi-Modal Neuroimaging*. Invited presentation at the DARPA Sleep Workshop 2015, Arlington, VA *[Invited Lecture]*

2015 Symposium Entitled: *The Brain and Food: How your (sleepy) Eyes Might be the Gateway to Excess*, Invited Faculty Presenter at the 2015 University of Arizona Update on Psychiatry, Tucson, AZ [*Invited Symposium*].

2015 Oral Platform presentation entitled *Multimodal Neuroimaging to Predict Resistance to Sleep Deprivation*, Associated Professional Sleep Societies (APSS) SLEEP meeting, Seattle, WA *[Invited Lecture]*

2015 Symposium Entitled presentation entitled *Sleep Deprivation and Emotional Decision Making*, Virginia Tech Sleep Workshop, Arlington, VA *[Invited Symposium]*

2016 Oral Platform presentation entitled *Default Mode Activation Predicts Vulnerability to Sleep Deprivation in the Domains of Mood, Sleepiness, and Vigilance*. Presentation given at the Associated Professional Sleep Societies (APSS) SLEEP meeting, Denver, CO *[Invited Lecture]*

2016 Symposium presentation entitled *Short Wavelength Light Therapy Facilitates Recovery from Mild Traumatic Brain Injury*, 2016 Military Health Systems Research Symposium (MHSRS), Orlando, FL *[Invited Lecture]*

2017 Lecture Entitled: *Military Update on Blue Light Therapy for mTBI*. Lecture presented at the DoD Sleep Research Meeting breakout session at the Associated Professional Sleep Societies (APSS) SLEEP meeting, Boston, MA *[Invited Lecture]*

2017 Symposium entitled: *Judgment and Decision Making During Sleep Loss*. Invited symposium presentation at the SLEEP 2017 Trainee Symposium Series, Associated Professional Sleep Societies (APSS) SLEEP meeting, Boston, MA *[Invited Lecture]*

2017 Oral Platform presentation entitled *Short Wavelength Light Therapy Facilitates Recovery from Mild Traumatic Brain Injury*. Presentation given at the Associated Professional Sleep Societies (APSS) SLEEP meeting, Boston, MA *[Invited Lecture]*

2017 Symposium entitled: What makes a super-soldier: Identifying the neural correlates of individual differences in resilience against sleep deprivation. Invited symposium presentation at the 2017 Military Health Systems Research Symposium (MHSRS), Orlando, FL *[Invited Lecture]*

2018 Oral Platform presentation entitled: Short Wavelength Light Therapy Enhances Brain and Cognitive Recovery Following Mild Traumatic Brain Injury. Presentation given at the Arizona Research Institute for Biomedical Imaging (ARIBI) Workshop, Tucson, AZ *[Invited Lecture]*

2018 Session Chair: Healthy Shiftwork? Measures, Mitigation and Functional Outcomes. Session presented at the Associated Professional Sleep Societies (APSS) SLEEP Conference (Session O02), Baltimore, MD *[Session Chair]*

2018 Lecture Entitled: *Lapses During Sleep Loss are Predicted by Gray Matter Volume of the Ascending Reticular Activating Systems*. Lecture presented at the 2nd Annual DoD Sleep Research Meeting breakout session at the Associated Professional Sleep Societies (APSS) SLEEP meeting, Baltimore, MD *[Invited Lecture]*

2018 Oral Platform presentation entitled *Resistance to Sleep Deprivation is Predicted by Gray Matter Volume in the Posterior Brain Stem*. Presentation given at the Associated Professional Sleep Societies (APSS) SLEEP meeting, Baltimore, MD *[Invited Lecture]*

2018 Oral Platform presentation entitled *Why Can't You Just Stay Awake? Resistance to Sleep Deprivation is Associated with Measurable Differences in Brainstem Gray Matter*. Presentation given at the Military Health Systems Research Symposium (MHSRS) 2018 Meeting, Orlando, FL *[Invited Lecture]*

2019 Oral Platform presentation entitled Morning Blue Light Exposure Improves Sleep and Fear Extinction Recall in PTSD. Presentation given at the Associated Professional Sleep Societies (APSS) SLEEP 2019 meeting, San Antonio, TX *[Invited Lecture]*

2019 Oral Platform presentation entitled Blue Light Exposure Enhances Sleep and Fear Extinction Recall in PTSD. Presentation given at the Military Health Systems Research Symposium (MHSRS) 2019 Meeting, Orlando, FL *[Invited Lecture]*

2019 Oral Platform presentation entitled Baseline GABA Levels are Associated with Time-on-Task Performance During Sleep Deprivation. Presentation given at the Military Health Systems Research Symposium (MHSRS) 2019 Meeting, Orlando, FL *[Invited Lecture]*

PEER REVIEWED PUBLISHED ABSTRACTS

1. **Killgore, WD.** Development and validation of a new instrument for the measurement of transient mood states: The facial analogue mood scale (FAMS) [Abstract]. Dissertation Abstracts International: Section B: The Sciences & Engineering 1995; 56 (6-B): 3500.

2. **Killgore, WD,** & Locke, B. A nonverbal instrument for the measurement of transient mood states: The Facial Analogue Mood Scale (FAMS) [Abstract]. Proceedings of the Annual Conference of the Oklahoma Center for Neurosciences 1996, Oklahoma City, OK.

3. **Killgore, WD,** Scott, JG, Oommen, KJ, & Jones, H. Lateralization of seizure focus and performance on the MMPI-2 [Abstract]. Proceedings of the Annual Conference of the Oklahoma Center for Neurosciences 1996, Oklahoma City, OK.

4. **Killgore, WD,** & Adams, RL. Vocabulary ability and Boston Naming Test performance:

Preliminary guidelines for interpretation [Abstract]. Archives of Clinical Neuropsychology 1997; 13(1).

5. **Killgore, WD**, Glosser, G, Cooke, AN, Grossman, M, Maldjian, J, Judy, K, Baltuch, G, King, D, Alsop, D, & Detre, JA. Functional activation during verbal memory encoding in patients with lateralized focal lesions [Abstract]. Epilepsia 1998; 39(Suppl. 6): 99.

6. **Killgore, WD.** A new method for assessing subtle cognitive deficits: The Clock Trail Making Test [Abstract]. Archives of Clinical Neuropsychology 1998; 14(1): 92.

7. **Killgore, WD,** & DellaPietra, L. Item response biases on the WMS-III Auditory Delayed Recognition Subtests [Abstract]. Archives of Clinical Neuropsychology 1998; 14(1): 92.

8. **Killgore, WD,** Glosser, G, Alsop, DC, Cooke, AN, McSorley, C, Grossman, M, & Detre, JA. Functional activation during material specific memory encoding [Abstract]. NeuroImage 1998; 7: 811.

9. **Killgore, WD,** & DellaPietra, L. Using the WMS-III to detect malingering: Empirical development of the Rarely Missed Index. [Abstract]. Journal of the International Neuropsychological Society 1999; 5(2).

10. **Killgore, WD,** Glosser, G, & Detre, JA. Prediction of seizure outcome following anterior temporal lobectomy: fMRI vs. IAT [Abstract]. Archives of Clinical Neuropsychology 1999; 14(1): 143.

11. **Killgore, WD,** Glosser, G, King, D, French, JA, Baltuch, G, & Detre, JA. Functional MRI lateralization during memory encoding predicts seizure outcome following anterior temporal lobectomy [Abstract]. Journal of the International Neuropsychological Society 1999; 5(2): 122.

12. **Killgore, WD,** Casasanto, DJ, Maldjian, JA, Alsop, DC, Glosser, G, French, J, & Detre, J. A. Functional activation of mesial temporal lobe during nonverbal encoding [abstract]. Epilepsia, 1999; 40 (Supplement 7): 188.

13. **Killgore, WD,** Casasanto, DJ, Maldjian, JA, Gonzales-Atavales, J, & Detre, JA. Associative memory for faces preferentially activates the left amygdala and hippocampus [abstract]. Journal of the International Neuropsychological Society, 2000; 6: 157.

14. Casasanto, DJ, **Killgore, WD,** Maldjian, JA, Gonzales-Atavales, J, Glosser, G, & Detre, JA. Task-dependent and task-invariant activation in mesial temporal lobe structures during fMRI explicit encoding tasks [abstract]. Journal of the International Neuropsychological Society, 2000; 6: 134. ***[*Winner of Rennick Research Award for Best Research by a Graduate Student]***.

15. **Killgore, WD,** Glahn, D, & Casasanto, DJ. Development and validation of the Design Organization Test (DOT): A rapid screening instrument for assessing for visuospatial ability [abstract]. Journal of the International Neuropsychological Society, 2000; 6: 147.

16. Casasanto DJ, **Killgore, WD,** Glosser, G, Maldjian, JA, & Detre, JA. Hemispheric specialization during episodic memory encoding in the human hippocampus and MTL. Proceedings of the

Society for Cognitive Science 2000: Philadelphia, PA.

17. Casasanto, DJ, Glosser, G, **Killgore, WD,** Siddiqi, F, Falk, M, Maldjian, J, Lev-Reis, I, & Detre, JA. FMRI evidence for the functional reserve model of post-ATL neuropsychological outcome prediction. Poster Presented at the David Mahoney Institute of Neurological Sciences 17th Annual Neuroscience Retreat, University of Pennsylvania, April 17, 2000.

18. Casasanto, DJ, **Killgore, WD,** Maldjian, JA, Glosser, G, Grossman, M, Alsop, D. C, & Detre, JA. Neural Correlates of Successful and Unsuccessful Verbal Encoding [abstract]. Neuroimage, 2000 11: S381.

19. Siddiqui, F, Casasanto, DJ, **Killgore, WD,** Detre, JA, Glosser, G, Alsop, DC, & Maldjian, JA. Hemispheric effects of frontal lobe tumors on mesial temporal lobe activation during scene encoding [abstract]. Neuroimage, 2000 11: S448.

20. Oki, M, Gruber, SA, **Killgore, WD,** Yurgelun-Todd, DA. Bilateral thalamic activation occurs during lexical but not semantic processing [abstract]. Neuroimage, 2000 11: S353.

21. Yurgelun-Todd, DA, Gruber, SA, **Killgore, WD,** & Tohen, M. Neuropsychological performance in first-episode bipolar disorder [Abstract]. Collegium Internationale Neuro-Psychopharmacologicum. Brussels, Belgium. July, 2000.

22. **Killgore, WD,** & DellaPietra, L. Detecting malingering with the WMS-III: A revision of the Rarely Missed Index (RMI) [abstract]. Journal of the International Neuropsychological Society, 2001; 7 (2): 143-144.

23. Casasanto, DJ, Glosser, G, **Killgore, WD,** Siddiqi, F, Falk, M, Roc, A, Maldjian, JA, Levy-Reis, I, Baltuch, G, & Detre, JA. Presurgical fMRI predicts memory outcome following anterior temporal lobectomy [abstract]. Journal of the International Neuropsychological Society, 2001; 7 (2): 183.

24. **Killgore, WD,** & Yurgelun-Todd, DA. Amygdala but not hippocampal size predicts verbal memory performance in bipolar disorder [abstract]. Journal of the International Neuropsychological Society, 2001; 7 (2): 250-251.

25. **Killgore, WD,** Kanayama, G, & Yurgelun-Todd, DA. Sex differences in functional activation of the amygdala during the perception of happy faces [abstract]. Journal of the International Neuropsychological Society, 2001; 7 (2): 198.

26. **Killgore, WD,** Gruber, SA, Oki, M, & Yurgelun-Todd, DA. Amygdalar volume and verbal memory in schizophrenia and bipolar disorder: A correlative MRI study [abstract]. Meeting of the International Congress on Schizophrenia Research. Whistler, British Columbia. April 2001.

27. Kanayama, G, **Killgore, WD,** Gruber, SA, & Yurgelun-Todd, DA. FMRI BOLD activation of the supramarginal gyrus in schizophrenia [abstract]. Meeting of the International Congress on Schizophrenia Research. Whistler, British Columbia. April 2001.

28. Gruber, SA, **Killgore, WD,** Renshaw, PF, Pope, HG. Jr, Yurgelun-Todd, DA. Gender

differences in cerebral blood volume after a 28-day washout period in chronic marijuana smokers [abstract]. Meeting of the International Congress on Schizophrenia Research. Whistler, British Columbia. April 2001.

29. Rohan, ML, **Killgore, WD,** Eskesen, JG, Renshaw, PF, & Yurgelun-Todd, DA. Match-warped EPI anatomic images and the amygdala: Imaging in hard places. Proceedings of the International Society for Magnetic Resonance in Medicine, 2001; 9: 1237.

30. **Killgore, WD** & Yurgelun-Todd, DA. Developmental changes in the lateralized activation of the prefrontal cortex and amygdala during the processing of facial affect [Abstract]. Oral platform paper presented at the 30th Annual Meeting of the International Neuropsychological Society, Toronto, Ontario, Canada, February 13-16, 2002.

31. Yurgelun-Todd, DA. & **Killgore, WD.** Gray and white matter volume during adolescence correlates with cognitive performance: A morphometric MRI study [Abstract]. Oral platform paper presented at the 30th Annual Meeting of the International Neuropsychological Society, Toronto, Ontario, Canada, February 13-16, 2002.

32. **Killgore, WD,** Reichardt, R. Kautz, M, Belenky, G, Balkin, T, & Wesensten, N. Daytime melatonin-zolpidem cocktail: III. Effects on salivary melatonin and performance [abstract]. Poster presented at the 17th Annual Meeting of the Associated Professional Sleep Societies, Chicago, Illinois, June 3-8, 2003.

33. **Killgore, WD,** Young, AD, Femia, LA, Bogorodzki, P, Rogowska, J, & Yurgelun-Todd, DA. Cortical and limbic activation during viewing of high- versus low-calorie foods [abstract]. Poster Presented at the Organization for Human Brain Mapping Annual Meeting, New York, NY, June 18-22, 2003.

34. **Killgore, WD,** & Yurgelun-Todd, DA. Amygdala activation during masked presentations of sad and happy faces [abstract]. Poster presented at the Organization for Human Brain Mapping Annual Meeting, New York, NY, June 18-22, 2003.

35. **Killgore, WD,** Stetz, MC, Castro, CA, & Hoge, CW. Somatic and emotional stress symptom expression prior to deployment by soldiers with and without previous combat experience [abstract]. Poster presented at the 6th Annual Force Health Protection Conference, Albuquerque, NM, August, 11-17, 2003. ***[*Winner: Best Paper Award]***

36. Wesensten, NJ, Balkin, TJ, Thorne, D, **Killgore, WD,** Reichardt, R, & Belenky, G. Caffeine, dextroamphetamine, and modafinil during 85 hours of sleep deprivation: I. Performance and alertness effects [abstract]. Poster presented at the 75th Annual Meeting of the Aerospace Medical Association, Anchorage, AK, May 2-6 2004.

37. **Killgore, WD,** Braun, AR, Belenky, G, Wesensten, NJ, & Balkin, TJ. Regional cerebral metabolic correlates of electroencephalographic activity during stage-2 and slow-wave sleep: An H215O PET Study [abstract]. Oral platform presentation at the 18th Associated Professional Sleep Societies Annual Meeting, Philadelphia, PA, June 5-10, 2004.

38. **Killgore, WD,** Arora, NS, Braun, AR, Belenky, G, Wesensten, NJ, & Balkin, TJ. Sleep

strengthens the effective connectivity among cortical and subcortical regions: Evidence for the restorative effects of sleep using H215O PET [abstract]. Poster presented at the 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 5-9, 2004.

39. **Killgore, WD,** Arora, NS, Braun, AR, Belenky, G, Wesensten, NJ, & Balkin, TJ An H215O PET study of regional cerebral activation during stage 2 sleep [abstract]. Poster presented at the 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 5-9, 2004.

40. Wesensten, N, **Killgore, WD,** Belenky, G, Reichardt, R, Thorne, D, & Balkin, T. Caffeine, dextroamphetamine, and modafinil during 85 H of sleep deprivation. II. Effects of tasks of executive function [abstract]. Poster presented at the 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 5-9, 2004.

41. Balkin, T, Reichardt, R, Thorne, D, **Killgore, WD,** Belenky, G, & Wesensten, N. Caffeine, dextroamphetamine, and modafinil during 85 hours of sleep deprivation. I. Psychomotor vigilance and objective alertness effects [abstract]. Oral paper presentation at the 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 5-9, 2004.

42. Belenky, G, Reichardt, R, Thorne, D, **Killgore, WD,** Balkin, T, & Wesensten, N. Caffeine, dextroamphetamine, and modafinil during 85 hours of sleep deprivation. III. Effect on recovery sleep and post-recovery sleep performance [abstract]. Oral paper presentation at the 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 5-9, 2004.

43. Vo, A, Green, J, Campbell, W, **Killgore, WD,** Labutta, R, & Redmond, D. The quantification of disrupted sleep in migraine via actigraphy: A pilot study [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A281.

44. Kendall, AP, **Killgore, WD,** Kautz, M, & Russo, MB. Left-visual field deficits in attentional processing after 40 hours of sleep deprivation [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A143.

45. Reichardt, RM, Grugle, NL, Balkin, TJ, & **Killgore, WD.** Stimulant countermeasures, risk propensity, and IQ across 2 nights of sleep deprivation [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A145.

46. Killgore, DB, McBride, SA, Balkin, TJ, & **Killgore, WD.** Post-stimulant hangover: The effects of caffeine, modafinil, and dextroamphetamine on sustained verbal fluency following sleep deprivation and recovery sleep [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A137.

47. **Killgore, WD,** Balkin, TJ, & Wesensten, NJ. Impaired decision-making following 49 hours of sleep deprivation [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A138.

48. **Killgore, WD,** McBride, SA, Killgore, DB, & Balkin, TJ. Stimulant countermeasures and risk propensity across 2 nights of sleep deprivation [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A136.

49. McBride, SA, Balkin, TJ, & **Killgore, WD.** The effects of 24 hours of sleep deprivation on odor identification accuracy [abstract]. Abstract presented at the Associated Professional Sleep Societies 19th Annual Meeting, Denver, CO, June 18-23, 2005. SLEEP, 28 (Supplement), A137.

50. Picchioni, D, **Killgore, WD,** Braun, AR, & Balkin, TJ. PET correlates of EEG activity during non-REM sleep. Poster presentation at the annual UCLA/Websciences Sleep Training Workshop, Lake Arrowhead, CA, September, 2005.

51. **Killgore, WD,** Killgore, DB, McBride, SA, & Balkin, TJ. Sustained verbal fluency following sleep deprivation and recovery sleep: The effects of caffeine, modafinil, and dextroamphetamine. Poster presented at the 34th Meeting of the International Neuropsychological Society, Boston, MA, February 1-4, 2006.

52. **Killgore, WD,** Balkin, TJ, & Wesensten, NJ. Decision-making is impaired following 2-days of sleep deprivation. Poster presented at the 34th Meeting of the International Neuropsychological Society, Boston, MA, February 1-4, 2006.

53. **Killgore, WD,** & Yurgelun-Todd, DA. Neural correlates of emotional intelligence in adolescent children. Poster presented at the 34th Meeting of the International Neuropsychological Society, Boston, MA, February 1-4, 2006.

54. **Killgore, WD,** & Yurgelun-Todd, DA. Social anxiety predicts amygdala activation in adolescents viewing fearful faces. Poster presented at the 34th Meeting of the International Neuropsychological Society, Boston, MA, February 1-4, 2006.

55. McBride, SA & **Killgore, WD.** Sleepy people smell worse: Olfactory deficits following extended wakefulness. Paper presented at the Workshop on Trace Gas Detection Using Artificial, Biological, and Computational Olfaction. Monell Chemical Senses Center, Philadelphia, PA, March 29-31, 2006.

56. **Killgore, WD,** Day LM, Li, C, Kamimori, GH, Balkin, TJ, & Killgore DB. Moral reasoning is affected by sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A137.

57. **Killgore, WD,** Killgore DB, Kahn-Green, E, Conrad, A, Balkin, TJ, & Kamimori, G. H. Introversion-Extroversion predicts resilience to sleep loss [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A137.

58. Newman, R, Kamimori, GH, **Killgore, WD.** Sleep deprivation diminishes constructive thinking [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies,

Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A136-137.

59. Huck, NO, Kendall, AP, McBride, SA, **Killgore, WD.** The perception of facial emotion is enhanced by psychostimulants following two nights of sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A136.

60. O'Sullivan, M, Reichardt, RM, Krugler, AL, Killgore, DB, & **Killgore, WD.** Premorbid intelligence correlates with duration and quality of recovery sleep following sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A372.

61. McBride, SA, **Killgore, WD,** Kahn-Green, E, Conrad, A, & Kamimori, GH. Caffeine administered to maintain overnight alertness does not disrupt performance during the daytime withdrawal period [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A136.

62. McBride, SA, Killgore DB, Balkin, TJ, Kamimori, GH, & **Killgore, WD.** Sleepy people smell worse: Olfactory decrements as a function of sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A135.

63. Day, LM, Li, C, Killgore, DB, Kamimori, GH, & **Killgore, WD.** Emotional intelligence moderates the effect of sleep deprivation on moral reasoning [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A135.

64. Murray, CJ, Killgore, DB, Kamimori, GH, & **Killgore, WD.** Individual differences in stress management capacity predict responsiveness to caffeine during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A43.

65. Murray, CJ, Newman, R, O'Sullivan, M, Killgore, DB, Balkin, TJ, & **Killgore, WD.** Caffeine, dextroamphetamine, and modafinil fail to restore Stroop performance during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A370-371.

66. Richards, J, Killgore, DB, & **Killgore, WD.** The effect of 44 hours of sleep deprivation on mood using the Visual Analog Mood Scales [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A132.

67. Richards, J, & **Killgore, WD.** The effect of caffeine, dextroamphetamine, and modafinil on alertness and mood during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A43.

68. Lipizzi, EL, Leavitt, BP, Killgore, DB, Kamimori, GH, & **Killgore, WD.** Decision making capabilities decline with increasing duration of wakefulness [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A131.

69. Lipizzi, EL, Killgore, DB, Kahn-Green, E, Kamimori, GH, & **Killgore, WD.** Emotional intelligence scores decline during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A131.

70. Kahn-Green, E, Day, L, Conrad, A, Leavitt, BP, Killgore, DB, & **Killgore, WD.** Short-term vs. long-term planning abilities: Differential effects of stimulants on executive function in sleep deprived individuals [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A370.

71. Kahn-Green, E, Conrad, A, Killgore, DB, Kamimori, GH, & **Killgore, WD.** Tired and frustrated: Using a projective technique for assessing responses to stress during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A130.

72. Killgore, DB, Kahn-Green, E, Balkin, TJ, Kamimori, GH, & **Killgore, WD.** 56 hours of wakefulness is associated with a sub-clinical increase in symptoms of psychopathology [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A130.

73. Killgore, DB, McBride, SA, Balkin, TJ, Leavitt, BP, & **Killgore, WD.** Modafinil improves humor appreciation during sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A42.

74. Reichardt, RM, Killgore, DB, Lipizzi, EL, Li, CJ, Krugler, AL, & **Killgore, WD.** The effects of stimulants on recovery sleep and post-recovery verbal performance following 61-hours of sleep deprivation [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A42.

75. Bailey, JD, Richards, J, & **Killgore, WD.** Prediction of mood fluctuations during sleep deprivation with the SAFTE Model [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A60.

76. Kendall, AP, McBride, S. A, & **Killgore, WD.** Visuospatial perception of line orientation is resistant to one night of sleep loss [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A369.

77. Kendall, AP, McBride, SA, Kamimori, GH, & **Killgore, WD.** The interaction of coping skills and stimulants on sustaining vigilance: Poor coping may keep yoiu up at night [abstract].

Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A129.

78. Muckle, A, Killgore, DB, & **Killgore, WD.** Gender differences in the effects of stimulant medications on the ability to estimate unknown quantities when sleep deprived [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A369.

79. Krugler, AL, **Killgore, WD,** & Kamimori, G. H. Trait anger predicts resistance to sleep loss [abstract]. Abstract presented at the 20th Meeting of the Associated Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. SLEEP, 29 (Supplement), A129.

80. **Killgore, WD,** Cotting, DI, Vo, A. H, Castro, CA, & Hoge, CW. The invincibility syndrome: Combat experiences predict risk-taking propensity following redeployment [abstract]. Abstract presented at the 9th Annual Force Health Protection Conference, Albuquerque, NM, August 6-11, 2006.

81. **Killgore, WD,** Wesensten, NJ, & Balkin, TJ. Stimulants improve tactical but not strategic planning during prolonged wakefulness [abstract]. Abstract presented at the 9th Annual Force Health Protection Conference, Albuquerque, NM, August 6-11, 2006.

82. **Killgore, WD,** Balkin, TJ, Wesensten, NJ, & Kamimori, G. H. The effects of sleep loss and caffeine on decision-making [abstract]. Abstract presented at the 9th Annual Force Health Protection Conference, Albuquerque, NM, August 6-11, 2006.

83. **Killgore, WD,** Balkin, TJ, & Kamimori, GH. Sleep loss can impair moral judgment [abstract]. Abstract presented at the 9th Annual Force Health Protection Conference, Albuquerque, NM, August 6-11, 2006.

84. **Killgore, WD,** Lipizzi, EL, Reichardt, RM, Kamimori, GH, & Balkin, TJ. Can stimulants reverse the effects of sleep deprivation on risky decision-making [abstract]? Abstract presented at the 25th Army Science Conference, Orlando, FL, November 27-30, 2006.

85. **Killgore, WD,** Killgore, DB, Kamimori, GH, & Balkin, TJ. Sleep deprivation impairs the emotional intelligence and moral judgment capacities of Soldiers [abstract]. Abstract presented at the 25th Army Science Conference, Orlando, FL, November 27-30, 2006.

86. **Killgore, WD,** Cotting, DI, Vo, AH, Castro, C.A, & Hoge, CW. The post-combat invincibility syndrome: Combat experiences increase risk-taking propensity following deployment [abstract]. Abstract presented at the 25th Army Science Conference, Orlando, FL, November 27-30, 2006.

87. Adam, GE, Szelenyi, ER, **Killgore, WD,** & Lieberman, HR. A double-blind study of two days of caloric deprivation: Effects on judgment and decision-making. Oral paper presentation at the Annual Scientific Meeting of the Aerospace Medical Association, New Orleans, LA, May, 2007.

88. Killgore, DB, Kahn-Greene, ET, Kamimori, GH, & **Killgore, WD.** The effects of acute caffeine withdrawal on short category test performance in sleep deprived individuals [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN,

June 9-14, 2007. SLEEP, 30 (Supplement), A43.

89. Richards, JM, Lipizzi, EL, Kamimori, GH, & **Killgore, WD.** Extroversion predicts change in attentional lapses during sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A137.

90. Lipizzi, EL, Richards, JM, Balkin, TJ, Grugle, NL, & **Killgore, WD.** Morningness-Eveningness and Intelligence [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A345.

91. Lipizzi, EL, Richards, JM, Balkin, TJ, Grugle, NL, & **Killgore WD.** Morningness-Eveningness affects risk-taking propensity during sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A136.

92. McBride, SA, Ganesan, G, Kamimori, GH, & **Killgore, WD.** Odor identification ability predicts vulnerability to attentional lapses during 77 hours of sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A135.

93. Smith, KL, McBride, S. A, Kamimori, GH, & **Killgore, WD.** Individual differences in odor discrimination predict mood dysregulation following 56 hours of sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A136.

94. McBride, SA, Leavitt, BP, Kamimori, GH, & **Killgore, WD.** Odor identification accuracy predicts resistance to sleep loss. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A137.

95. Killgore, DB, McBride, SA, Balkin, TJ, Grugle, NL. & **Killgore, WD.** Changes in odor discrimination predict executive function deficits following 45 hours of wakefulness [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A136.

96. Rupp, TL, Killgore, DB, Balkin, TJ, Grugle, NL, & **Killgore, WD.** The effects of modafinil, dextroamphetamine, and caffeine on verbal and nonverbal fluency in sleep deprived individuals [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A43.

97. Newman, RA, Krugler, AL, Kamimori, GH, & **Killgore, WD.** Changes in state and trait anger following 56 hours of sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A138.

98. Rupp, TL, Grugle, NL, Krugler, AL, Balkin, TJ, & **Killgore, WD.** Caffeine, dextroamphetamine, and modafinil improve PVT performance after sleep deprivation and

recovery sleep [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A44.

99. **Killgore, WD,** Lipizzi, EL, Balkin, TJ, Grugle, NL, & Killgore, DB. The effects of sleep deprivation and stimulants on self-reported sensation seeking propensity [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A42.

100. **Killgore, WD,** Richards, JM, Balkin, TJ, Grugle, NL, & Killgore DB. The effects of sleep deprivation and stimulants on risky behavior [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A41.

101. Newman, RA, Smith, KL, Balkin, TJ, Grugle, NL, & **Killgore, WD.** The effects of caffeine, dextroamphetamine, and modafinil on executive functioning following 45 hours of sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A45.

102. Richards, JM, Lipizzi, EL, Balkin, TJ, Grugle, NL, & **Killgore, WD.** Objective alertness predicts mood changes during 44 hours of sleep deprivation [abstract]. Abstract presented at the 21st Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 9-14, 2007. SLEEP, 30 (Supplement), A56.

103. **Killgore, WD,** & Yurgelun-Todd, DA. Cortical and Limbic Activation in Response to Visual Images of Low and High-Caloric Food [abstract]. Oral symposium presented at the 6th Annual Conference of the Society of Behavioral Nutrition and Physical Activity (ISBNPA), Oslo, Norway, June 20-23, 2007. Proceedings of the ISBNPA, 2007, 75.

104. Estrada, A, **Killgore, WD,** Rouse, T, Balkin, TJ, & Wildzunas, RM. Total sleep time measured by actigraphy predicts academic performance during military training [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A134.

105. **Killgore, WD,** Lipizzi, EL, Smith, KL, Killgore, DB, Rupp, TL, Kamimori, GH, & Balkin, T. J. Nonverbal intelligence is inversely related to the ability to resist sleep loss [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A134.

106. **Killgore, WD,** Lipizzi, EL, Killgore, DB, Rupp, TL, Kamimori, GH, & Balkin, TJ. Emotional intelligence predicts declines in emotion-based decision-making following sleep deprivation [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A134.

107. Reid, CT, Smith, K, **Killgore, WD,** Rupp, TL, & Balkin, TJ. Higher intelligence is associated with less subjective sleepiness during sleep restriction [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A375.

108. Newman, R, **Killgore, WD,** Rupp, T. L, & Balkin, TJ. Better baseline olfactory discrimination is associated with worse PVT and MWT performance with sleep restriction and recovery [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A375.

109. Smith, KL, Reid, CT, **Killgore, WD,** Rupp, TL, & Balkin, TJ. Personality factors associated with performance and sleepiness during sleep restriction and recovery [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A376.

110. Lipizzi, EL, **Killgore, WD,** Rupp, TL, & Balkin, TJ. Risk-taking behavior is elevated during recovery from sleep restriction [abstract]. Abstract presented at the 22nd Meeting of the Associated Professional Sleep Societies, Baltimore, MD, June 7-12, 2008. SLEEP, 31 (Supplement), A376.

111. Lipizzi, EL, Rupp, TL, **Killgore, WD,** & Balkin, TJ. Sleep restriction increases risk-taking behavior [abstract]. Poster presented at the 11th Annual Force Health Protection Conference, Albuquerque, NM, August, 9-15, 2008.

112. **Killgore, WD,** Estrada, A, Balkin, TJ, & Wildzunas, RM. Sleep duration during army training predicts course performance [abstract]. Poster presented at the 11th Annual Force Health Protection Conference, Albuquerque, NM, August, 11-17, 2008.

113. **Killgore, WD,** Lipizzi, EL, Smith, KL, Killgore, DB, Rupp, TL, Kamimori, GH, & Balkin, TJ. Higher cognitive ability is associated with reduced relative resistance to sleep loss [abstract]. Poster presented at the 11th Annual Force Health Protection Conference, Albuquerque, NM, August, 11-17, 2008.

114. **Killgore, WD,** Rupp, TL, Grugle, NL, Lipizzi, EL, & Balkin, TJ. Maintaining alertness during sustained operations: Which stimulant is most effective after 44 hours without sleep [abstract]? Poster presented at the 11th Annual Force Health Protection Conference, Albuquerque, NM, August, 11-17, 2008.

115. **Killgore, WD,** Newman, RA, Lipizzi, EL, Kamimori, GH, & Balkin, TJ. Sleep deprivation increases feelings of anger but reduces verbal and physical aggression in Soldiers [abstract]. Poster presented at the 11th Annual Force Health Protection Conference, Albuquerque, NM, August, 11-17, 2008.

116. Kelley, AM, Dretsch, M, **Killgore, WD,** & Athy, JR. Risky behaviors and attitudes about risk in Soldiers. Abstract presented at the 29th Annual Meeting of the Society for Judgment and Decision Making, Chicago, IL, November, 2008.

117. **Killgore, WD,** Ross, AJ, Silveri, MM, Gruber, SA, Kamiya, T, Kawada, Y, Renshaw, PF, & Yurgelun-Todd, DA. Citicoline affects appetite and cortico-limbic responses to images of high calorie foods. Abstract presented at the Society for Neuroscience, Washington DC, November 19, 2008.

118. Britton, JC, Stewart, SE, Price, LM, **Killgore, WD,** Gold, AL, Jenike, MA, & Rauch, SL.

Reduced amygdalar activation in response to emotional faces in pediatric Obsessive-Compulsive Disorder. Abstract presented at the Annual meeting of the American College of Neuropsychopharmacology, Scottsdale, AZ, December 7-11, 2008.

119. **Killgore, WD,** Balkin, TJ, Estrada, A, & Wildzunas, RM. Sleep and performance measures in soldiers undergoing military relevant training. Abstract presented at the 26th Army Science Conference, Orlando, FL, December 1-4, 2008.

120. **Killgore, WD** & Yurgelun-Todd, DA. Cerebral correlates of amygdala responses during non-conscious perception of affective faces in adolescent children. Abstract presented at the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

121. **Killgore, WD,** Killgore, DB, Grugle, NL, & Balkin, TJ. Odor identification ability predicts executive function deficits following sleep deprivation. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

122. **Killgore, WD,** Rupp, TL, Killgore, DB, Grugle, NL, and Balkin, TJ. Differential effects of stimulant medications on verbal and nonverbal fluency during sleep deprivation. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

123. **Killgore, WD,** Killgore, DB, Kamimori, GH, & Balkin, TJ. When being smart is a liability: More intelligent individuals may be less resistant to sleep deprivation. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

124. **Killgore, WD,** Britton, JC, Price, LM, Gold, AL, Deckersbach, T, & Rauch, SL. Introversion is associated with greater amygdala and insula activation during viewing of masked affective stimuli. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

125. **Killgore, WD,** Britton, JC, Price, LM, Gold, AL, Deckersbach, T, & Rauch, SL. Amygdala responses of specific animal phobics do not differ from healthy controls during masked fearful face perception. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009.

126. **Killgore, WD,** Britton, JC, Price, LM, Gold, AL, Deckersbach, T, & Rauch, SL. Small animal phobics show sustained amygdala activation in response to masked happy facial expressions. Abstract presented the 37th Annual Meeting of the International Neuropsychological Society, Atlanta, GA, February 11-14, 2009. ***[*Merit Poster Award]***

127. Price, LM, **Killgore, WD,** Britton, JC, Kaufman, ML, Gold, AL, Deckersbach, T, & Rauch, SL. Anxiety sensitivity correlates with insula activation in response to masked fearful faces in specific animal phobics and healthy subjects. Abstract presented at the Annual Conference of the Anxiety Disorders Association of America, Santa Ana Pueblo, New Mexico, March 12-15, 2009.

128. **Killgore, WD,** Britton, JC, Price, LM, Gold, AL, Deckersbach, T, & Rauch, SL. Neuroticism is

inversely correlated with amygdala and insula activation during masked presentations of affective stimuli. Abstract presented at the Annual Conference of the Anxiety Disorders Association of America, Santa Ana Pueblo, New Mexico, March 12-15, 2009.

129. **Killgore, WD,** Kelley, AM, & Balkin, TJ. Development and validation of a scale to measure the perception of invincibility. Abstract presented at the Annual Conference of the Anxiety Disorders Association of America, Santa Ana Pueblo, New Mexico, March 12-15, 2009.

130. Kelly, AM, **Killgore WD,** Athy, J, & Dretsch, M. Risk propensity, risk perception, risk aversion, and sensation seeking in U.S. Army soldiers. Abstract presented at the 80th Annual Scientific Meeting of the Aerospace Medical Association, Los Angeles, CA, May 3-7, 2009.

131. Britton, JC, Stewart, SE, Price, LM, **Killgore, WD,** Jenike, MA, & Rauch, SL. The neural correlates of negative priming in pediatric obsessive-compulsive disorder (OCD). Abstract presented at the 64th Annual Scientific Meeting of the Society of Biological Psychiatry, Vancouver, Canada, May 14-16, 2009.

132. **Killgore, WD,** Killgore, DB, Kamimori, GH, & Balkin, TJ. Caffeine protects against increased risk-taking behavior during severe sleep deprivation. Abstract presented at the 23rd Annual Meeting of the Associated Professional Sleep Societies, Seattle, Washington, June 7-12, 2009.

133. Killgore, DB, **Killgore, WD,** Grugle, NL, & Balkin, TJ. Executive functions predict the ability to sustain psychomotor vigilance during sleep loss. Abstract presented at the 23rd Annual Meeting of the Associated Professional Sleep Societies, Seattle, Washington, June 7-12, 2009.

134. **Killgore, WD,** & Yurgelun-Todd, DA. Trouble falling asleep is associated with reduced activation of dorsolateral prefrontal cortex during a simple attention task. Abstract presented at the 23rd Annual Meeting of the Associated Professional Sleep Societies, Seattle, Washington, June 7-12, 2009.

135. **Killgore, WD,** Kelley, AM, & Balkin, TJ. A new scale for measuring the perception of invincibility. Abstract presented at the 12th Annual Force Health Protection Conference, Albuquerque, New Mexico, August 14-21, 2009.

136. **Killgore, WD,** Killgore, DB, Grugle, NL, & Balkin, TJ. Executive functions contribute to the ability to resist sleep loss. Abstract presented at the 12th Annual Force Health Protection Conference, Albuquerque, New Mexico, August 14-21, 2009.

137. **Killgore, WD,** Killgore, DB, Kamimori, GH, & Balkin, TJ. Caffeine reduces risk-taking behavior during severe sleep deprivation. Abstract presented at the 12th Annual Force Health Protection Conference, Albuquerque, New Mexico, August 14-21, 2009. ***[*Winner Best Paper Award: Research]***

138. **Killgore, WD,** Castro, CA, & Hoge, CW. Normative data for the Evaluation of Risks Scale—Bubble Sheet Version (EVAR-B) for large scale surveys of returning combat veterans. Abstract presented at the 12th Annual Force Health Protection Conference, Albuquerque, New Mexico, August 14-21, 2009.

139. **Killgore, WD,** Castro, CA, & Hoge, CW. Combat exposure and post-deployment risky behavior. Abstract presented at the 12th Annual Force Health Protection Conference, Albuquerque, New Mexico, August 14-21, 2009.

140. **Killgore, WD**, Price, LM, Britton, JC, Simon, N, Pollack, MH, Weiner, MR, Schwab, ZJ, Rosso, IM, & Rauch, SL. Paralimbic responses to masked emotional faces in PTSD: Disorder and valence specificity. Abstract presented at the Annual McLean Hospital Research Day, January 29, 2010.

141. **Killgore, WD**, Killgore, DB, Kamimori, GH, & Balkin, TJ. Caffeine minimizes behavioral risk-taking during 75 hours of sleep deprivation. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

142. **Killgore, WD** & Balkin, TJ. Vulnerability to sleep loss is affected by baseline executive function capacity. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

143. **Killgore, WD**, Smith, KL, Reichardt, RM., Killgore, DB, & Balkin, TJ. Intellectual capacity is related to REM sleep following sleep deprivation. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

144. **Killgore, WD** & Yurgelun-Todd, DA. Cerebral correlates of amygdala responses to masked fear, anger, and happiness in adolescent and pre-adolescent children. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

145. **Killgore, WD**, Post, A, & Yurgelun-Todd, DA. Sex differences in cortico-limbic responses to images of high calorie food. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

146. **Killgore, WD** & Yurgelun-Todd, DA. Self-reported insomnia is associated with increased activation within the default-mode network during a simple attention task. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

147. **Killgore, WD**, Price, LM, Britton, JC, Gold, AL, Deckersbach, T, & Rauch, SL. Neural correlates of anxiety sensitivity factors during presentation of masked fearful faces. Abstract presented at the 38th Annual Meeting of the International Neuropsychological Society, Acapulco, Mexico, February 3-6, 2010.

148. **Killgore, WD**, Grugle, NL, Conrad, TA, & Balkin, TJ. Baseline executive function abilities predict risky behavior following sleep deprivation. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

149. **Killgore, WD**, Grugle, NL, & Balkin, TJ. Judgment of objective vigilance performance is affected by sleep deprivation and stimulants. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

150. Killgore, DB, **Killgore, WD**, Grugle, NL, & Balkin, TJ. Resistance to sleep loss and its relationship to decision making during sleep deprivation. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

151. Killgore DB, **Killgore, WD**, Grugle, NL, & Balkin, TJ. Subjective sleepiness and objective performance: Differential effects of stimulants during sleep deprivation. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

152. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Vulnerability to sleep deprivation is differentially mediated by social exposure in extraverts vs. introverts. Oral presentation at the "Data Blitz" section at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

153. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Extraverts may be more vulnerable than introverts to sleep deprivation on some measures of risk-taking and executive functioning. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

154. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Vulnerability to sleep deprivation is differentially mediated by social exposure in extraverts vs. introverts. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

155. Capaldi, VF, Guerrero, ML, & **Killgore, WD**. Sleep disorders among OIF and OEF Soldiers. Abstract presented at the 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.

156. **Killgore, WD**, Killgore, DB, Kamimori, GH, & Balkin, TJ. Caffeine reduces behavioral risk-taking during sleep deprivation. Abstract presented at the 65th Annual Meeting of the Society for Biological Psychiatry, New Orleans, Louisiana, May 20-22, 2010.

157. **Killgore, WD**, Price, LM, Britton, JC, Simon, N, Pollack, MH, Weiner, MR, Schwab, ZJ, Rosso, IM, & Rauch, SL. Paralimbic responses to masked emotional faces in PTSD: Disorder and valence specificity. Abstract presented at the 65th Annual Meeting of the Society for Biological Psychiatry, New Orleans, Louisiana, May 20-22, 2010.

158. Rosso, IM, Makris, N, Britton, JC, Price, LM, Gold, AL, Deckersbach, T, **Killgore, WD**, & Rauch SL. Anxiety sensitivity correlates with insular cortex volume and thickness in specific animal phobia. Abstract presented at the 65th Annual Meeting of the Society for Biological Psychiatry, New Orleans, Louisiana, May 20-22, 2010.

159. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Vulnerability to sleep deprivation is mediated by social exposure in extraverts versus introverts. Oral platform presentation at the 20th Congress of the European Sleep Research Society, Lisbon, Portugal, September 14-18, 2010.

160. **Killgore, WD**, Estrada, A, & Balkin, TJ. A tool for monitoring soldier fatigue and predicting cognitive readiness: The Sleep History and Readiness Predictor (SHARP). Abstract presented at the 27th Army Science Conference, Orlando, FL, November 29-December 2, 2010.

161. **Killgore, WD**, Kamimori, GH, & Balkin, TJ. Caffeinated gum minimizes risk-taking in soldiers during prolonged sleep deprivation. Abstract presented at the 27th Army Science Conference, Orlando, FL, November 29-December 2, 2010.

162. **Killgore, WD**, Britton, JC, Schwab, ZJ, Weiner, MR, Rosso, IM, & Rauch, SL. Exaggerated amygdala responses to masked fearful faces are specific to PTSD versus simple phobia. Oral platform presentation at the 27th Army Science Conference, Orlando, FL, November 29-December 2, 2010. ***[*Winner Best Paper in Neuroscience]***

163. **Killgore, WD**, Kamimori, GH, & Balkin, TJ. Sleep deprivation selectively impairs emotional aspects of cognitive functioning. Oral platform presentation at the 27th Army Science Conference, Orlando, FL, November 29-December 2, 2010.

164. Rupp, TL, **Killgore, WD**, & Balkin, TJ. Evaluation of personality and social exposure as individual difference factors influencing response to sleep deprivation. Oral platform presentation at the 27th Army Science Conference, Orlando, FL, November 29-December 2, 2010.

165. **Killgore, WD**, Britton, JC, Rosso, IM, Schwab, ZJ, Weiner, MR, & Rauch, SL. Shared and differential patterns of amygdalo-cortical activation across anxiety disorders. Abstract presented at the 49th Annual Meeting of the American College of Neuropsychopharmacology, Miami Beach, FL, December 5-9, 2010.

166. Rosso, IM, **Killgore, WD**, Britton, JC, Weiner, MR, Schwab, ZJ, & Rauch, SL. Neural correlates of PTSD symptom dimensions during emotional processing: A functional magnetic resonance imaging study. Abstract presented at the 49th Annual Meeting of the American College of Neuropsychopharmacology, Miami Beach, FL, December 5-9, 2010.

167. **Killgore, WD,** Rosso, IM, Britton, JC, Schwab, ZJ, Weiner, MR, & Rauch, SL. Cortico-limbic activation differentiates among anxiety disorders with and without a generalized threat response. Abstract presented at the McLean Hospital Research Day, January 13, 2011.

168. Weiner, MR, Schwab, ZJ, Rauch, SL, & **Killgore WD**. Personality factors predict brain responses to images of high-calorie foods. Abstract presented at the McLean Hospital Research Day, January 13, 2011.

169. Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD.** Emotional and cognitive intelligence: Support for the neural efficiency hypothesis. Abstract presented at the McLean Hospital Research Day, January 13, 2011.

170. Crowley, DJ, Covell, MJ, **Killgore, WD**, Schwab, ZJ, Weiner, MR, Acharya, D, Rosso, IM, & Silveri, MM. Differential influence of facial expression on inhibitory capacity in adolescents versus adults. Abstract presented at the McLean Hospital Research Day, January 13, 2011.

171. **Killgore, WD**, Britton, JC, Rosso, IM, Schwab, ZJ, Weiner, MR, & Rauch, SL. Similarities and differences in cortico-limbic responses to masked affect probes across anxiety disorders. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society,

Boston, MA, February 2-5, 2011.

172. Rosso, IM, **Killgore, WD**, Britton, JC, Weiner, MR, Schwab, ZJ, & Rauch, SL. Hyperarousal and reexperiencing symptoms of post-traumatic stress disorder are differentially associated with limbic-prefrontal brain responses to threatening stimuli. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

173. Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD**. Neural correlates of cognitive and emotional intelligence in adults. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

174. Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD**. Cognitive and emotional intelligences: Are they distinct or related constructs? Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

175. Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD**. Discrepancy scores between cognitive and emotional intelligence predict neural responses to affective stimuli. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

176. **Killgore, WD**, Schwab, ZJ, Weiner, MR, & Rauch, SL. Smart people go with their gut: Emotional intelligence correlates with non-conscious insular responses to facial trustworthiness. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

177. **Killgore, WD**, Weiner, MR, Schwab, ZJ, & Rauch, SL. Whom can you trust? Neural correlates of subliminal perception of facial trustworthiness. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

178. Weiner, MR, Schwab, ZJ, & Rauch, SL, **Killgore, WD**. Impulsiveness predicts responses of brain reward circuitry to high-calorie foods. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

179. Weiner, MR, Schwab, ZJ, & Rauch, SL, **Killgore, WD**. Conscientiousness predicts brain responses to images of high-calorie foods. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

180. Crowley, DJ, Covell, MJ, **Killgore, WD**, Schwab, ZJ, Weiner, MR, Acharya, D, Rosso, IM, & Silveri, MM. Differential influence of facial expression on inhibitory capacity in adolescents versus adults. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

181. Gruber, SA, Dahlgren, MK, **Killgore, WD**, Sagar, KA, & Racine, MT. Marijuana: Age of onset of use impacts executive function and brain activation. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

182. **Killgore, WD,** Conrad, TA, Grugle, NL, & Balkin, TJ. Baseline executive function abilities correlate with risky behavior following sleep deprivation. Abstract presented at the 39th Annual

Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

183. **Killgore, WD,** Grugle, NL, Killgore, DB, & Balkin, TJ. Resistance to sleep loss and decision making during sleep deprivation. Abstract presented at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 2-5, 2011.

184. **Killgore, WD,** Rosso, IM, Britton, JC, Schwab, ZJ, Weiner, MR, & Rauch, SL. Cortico-limbic activation differentiates among anxiety disorders with and without a generalized threat response. Abstract presented at the 66th Annual Meeting of the Society for Biological Psychiatry, San Francisco, CA, May 12-14, 2011. ***[*Blue Ribbon Finalist: Clinical/Translational]***

185. Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD.** Emotional and cognitive intelligence: Support for the neural efficiency hypothesis. Abstract presented at the 66th Annual Meeting of the Society for Biological Psychiatry, San Francisco, CA, May 12-14, 2011.

186. Weiner, MR, Schwab, ZJ, Rauch, SL, & **Killgore WD**. Personality factors predict brain responses to images of high-calorie foods. Abstract presented at the 66th Annual Meeting of the Society for Biological Psychiatry, San Francisco, CA, May 12-14, 2011.

187. **Killgore, WD,** Grugle, NL, & Balkin, TJ. Sleep deprivation impairs recognition of specific emotions. Abstract presented at the 25th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 11-15, 2011.

188. **Killgore, WD,** & Balkin, TJ. Does vulnerability to sleep deprivation influence the effectiveness of stimulants on psychomotor vigilance? Abstract presented at the 25th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 11-15, 2011.

189. Killgore, DB, **Killgore, WD,** Grugle, NJ, & Balkin, TJ. Sleep deprivation impairs recognition of specific emotions. Abstract presented at the 25th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 11-15, 2011.

190. Weiner, MR, Schwab, ZJ, & **Killgore, WD.** Daytime sleepiness is associated with altered brain activation during visual perception of high-calorie foods: An fMRI study. Abstract presented at the 25th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 11-15, 2011.

191. Schwab, ZJ, Weiner, MR, & **Killgore, WD.** Functional MRI correlates of morningness-eveningness during visual presentation of high calorie foods. Abstract presented at the 25th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, June 11-15, 2011.

192. **Killgore, WD,** Weiner, MR, & Schwab, ZJ. Daytime sleepiness affects prefrontal regulation of food intake. Abstract presented at the McLean Hospital Research Day, January 11, 2012.

193. Kipman, M, Schwab ZJ, Weiner, MR, DelDonno, S, Rauch SL, & **Killgore WD**. The insightful yet bitter comedian: The role of emotional versus cognitive intelligence in humor appreciation. Abstract presented at the McLean Hospital Research Day, January 11, 2012.

194. Weber, M, & **Killgore, WD**. Gray matter correlates of emotional intelligence. Abstract presented at the McLean Hospital Research Day, January 11, 2012.

195. Schwab, ZJ, & **Killgore, WD**. Sex differences in functional brain responses to food. Abstract presented at the McLean Hospital Research Day, January 11, 2012.

196. DelDonno, S, Schwab, ZJ, Kipman M, Rauch, SL, & **Killgore, WD**. The influence of cognitive and emotional intelligence on performance on the Iowa Gambling Task. Abstract presented at the McLean Hospital Research Day, January 11, 2012.

197. Song, CH, Kizielewicz, J, Schwab, ZJ, Weiner, MR, Rauch, SL, & **Killgore, WD**. Time is of the essence: The Design Organization Test as a valid, reliable, and brief measure of visuospatial ability. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

198. Kipman, M, Schwab, ZJ, DelDonno, S, & **Killgore, WD**. Gender differences in the contribution of cognitive and emotional intelligence to the left visual field bias for facial perception. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

199. Kipman, M., Schwab, ZJ, Weiner, MR, DelDonno, S, Rauch, SL, & **Killgore, WD**. Contributions of emotional versus cognitive intelligence in humor appreciation. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

200. Schwab, ZJ, & **Killgore, WD**. Disentangling emotional and cognitive intelligence. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

201. Schwab, ZJ, & **Killgore, WD**. Sex differences in functional brain responses to food. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

202. DelDonno, S, Schwab, ZJ, Kipman, M, Rauch, SL, & **Killgore, WD**. The influence of cognitive and emotional intelligence on performance on the Iowa Gambling Task. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

203. **Killgore, WD**, Britton, JC, Rosso, IM, Schwab, ZJ, Weiner, MR, & Rauch, SL. Shared and unique patterns of cortico-limbic activation across anxiety disorders. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

204. **Killgore, WD**, & Balkin, TJ. Sleep deprivation degrades recognition of specific emotions. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

205. **Killgore, WD**, & Schwab, ZJ. Emotional intelligence correlates with somatic marker circuitry

responses to subliminal cues of facial trustworthiness. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

206. **Killgore, WD**, & Schwab, ZJ. Trust me! Neural correlates of the ability to identify facial trustworthiness. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

207. **Killgore, WD**, Schwab, ZJ, Weiner, MR, Kipman, M, DelDonno, S, & Rauch SL. Overeating is associated with altered cortico-limbic responses to images of high calorie foods. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

208. **Killgore, WD**, Weiner, MR, & Schwab, ZJ. Daytime sleepiness affects prefrontal regulation of food intake. Abstract presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.

209. Weber, M, DelDonno, S, Kipman M, Schwab, ZJ, & **Killgore WD**. Grey matter correlates of self-reported sleep duration. Abstract presented at the Harvard Medical School Research Day, Boston, MA, March 28, 2012.

210. **Killgore, WD**. Overlapping and distinct patterns of neurocircuitry across PTSD, Panic Disorder, and Simple Phobia. Abstract presented at the 32nd Annual Conference of the Anxiety Disorders Association of America, Arlington, VA, April 12-15, 2012.

211. **Killgore, WD**, Britton, JC, Rosso, IM, Schwab, ZJ, & Rauch, SL. Shared and unique patterns of cortico-limbic activation across anxiety disorders. Abstract presented at the 67th Annual Meeting of the Society of Biological Psychiatry, Philadelphia, PA, May 3-5, 2012.

212. **Killgore, WD**, Schwab, ZJ, & Rauch, SL. Daytime sleepiness affects prefrontal inhibition of food consumption. Abstract presented at the 67th Annual Meeting of the Society of Biological Psychiatry, Philadelphia, PA, May 3-5, 2012.

213. Rosso, IM, Britton, JC, Makris, N, **Killgore, WD**, Rauch SL, & Stewart ES. Impact of major depression comorbidity on prefrontal and anterior cingulate volumes in pediatric OCD. Abstract presented at the 67th Annual Meeting of the Society of Biological Psychiatry, Philadelphia, PA, May 3-5, 2012.

214. Kipman, M, Weber, M, DelDonno, S., Schwab, ZJ, & **Killgore, WD**. Morningness-Eveningness correlates with orbitofrontal gray matter volume. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

215. Kipman, M, Schwab, ZJ, Weber, M, DelDonno, S, & **Killgore, WD**. Yawning frequency is correlated with reduced medial thalamic volume. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

216. Weber, M, DelDonno, S, Kipman M, Schwab, ZJ, & **Killgore WD**. Grey matter correlates of daytime sleepiness. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

217. Weber, M, DelDonno, S, Kipman M, Schwab, ZJ, & **Killgore WD**. Grey matter correlates of self-reported sleep duration. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

218. DelDonno, S, Weber, M, Kipman M, Schwab, ZJ, & **Killgore, WD**. Resistance to insufficient sleep correlates with olfactory cortex gray matter. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

219. DelDonno, S, Schwab, ZJ, Kipman, M, Weber, M, & **Killgore, WD**. Weekend sleep is related to greater coping and resilience capacities. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

220. Schwab, ZJ, DelDonno, S, Weber, M, Kipman M, & **Killgore, WD**. Habitual caffeine consumption and cerebral gray matter volume. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

221. Schwab, ZJ, & **Killgore, WD**. Daytime sleepiness affects prefrontal regulation of food intake. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

222. **Killgore, WD**, Schwab, ZJ, DelDonno S, Kipman, M, Weber M, & Rauch, SL. Greater nocturnal sleep time is associated with increased default mode functional connectivity. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

223. **Killgore, WD**, Kamimori, GH, & Balkin, TJ. Caffeine improves efficiency of planning and sequencing abilities during sleep deprivation. Abstract presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

224. Sneider, JT, **Killgore, WD**, Crowley, DJ, Cohen-Gilbert, JE, Schwab, ZJ, & Silveri, MM. Inhibitory capacity in emerging adult binge drinkers: Influence of Facial Cues. Abstract presented at the 35th Annual Scientific Meeting of the Research Society on Alcoholism, San Francisco, CA, June 23-27, 2012.

225. **Killgore WD**. Multimodal neuroimaging to predict cognitive resilience against sleep loss. Abstract presented at the DARPA Young Faculty Award 2012 Meeting, Arlington, VA, July 30-31, 2012. ***[*Winner Young Faculty Award in Neuroscience]***

226. Cohen-Gilbert, JE, **Killgore WD**, Crowley, DJ, Covell, MJ, Schwab, ZJ, Weiner, MR, Acharya, D, Sneider, JT, & Silveri, MM. Differential influence of safe versus threatening facial expressions on inhibitory control across adolescence and adulthood. Abstract presented at the Society for Neuroscience 2012 Meeting, New Orleans, LA, October 13-17, 2012.

227. Weber, M, DelDonno, S, Kipman M, Schwab, ZJ, & **Killgore WD**. Grey matter correlates of self-reported sleep duration. Abstract presented at the Harvard Division of Sleep Medicine Annual Poster Session, Boston, MA, September 27, 2012.

228. Weber, M, DelDonno, SR, Kipman, M, Preer, LA, Schwab ZJ, Weiner, MR, & **Killgore, WD.** The effect of morning bight light therapy on sleep, cognition and emotion following mild traumatic brain injury. Abstract presented at the 2012 Sleep Research Network Meeting, 22-23 October 2012, Bethesda, MD.

229. Sneider, JT, **Killgore, WD**, Crowley, DJ, Cohen-Gilbert, JE, Schwab, ZJ, & Silveri, MM. Inhibitory capacity in emerging adult binge drinkers: Influence of Facial Cues. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

230. Cohen-Gilbert, JE, **Killgore WD**, Crowley, DJ, Covell, MJ, Schwab, ZJ, Weiner, MR, Acharya, D, Sneider, JT, & Silveri, MM. Differential influence of safe versus threatening facial expressions on inhibitory control across adolescence and adulthood. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

231. Tkachenko, O, Schwab, ZJ, Kipman, M, DelDonno, S, Gogel, H., Preer, L, & **Killgore, WD**. Smarter women need less sleep. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

232. DelDonno, S, Kipman, M, Schwab, ZJ, & **Killgore, WD**. The contributions of emotional intelligence and facial perception to social intuition. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

233. Kipman, M, Schwab, ZJ, DelDonno, S, Weber, M, Rauch, SL, & **Killgore, WD**. The neurocircuitry of impulsive behavior. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

234. Preer, LA, Tkachenko, O, Gogel, H, Schwab, ZJ, Kipman, M, DelDonno, SR, Weber, M, Webb, CA, & **Killgore, WD**. Emotional intelligence as a mediator of the association between anxiety sensitivity and anxiety symptoms. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

235. Gogel, H, DelDonno, S, Kipman M, Preer, LA, Schwab, ZJ, Tkachenko, O, & **Killgore, WD**. Validation of the Design Organization Test (DOT) in a healthy population. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

236. Brennan, BP, Schwab, ZS, Athey, AJ, Ryan, EM, Pope, HG, **Killgore, WD**, Jenike, MA, & Rauch, SL. A functional magnetic resonance imaging study of rostral anterior cingulate cortex activation in obsessive-compulsive disorder using an emotional counting stroop paradigm. Abstract presented at the Annual McLean Hospital Research Day, January 16, 2013.

237. Cohen-Gilbert, JE, Schwab, ZJ, **Killgore, WD**, Crowley, DJ, & Silveri MM. Influence of Binge Drinking on the Neural Correlates of Inhibitory Control during Emotional Distraction in Young Adults. Abstract presented at the 3rd International Conference on Applications of Neuroimaging to Alcoholism (ICANA-3), New Haven, CT, February 15-18, 2013.

238. Weber, M, & **Killgore, WD**. The interrelationship between 'sleep credit', emotional intelligence and mental health – a voxel-based morphometric study. Abstract presented at Harvard Medical School Psychiatry Research Day, April 10, 2013.

239. Cohen-Gilbert, JE, Schwab, ZJ, **Killgore, WD**, Crowley, DJ, & Silveri MM. Influence of Binge Drinking on the Neural Correlates of Inhibitory Control during Emotional Distraction in Young Adults. Abstract presented at Harvard Medical School Psychiatry Research Day, April 10, 2013.

240. Mundy, EA, Weber, M, Rauch, SL, **Killgore, WD**, & Rosso, IM. The relationship between subjective stress levels in childhood and anxiety as well as perceived stress as an adult. Abstract presented at Harvard Medical School Psychiatry Research Day, April 10, 2013.

241. Webb, CA, **Killgore, WD**, Britton, JC, Schwab, ZJ, Price, LM, Weiner, MR, Gold, AL, Rosso, IM, Simon, NM, Pollack, MH, & Rauch, SL. Comparing categorical versus dimensional predictors of functional response across three anxiety disorders. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

242. Preer, LA, Tkachenko, O, Gogel, H, Schwab, ZJ, Kipman, M, DelDonno, SR, Weber, M, Webb, CA, Rauch, SL, & **Killgore, WD**. Linking Sleep Trouble to Neuroticism, Emotional Control, and Impulsiveness. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

243. Preer, LA, Tkachenko, O, Gogel, H, Schwab, ZJ, Kipman, M, DelDonno, SR, Weber, M, Webb, CA, Rauch, SL, & **Killgore, WD**. Emotional Intelligence as a Mediator of the Association between Anxiety Sensitivity and Anxiety Symptoms. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

244. Kipman, M, Schwab, ZJ, DelDonno, S, Weber, M, Rauch, SL, & **Killgore, WD**. The neurocircuitry of impulsive behavior. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

245. Weber, M, **Killgore, WD**, Rosso, IM, Britton, JC, Simon, NM, Pollack, MH, & Rauch, SL. Gray matter correlates of posttraumatic stress disorder—A voxel based morphometry study. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

246. Weber, M, Penetar, DM, Trksak, GH, DelDonno, SR, Kipman, M, Schwab, ZJ, & **Killgore, WD**. Morning blue wavelength light therapy improves sleep, cognition, emotion and brain function following mild traumatic brain injury. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

247. Tkachenko, O, Schwab, ZJ, Kipman, M, Preer, LA, Gogel, H, DelDonno, SR, Weber, M, Webb, CA, Rauch, SL, & **Killgore, WD**. Difficulty in falling asleep and staying asleep linked to a sub-clinical increase in symptoms of psychopathology. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

248. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, Rauch, SL, & Weber, M. Problems with sleep initiation and sleep maintenance correlate with functional connectivity among primary sensory cortices. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

249. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, Rauch, SL, & Weber, M. A Couple of Hours Can Make a Difference: Self-Reported Sleep Correlates with Prefrontal-Amygdala Connectivity and Emotional Functioning. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

250. Brennan, BP, Schwab, ZS, Athey, AJ, Ryan, EM, Pope, HG, **Killgore, WD**, Jenike, MA, & Rauch, SL. A functional magnetic resonance imaging study of rostral anterior cingulate cortex activation in obsessive-compulsive disorder using an emotional counting stroop paradigm. Abstract presented at the 68th Annual Meeting of the Society of Biological Psychiatry, San Francisco, CA, May 16-18, 2013.

251. Weber, M, & **Killgore, WD**. The interrelationship between 'sleep credit', emotional intelligence and mental health – a voxel-based morphometric study. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

252. Weber, M, Penetar, DM, Trksak, GH, DelDonno, SR, Kipman, M, Schwab, ZJ, & **Killgore, WD**. Morning blue wavelength light therapy improves sleep, cognition, emotion and brain function following mild traumatic brain injury. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

253. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, & Weber, M. Problems with Sleep Initiation and Sleep Maintenance Correlate with Functional Connectivity Among Primary Sensory Cortices. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

254. **Killgore, WD**, Schwab, ZJ, Kipman, M, DelDonno, SR, & Weber, M. A Couple of Hours Can Make a Difference: Self-Reported Sleep Correlates with Prefrontal-Amygdala Connectivity and Emotional Functioning. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

255. Tkachenko, O, Schwab, ZJ, Kipman, M, DelDonno, SR, Preer, LA, Gogel, H, Weber, M, Webb, CA, & **Killgore, WD**. Difficulty in falling asleep and staying asleep linked to a sub-clinical increase in symptoms of psychopathology. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

256. Preer, LA, Tkachenko, O, Gogel, H, Schwab, ZJ, Kipman, M, DelDonno, SR, Weber, M, Webb, CA, & **Killgore, WD**. Linking Sleep Initiation Trouble to Neuroticism, Emotional Control, and Impulsiveness. Abstract presented at the SLEEP 2013 Annual Meeting, Baltimore, MD, June 1-5, 2013.

257. **Killgore, WD**. Sleep duration contributes to cortico-limbic functional connectivity, emotional functioning, & psychological health. Abstract presented at the 52nd Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL, December 8-12, 2013.

258. Preer, L, Tkachenko, O, Gogel, H, Bark, JS, Kipman, M, Olson, EA, & **Killgore, WD**. The role of personality in sleep initiation problems. Abstract presented at the Annual McLean Hospital Research Day, January 22, 2014.

259. Demers, LA, Olson, EA, Weber, M, Divatia, S, Preer, L, & **Killgore, WD**. Paranoid traits are related to deficits in complex social decision-making and reduced superior temporal sulcus volume. Abstract presented at the Annual McLean Hospital Research Day, January 22, 2014.

260. Tkachenko, O, Weber, M, Gogel, H, & **Killgore, WD**. Predisposition towards unhealthy foods linked with increased gray matter in the cerebellum. Abstract presented at the Annual McLean Hospital Research Day, January 22, 2014.

261. Olson, EA, Weber, M, Tkachenko, O, & **Killgore, WD**. Daytime sleepiness is associated with decreased integration of remote outcomes on the IGT. Abstract presented at the Annual McLean Hospital Research Day, January 22, 2014.

262. Cui, J, Tkachenko, O, & **Killgore, WD**. Can the activation of anterior cingulate predict the emotional suppression? An fMRI study with masked faces. Abstract presented at the Annual McLean Hospital Research Day, January 22, 2014.

263. Gogel, H, & **Killgore WDS**. A psychometric validation of the Design Organization Test (DOT) in a healthy sample. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

264. **Killgore, WD**, Kipman, M, Tkachenko, O, Gogel, H., Preer, L, Demers, LA, Divatia, SC, Olson, EA, & Weber, M. Predicting resilience against sleep loss with multi-modal neuroimaging. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

265. **Killgore, WD**, Weber, M, Bark, JS, Kipman, M, Gogel, H, Preer, L, Tkachenko, O, Demers, LA, Divatia, SC, & Olson, EA. Physical exercise correlates with hippocampal volume in healthy adults. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

266. **Killgore, WD**, Tkachenko, O, Weber, M, Kipman, M, Preer, L, Gogel, H, & Olson, EA. The association between sleep, functional connectivity, and emotional functioning. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

267. Preer, L, Tkachenko, O, Gogel, H, Bark, JS, Kipman, M, Olson, EA, & **Killgore, WD**. The role of personality in sleep initiation problems. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

268. Tkachenko, O, Weber, M, Olson, EA, Gogel, H, Preer, LA, Divatia, SC, Demers, LA, & **Killgore, WD**. Gray matter volume within the medial prefrontal cortex correlates with behavioral risk taking. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

269. Olson, EA, Weber, M, Bark JS, Demers L, Divatia, SC, Gogel, H, Kipman M, Preer, L, Tkachenko, O, & **Killgore, WD**. Sex differences in threat evaluation of emotionally neutral faces. Abstract presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle WA, February 12-15, 2014.

270. Cui, J, Tkachenko, O, & **Killgore, WD**. Can the activation of anterior cingulate predict the emotional suppression? An fMRI study with masked faces. Abstract presented at the 36nd Annual Conference of the Anxiety Disorders Association of America, Chicago, IL, March 27-30, 2014.

271. Webb, CA, Weber, M, Mundy, EA, & **Killgore, WD**. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of depressive symptoms: A voxel-based morphometric analysis. Abstract presented at the 36nd Annual Conference of the Anxiety Disorders Association of America, Chicago, IL, March 27-30, 2014.

272. Weber, M, Penetar, DM, Trksak, GH, Kipman, M, Tkachenko, O, Bark, JS, Jorgensen, AL, Rauch, SL, & **Killgore, WD**. Light therapy may improve sleep and facilitate recovery from mild traumatic brain injury. Abstract presented at the 10th World Congress on Brain Injury, San Francisco, CA, March 19-22, 2014.

273. Cui, J, Tkachenko, O, & **Killgore, WD**. Can the activation of anterior cingulate predict the emotional suppression? An fMRI study with masked faces. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

274. Divatia, S, Demers, LA, Preer, L, Olson, EA, Weber, M, & **Killgore, WD**. Advantageous decision making linked with increased gray matter volume in the ventromedial prefrontal cortex. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

275. Demers, LA, Olson, EA, Weber, M, Divatia, S, Preer, L, & **Killgore, WD**. Paranoid traits are related to deficits in complex social decision making and reduced superior temporal sulcus volume. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

276. Preer, LA, Weber, M, Tkachenko, O, Divatia, S, Demers, LA, Olson, EA, & **Killgore, WD**. Gray matter volume in the amygdala is associated with facial assessments of trustworthiness. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

277. Tkachenko, O, Weber, M, Gogel, H, & **Killgore, WD**. Predisposition towards unhealthy foods linked with increased gray matter volume in the cerebellum. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

278. Olson, EA, Weber, M, Gogel, H, & **Killgore, WD**. Daytime sleepiness is associated with decreased integration of remote outcomes on the IGT. Abstract presented at the 21st Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, April 5-8, 2014.

279. Demers, LA, Preer, LA, Gogel, H, Olson, EA, Weber, M, & **Killgore, WD**. Left-hemifield bias on sad chimeric face task correlates with interpersonal emotional intelligence. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.

280. Weber, M, **Killgore, WD**, Olson, EA, Rosso, IM, & Rauch, SL. Morphological brain network organization in relation to trauma and posttraumatic stress disorder. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.

281. Divatia, S, Demers, LA, Preer, L, Gogel, H, Kipman, M, & **Killgore, WD**. Schizotypal and manic traits are associated with poorer perception of emotions in healthy individuals. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.

282. **Killgore, WD**, Weber, M, Olson, EA, & Rauch, SL. Sleep reduction and functioning of the emotion regulation circuitry. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014. ***[*Blue Ribbon Finalist for Top Poster Award: Basic Neuroscience]***

283. Webb, CA, Weber, M, Mundy, EA, & **Killgore, WD**. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of depressive symptoms: A voxel-based morphometric analysis. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.

284. Marin MF, Song H, Landau AJ, Lasko NB, Foy Preer LA, Campbell A, Pace-Schott EF, **Killgore WD**, Orr SP, Pitman RK, Simon NM, Milad MR (2014). Psychophysiological and Neuroimaging Correlates of Fear Extinction Deficits Across Anxiety Disorders. Abstract presented at the 69th Annual Meeting of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.

285. **Killgore, WD**. The effects of sleep loss on food preference. Abstract presented at SLEEP 2014, Minneapolis, MN, May 31-June 4, 2014.

286. Weber, M, & **Killgore, WD**. Sleep habits reflect in functional brain network organization. Abstract presented at SLEEP 2014, Minneapolis, MN, May 31-June 4, 2014. ***[*2014 AASM Young Investigator Award, Honorable Mention]***

287. Freed, MC, Novak, LA, **Killgore, WD**, Koehlmoos, TP, Ginsberg, JP, Krupnick, J, Rauch S, Rizzo, A, Engle, CC. DoD IRB delays: Do they really matter? And if so, why and for whom? Abstract presented at the Military Health System Research Symposium, Fort Lauderdale, FL, August 18-21, 2014.

288. Freed, MC, Novak, LA, **Killgore, WD**, Koehlmoos, TP, Ginsberg, JP, Krupnick, J, Rauch S, Rizzo, A, Engle, CC. DoD IRB delays: Do they really matter? And if so, why and for whom? Abstract presented at the AMSUS Annual Meeting, Washington DC, December 2-5, 2014.

289. **Killgore, WD**, Demers, LA, Olson, EA, Rosso, IM, Webb, CA, & Rauch, SL. Anterior cingulate gyrus and sulcus thickness: A potential predictor of remission following internet-based cognitive behavioral therapy for major depressive disorder. Abstract presented at the 53rd Annual Meeting of the American College of Neuropsychopharmacology, Phoenix, AZ, December 7-11, 2014.

290. Olson, EA, Buchholz, J, Rosso, IM, **Killgore, WD**, Webb, CA, Gogel, H, & Rauch, SL. Internet-based cognitive behavioral therapy effects on symptom severity in major depressive disorder: preliminary results from a randomized controlled trial. Abstract presented at the 53rd Annual

Meeting of the American College of Neuropsychopharmacology, Phoenix, AZ, December 7-11, 2014.

291. Brennan, B, Tkachenko, O, Schwab, Z, Ryan, E, Athey, A, Pope, H, Dougherty, D, Jenike, M, **Killgore, WD**, Hudson, J, Jensen, E, & Rauch SL. Abstract presented at the 53rd Annual Meeting of the American College of Neuropsychopharmacology, Phoenix, AZ, December 7-11, 2014.

292. Alkozei, A, Pisner, D, & **Killgore, WD**. Emotional intelligence is differentially correlated with prefrontal cortical responses to backward masked fearful and angry faces. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

293. Alkozei, A, Schwab, Z, & **Killgore, WD**. Looking for evil intent: Emotional intelligence and the use of socially relevant facial cues during an emotional decision making task. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

294. Shane, BR, Alkozei, A, & **Killgore, WD**. The contribution of general intelligence and emotional intelligence to the ability to appreciate humor. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

295. Markowski, SM, Alkozei, A, & **Killgore, WD**. Sleep onset latency and duration are associated with self-perceived invincibility. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

296. Pisner, D, Alkozei, A, & **Killgore, WD**. Visuospatial reasoning mediates the relationship between emotion recognition and emotional intelligence. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

297. Vanuk, JR, Fridman, A, Demers, LA, Divatia, S, & **Killgore, WD**. Engaging in meditation and internet based training as a means of enhancing emotional intelligence. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

298. Vanuk, JR, Divatia, S, Demers, LA, Markowski, SM, & **Killgore, WD**. Napping in conjunction with brief internet-based training as a means of enhancing emotional intelligence. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

299. Cui, J, Tkachenko, O, Gogel, H, Kipman, M, Preer, LA, Weber, M, Divatia, SC, Demers, LA, Olson, EA, Buchholz, JL, Bark, JS, Rosso, IM, Rauch, SL, & **Killgore, WD**. Fractional Anisotropy of frontoparietal connections presicts individual resistance to sleep deprivation. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

300. **Killgore, WD**, Olson, EA, Weber, M, Rauch, SL, & Nickerson, LD. Emotional intelligence is associated with coordinated resting state activity between emotion regulation and interoceptive

experience networks. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

301. **Killgore, WD**, Demers, LA, Divatia, S, Kipman, M, Tkachenko, O, Weber, M, Preer, LA, Gogel, H, Olson, EA, Vanuk, JR, & Rauch, SL. Enhancing emotional intelligence via brief internet-based training. Abstract presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.

302. Buchholz, JL, Rosso, IM, Olson, EA, **Killgore, WD**, Fukunaga, R, Webb, CA, & Rauch, SL. Internet-based cognitive behavioral therapy is associated with symptom reduction and cognitive restructuring in adults with major depressive disorder. Abstract presented at the Anxiety and Depression Conference, Miami, FL, April 9-12, 2015.

303. Alkozei, A, Pisner, D, Rauch, SL, & **Killgore, WD**. Emotional intelligence and subliminal presentations of social threat. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

304. Shane, BR, Alkozei, A, Vanuk, JR, Weber, M, & **Killgore, WD**. The effect of bright light therapy for improving sleep among individuals with mild traumatic brain injury. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

305. Vanuk, JR, Shane, BR, Alkozei, A, & **Killgore, WD**. Trait emotional intelligence is associated with greater resting state functional connectivity within the default mode and task positive networks. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

306. Vanuk, JR, Fridman, A, Demers, LA, & **Killgore, WD**. Engaging in meditation and internet-based training as a means of enhancing emotional intelligence. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

307. Pisner, D, Alkozei, A, & **Killgore, WD**. Trait emotional suppression is associated with decreased activation of the insula and thalamus in response to masked angry faces. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

308. Markowski, SM, Alkozei, A, & **Killgore, WD**. The trait of neuroticism predicts neurocognitive performance in healthy individuals. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

309. Buchholz, JL, Rosso, IM, **Killgore, WD**, Fukunaga, R, Olson, EA, Demers, LA, & Rauch, SL. Amygdala volume is associated with helplessness in adults with major depressive disorder (MDD). Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

310. Sneider, JT, **Killgore, WD**, Rauch, SL, Jensen, JE, & Silveri, MM. Sex differences in the associations between prefrontal GABA and resistance to sleep deprivation. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-

16, 2015.

311. **Killgore, WD**, Rosso, IM, Rauch, SL, & Nickerson, LD. Emotional intelligence correlates with coordinated resting state activity between brain networks involved in emotion regulation and interoceptive experience. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

312. **Killgore, WD**, Demers, LA, Divatia, S, Rosso, IM, & Rauch, SL. Boosting Emotional intelligence with a brief internet-based program. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

313. **Killgore, WD**, Vanuk, JR, Alkozei, A, Markowski, SM, Pisner, D, Shane, BR, Fridman, A, & Knight, SA. Greater daytime sleepiness correlates with altered thalamocortical connectivity. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

314. **Killgore, WD**, Tkachenko, O, Gogel, H, Kipman, M, Sonis, LA, Divatia, SC, Demers, LA, Olson, EA, Buchholz, JL, Rosso, IM, & Rauch, SL. Activation of the ventral striatum predicts overeating during subsequent sleep loss. Abstract presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, CA, May 14-16, 2015.

315. Alkozei, A, Markowski, SM, Shane, BR, Rauch, SL, & **Killgore, WD**. Emotional resilience is not associated with increased emotional resistance to sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

316. Alkozei, A, Pisner, D, Markowski, SM, Rauch, SL, & **Killgore, WD**. The effect of emotional resilience on changes in appetitie for high-sugary food during sleep loss. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

317. Markowski, SM, Alkozei, A, Rauch, SL, & **Killgore, WD**. Self-perceived invincibility is associated with sleep onset latency and duration. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

318. Markowski, SM, Alkozei, A, Rauch, SL, & **Killgore, WD**. Sex differences in the association between personality and resistance to sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

319. Shane, BR, Alkozei, A, & **Killgore, WD**. Physical exercise may contribute to vulnerability to sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

320. Cui, J, Tkachenko, O, Gogel, H, Kipman, M, Sonis, LA, Weber, M, Divatia, SC, Demers, LA, Olson, EA, Buchholz, JL, Rosso, IM, Rauch, SL, & **Killgore, WD**. Resistance to sleep deprivation involves greater functional activation and white matter connectivity within a fronto-parietal network. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

321. Vanuk, JR, Rosso, IM, Rauch, SL, Alkozei, A, Markowski, SM, Pisner, D, Shane, BR, Fridman A, Knight, SA, & **Killgore, WD**. Daytime sleepiness is associated with altered thalamocortical connectivity. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

322. Sneider, JT, Jensen JE, Silveri, MM, & **Killgore, WD**. Prefrontal GABA predicts resistance to sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

323. **Killgore, WD**, Tkachenko, O, Gogel, H, Kipman, M, Sonis, LA, Weber, M, Divatia, SC, Demers, LA, Olson, EA, Buchholz, JL, Rosso, IM, & Rauch, SL. Individual differences in rested activation of the ventral striatum predict overeating during sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

324. **Killgore, WD**, Tkachenko, O, Rosso, IM, Rauch, SL, & Nickerson, LA. Multimodal neuroimaging to predict resistance to sleep deprivation. Abstract presented at the SLEEP 2015 Meeting, Seattle, WA, June 6-10, 2015.

325. Nickerson, LD & **Killgore, WD**. Resting state brain circuits underpinning a neurobiological model of Theory of Mind and Mentalizing. Abstract presented at the Organization for Human Brain Mapping Annual Meeting, 2015, Honolulu, HI, June 14-18, 2015.

326. Rosso, IM, Olson, EA, **Killgore WD**, Fukunaga, R, Webb, CA, & Rauch SL. A randomized trial of internet-based cognitive behavioral therapy for major depressive disorder. Abstract presented at the 54th Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL, December 6-10, 2015.

327. Alkozei, A & **Killgore, WD**. Exposure to blue wavelength light is associated with increased dorsolateral prefrontal cortex responses during a working memory task. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

328. Klimova, A, Pisner, D & **Killgore, WD**. Neural correlates of cognitive and emotional impairments in acute versus chronic mild traumatic brain injury: a diffusion tensor imaging study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

329. Markowski, S, Alkozei, A, & **Killgore, WD.** Greater neuroticism predicts higher performance in immediate memory, language, and attention in healthy individuals. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

330. Alkozei, A & **Killgore, WD.** Exposure to blue wavelength light suppresses anterior cingulate cortex activation in response to uncertainty during anticipation of negative or positive stimuli. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

331. Smith, R, Alkozei, A, Bao, J, & **Killgore, WD.** Successful goal-directed memory suppression is associated with increased inter-hemispheric coordination between right and left fronto-parietal control networks. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

332. Singh, P, Fridman, A, Pisner, D, Singh, A, & **Killgore, WD.** A voxel based morphometric

analysis of ventromedial prefrontal cortex volume related with executive function task performance post mild traumatic injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

333. **Killgore, WD.** Baseline responsiveness of the ventral striatum predicts overeating during subsequent sleep deprivation. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

334. **Killgore, WD** & Nickerson, LD. Predicting resistance to sleep deprivation using multimodal neuroimaging. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

335. Sneider, J, Jensen, JE, Silveri, MM, & **Killgore, WD.** Prefrontal GABA correlates with the ability to sustain vigilance during sleep deprivation. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

336. Buchholz, JL, Olson, EA, Fukunaga, R, Webb, CA, **Killgore, WD**, Rauch, SL, & Rosso, IM. Expressive suppression is associated with greater lateral orbitofrontal cortex volume in adults with major depressive disorder. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

337. Fridman, A, Pisner, D, Singh, P, & **Killgore, WD**. Gray matter volume in left medial prefrontal cortex is related to life satisfaction in individuals with mild traumatic brain injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

338. Singh, P, Pisner, D, Fridman, A, Roberts, S, & **Killgore, WD.** Volumetric differences in gray matter in healthy versus overweight/obese individuals post mild traumatic brain injury: A voxel based morphometric study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

339. **Killgore, WD** & Weber, M. Blue wavelength light therapy reduces daytime sleepiness following mild traumatic brain injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

340. **Killgore, WD**, Weber, M, & Penetar, D. Blue wavelength light therapy improves balance following mild traumatic brain injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

341. Pisner, D, Smith, R, Alkozei, A, Klimova, A, & **Killgore, WD.** Highways of the emotional intellect: White matter microstructural correlates of an ability-based measure of emotional intelligence. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

342. Vanuk, JR, Smith, R, Knight, S, & **Killgore, WD.** Resting RSA correlates with coordinated resting state activity between brain networks involved in emotion perception. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

343. Vanuk, JR, Alkozei, A, Markowski, S, & **Killgore WD.** Greater resting state functional connectivity within the default mode and task positive networks is associated with trait emotional intelligence. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

344. Fukunaga, R, Webb, CA, Olson, EA, **Killgore, WD**, Rauch, SL, & Rosso, IM. Reduced rostral anterior cingulate volume is associated with greater frequency of negative automatic thoughts in adults with major depressive disorder. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

345. Olson, EA, Fukunaga, R., Webb, CA, Rosso, IM, **Killgore, WD**, & Rauch, SL. Delay discounting and anhedonia are independently associated with suicidal ideation in depression. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

346. Pisner, D, Singh, P, Fridman, A, & **Killgore, WD**. Resilience following mild traumatic brain injury is associated with gray matter volume in the left precentral gyrus. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

347. Sing, P, Fridman, A, Pisner, D, & **Killgore, WD.** Time dependent differences in gray matter volume in individuals post mild traumatic brain injury: A voxel based morphometric study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

348. Smith, C, Smith, R, Sanova, A, & **Killgore, WD.** The neural basis of emotional working memory and its relation to adaptive emotional functioning. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

349. Quan, M, Gruber, SA, Lukas, SE, Hill, KP, **Killgore, WD**, & Nickerson, LD. Altered functional connectivity within large-scale brain networks during a cognitive task in chronic marijuana smokers. Abstract presented at the Harvard Psychiatry Research Day, Boston, MA, March 23, 2016. ***[*Semi Finalist Poster: Harvard Medical School Mysell Award]***

350. Fukunaga, R, Webb, CA, Olson, EA, **Killgore, WD**, Rauch, SL, & Rosso, IM. Improvement in negative automatic thoughts as a mediator of symptom improvement in internet-based cognitive behavioral therapy for major depressive disorder. Abstract presented at the 2016 Meeting of the Anxiety and Depression Association of America, Philadelphia, PA, March 31-April 3, 2016.

351. Bernstein, AS, Pisner, D, Klimova, A, Umapathy, L, Do, L, Squire, S, **Killgore, WD**, & Trouard, T. Effects of multiband acceleration on high angular resolution diffusion imaging data collection, processing, and analysis. Abstract presented at the 24th Annual Meeting of the International Society for Magnetic Resonance in Medicine (IMSRM), Singapore, May 7-8, 2016.

352. Alkozei, A, Markowski, SM, Pisner, D, Fridman, A, Shane, BR, Vanuk, JR, Knight, SA, & **Killgore, WD.** Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli. Abstract presented at the 71st

Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

353. Alkozei, A., Pisner, D, Markowski, SM, Vanuk, JR, Fridman, A, Shane, BR, Knight SA, & **Killgore, WD.** Increases in prefrontal activation after exposure to blue versus amber wavelength light during cognitive load. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

354. Pisner, DA, Smith, R, Alkozei, A, Klimova, A, Millan, M, & **Killgore, WD.** Highways of the emotional intellect: White matter mictrostructural correlates of an ability-based measure of emotional intelligence. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

355. Singh, P, Pisner, D, Fridman, A, Singh A, Millan, M, & **Killgore, WD.** A voxel based morphometric analysis of ventromedial prefrontal cortex volume related with executive function task performance post mild traumatic brain injury. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

356. Smith, R, Smith, C, Khodr, O, Nettles, M, Sanova, A, & **Killgore, WD.** Emotional working memory: A relatively unexplored aspect of emotional and cognitive ability. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

357. Smith, R, Nettles, M, Khodr, O, Sanova, A, Smith, C, Alkozei, A, & **Killgore, WD.** Conflict-related dorsomedial frontal activation during healthy food decisions is associated with increased cravings for high-fat foods. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

358. Smith, R, Sanova, A, Nettles, M, Khodr, O, Smith, C, Alkozei, A, Lane, RD, & **Killgore, WD**. Unwanted reminders: The effects of emotional memory suppression on later neuro-cognitive processing. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

359. **Killgore, WD**, Weber, M, Palmer, W, & Penetar, D. Blue wavelength light therapy improves balance following mild traumatic brain injury. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

360. **Killgore, WD**, Tkachenko, O, Palmer, W, & Rauch, SL. Default mode activation predicts vulnerability to sleep deprivation in domains of mood, sleepiness, and vigilance. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

361. Alkozei, A, Markowski, SM, Pisner, D, Fridman, A, Shane, BR, Vanuk, JR, Knight, SA, Grandner, MA, & **Killgore, WD.** Exposure to blue wavelength light reduces activation within the anterior cingulate cortex during anticipation of certain reward stimuli. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

362. Alkozei, A, Pisner, D, Markowski, SM, Vanuk, JR, Fridman, A, Shane, BR, Knight, SA, Grandner, MA, & **Killgore, WD.** Exposure to blue wavelength light is associated with increased dorsolateral prefrontal cortex responses and increases in response times during a working memory task. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

363. Davis, B, Yang, R, **Killgore, WD**, Gallagher, RA, Carrazco, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Nightmares in a community sample: Prevalence and associations with daytime function independent of poor sleep quality and depression. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

364. Fisseha, E, Havens, C, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Sleep duration's important role in the relationship among difficulty concentrating, fatigue, stress, and depressed mood: Data from the SHADES study. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

365. Graham, PM, Goldstein, M, David, BM, Perlis, ML, Perfect, MM, Frye, S, **Killgore, WD**, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Longitudinal analysis of sleep duration using actigraphy and sleep diary: Stability and agreement over 8-11 months. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

366. Granados, K, Rojo-Wissar, DM, Chakravorty, S, Prather, A, Perfect, MM, Frye, S, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Adverse childhood exposures associated with adult insomnia symptoms. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

367. Grandner, MA, **Killgore, WD**, Khader, W, & Perlis, ML. Positive and negative mood ratings across 24-hours. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

368. Hall, C, Forbush, S, Youngstedt, S, **Killgore, WD**, Barilla, H, Gehrels, J, Alfonso-Miller, P, Palmer, W, Carrazco, N, & Grandner, MA. Habitual sleep duration and health: A possible role for exercise. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

369. Jackson, N, Patterson, F, Seixas, A, Jean-Louis, G, **Killgore, WD**, & Grandner, MA. Using big data to determine the social, behavioral, and environmental, determinants of sleep duration in the U.S. population: Application of a machine learning approach to data from approximately 700,000 Americans. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

370. **Killgore, WD**, Tkachenko, O, Grandner, MA, & Rauch, SL. Default mode activation predicts vulnerability to sleep deprivation in the domains of mood, sleepiness, and vigilance. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP

2016), Denver, CO, June 11-15, 2016.

371. **Killgore, WD**, Weber, M, Grandner, MA, & Penetar, DM. Blue wavelength light therapy improves balance following mild traumatic brain injury. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

372. Knight, SA & Killgore, WD. Typical sleep duration is associated with constructive thinking patterns. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

373. Kotzin, MD, Alkozei, A, Knight, SA, Grandner, MA, & **Killgore, WD**. The effects of trait gratitude on quality of sleep, intrusiveness, of pre-sleep cognitions, and daytime energy in healthy individuals. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

374. Markowski, SM, Alkozei, A, McIntosh, MB, Grandner, MA, & **Killgore, WD**. Chronotype and risk-taking propensity. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

375. McIntosh, MB, Markowski, SM, Grandner, MA, & **Killgore, WD**. Prior-night sleep duration is negatively associated with impulsivity in women. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

376. Ocano, D, Jean-Louis, G, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Sleep duration and decreased social support from family, friends, and significant other: Influence of insomnia and perceived stress level. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

377. Okuagu, A, Perlis, ML, Ellis, JA, Prather, AA, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Does thinking keep people awake? Or does it matter what they are thinking about? Self-directed cognitions associated with insomnia and insufficient sleep. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

378. Olivier, K, Gallagher, RA, **Killgore, WD**, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Development and initial validation of the Assessment of Sleep Environment: A novel inventory for describing and quantifying the impact of environmental factors on sleep. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

379. Paine, KN, Forbush, S, Ellis, J, Nowakowski, S, Newman-Smith, K, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Sleep duration and satisfaction with life, health, finances and relationship. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

380. Rhee, JU, Haynes, P, Chakravorty, S, Patterson, F, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Susceptibility to smoking during the day and its relationship with insomnia and sleep duration. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

381. Roberts, SE, Singh, P, Grandner, MA, & **Killgore, WD.** Later wake up time and impulsivity. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

382. Saccone, J, Davis, B, Chakravorty, S, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Habitual caffeine use and motivation to consume caffeine: Associations with sleep duration, sleepiness, fatigue, and insomnia severity. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

383. Singh, A, Fridman, A, Silveri, MM, Grandner, MA, & **Killgore, WD.** Medial prefrontal GABA predicts hunger ratings during sleep deprivation for men but not women. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

384. Vanuk, JR, Alkozei, A, Smith, R, Pisner, D, Markowski, SM, Shane, BR, Fridman, A, Knight, SA, Grandner, MA, & **Killgore, WD.** Changes in heart rate variability due to light exposure predict frontoparietal connectivity. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

385. Vanuk, JR, Alkozei, A, Knight, SA, Fridman, A, Markowski, SM, Pisner, D, Shane, BR, Grandner, MA, & **Killgore, WD.** The effects of light exposure on heart rate variability predict sleepiness and vigilance. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

386. Warlick, C, Chakravorty, S, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Timing of alcohol intake associated with insomnia symptoms. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

387. Waugaman, DL, Markowski, SM, Alkozei, A, Grandner, MA, & **Killgore, WD.** Chronotype and Emotional Intelligence. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

388. Weber, M, Grandner, MA, & **Killgore, WD.** Smaller gray matter volume of the visual cortex predicts vulnerability to sleep deprivation. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

389. Weber, M, Grandner, MA, & **Killgore, WD.** Blue wavelength light therapy reduces daytime sleepiness following mild traumatic brain injury. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

390. Yang, R, Ocano, D, Chakravorty, S, **Killgore, WD**, Gallagher, RA, Carrazco, N, Alfonso-Miller,

P, Gehrels, J, & Grandner, MA. Relationship between insomnia and depression moderated by caffeine. Abstract presented at the 30th Annual Meeting of the Associated Professional Sleep Societies (SLEEP 2016), Denver, CO, June 11-15, 2016.

391. **Killgore, WD**, Vanuk, JR, Pisner, D, Penetar, DM, & Weber, M. Short wavelength light therapy facilitates recovery from mild traumatic brain injury. Abstract presented at the 2016 Military Health System Research Symposium (MHSRS), Orlando, FL, August 15-18, 2016.

392. **Killgore, WD**, Alkozei, A, Smith, R, Divatia, S, & Demers, L. Enhancing emotional intelligence skills with a brief internet-based program: A pilot study. Abstract presented at the 2016 Military Health System Research Symposium (MHSRS), Orlando, FL, August 15-18, 2016.

393. **Killgore, WD**, Rosso, IM, Olson, EA, Webb, CA, Fukunaga, R, Gogel, H, Buchholz, JL, & Rauch, SL. Efficacy of an internet-based cognitive behavior therapy program for major depression. Abstract presented at the 2016 Military Health System Research Symposium (MHSRS), Orlando, FL, August 15-18, 2016.

394. **Killgore, WD**, & Nickerson, LA. Linked analysis of multimodal neuroimaging identifies neural systems associated with the ability to resist sleep deprivation. Abstract presented at the 2016 Military Health System Research Symposium (MHSRS), Orlando, FL, August 15-18, 2016.

395. Vanuk, JR, Allen, JJB, & **Killgore, WD**. Heart rate variability during light exposure and subsequent network connectivity patterns. Abstract presented at the Annual Meeting of the Society for Psychophysiological Research, Minneapolis, MN, September 21-25, 2016.

396. Haberman, JT, Olson, EA, Webb, CA, **Killgore, WD**, Rauch, SL, & Rosso, IM. The relation between treatment expectancies and outcome in internet-based cognitive behavioral therapy for major depressive disorder. Abstract presented at the Association for Behavioral and Cognitive Therapies, New York, NY, October 27-30, 2016.

397. Rosso, IM, Olson, EA, Thomas, MO, Webb, CA, **Killgore, WD**, & Rauch, SL. Anterior cingulate cortex morphology predicts remission from major depression following internet-based cognitive behavior therapy. Abstract presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL, December 4-8, 2016.

398. Shane, BR, Vanuk, JR, Bajaj, S, Millan, M, **Killgore, WD**. Multimodal brain imaging in patients receiving bright light therapy following a mild traumatic brain injury. Abstract presented at the Western Medical Research Conference, Carmel CA, January 26-28, 2017.

399. Franco, J, Millan, M, Shane, BR, Castellanos, A, **Killgore, WD**. Blue wavelength light therapy increases thalamic grey matter volume following mild traumatic brain injury. Abstract presented at the 45th Annual Meeting of the International Neuropsychological Society, New Orleans, LA, February 1-4, 2017.

400. Alkozei, A, Smith, R, Demers, LA, Divatia, S, Weber, M, Berryhill, SM, & **Killgore, WD**. Emotional intelligence can be trained via an online training program and is associated with better performance on the IGT. Abstract accepted for oral platform presentation at the 45th Annual Meeting of the International Neuropsychological Society, New Orleans, LA, February 1-4, 2017.

401. Li, H, Gruber, S, Lukas, S, Silveri, M, Hill, K, **Killgore, WD**, & Nickerson, LD. Data fusion to investigate the effect of chronic heavy marijuana use on brain structure. Abstract presented at the 2017 Harvard Psychiatry Research Day Poster Session, Boston, MA, April 12, 2017.

402. Challener, S, Alkozei, A, Fridman, A, Dormer A, & **Killgore, WD.** Higher depressive symptoms are associated with lower activation in the orbitofrontal cortex when anticipating negative stimuli in individuals with PTSD. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

403. Alkozei, A, Smith R, Fridman A, Dormer, A, Challener, S, & **Killgore, WD.** Neural responses to emotional stimuli in individuals with PTSD after daily morning blue light exposure. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

404. Alkozei, A, Smith R, Fridman, A, Dormer, A, Challener, S, & **Killgore, WD.** The role of trait gratitude on functional brain activation changes when anticipating negative events in individuals with PTSD. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

405. Fridman, AJ, Alkozei, A, Smith, R, Challener, S, Knight, SA, & **Killgore, WD**. Resiliency is associated with reduced activation within the retrosplenial cortex and secondary motor area for individuals with PTSD during anticipation of a negative event. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

406. Vanuk, JR, Millan, M, Shane, BR, Bajaj, S, & **Killgore, WD**. Blue light therapy following a mild traumatic brain injury improves MPFC-amygdala functional connectivity and mood. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

407. **Killgore, WD**, Shane, BR, Vanuk, JR, Franco, J, Castellanos, A, Millan, M, Grandner, MA, & Bajaj, S. Light therapy facilitates thalamo-cortical brain recovery from mild traumatic brain injury. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

408. Smith, R, Lane, RD, Alkozei, A, Bao J, Smith, C, Sanova, A, Nettles, M, & **Killgore, WD**. Common and unique neural systems underlying the maintenance of emotional vs. bodily reactions to affective stimuli: the moderating role of emotional awareness. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

409. Bajaj, S, Alkozei, A & **Killgore, WD**. Effect of bright light therapy on white matter abnormalities following a mild traumatic brain injury. Abstract presented at the 72nd Annual Convention of the Society for Biological Psychiatry, San Diego, CA, May 18-20, 2017.

410. Alkozei, A, Smith, R, Fridman, A, Dormer A, Challener, S, Grandner, MA, & **Killgore, WD**. Daily morning blue light exposure leads to changes in functional brain responses during emotional anticipation in individuals with PTSD. Abstract presented at the SLEEP Meeting,

Boston, MA, June 3-7, 2017.

411. Gottschlich, MK, Hyman, S, Millan M, Pisner, D, Singh, A, Knight, SA, Grandner, MA, & **Killgore, WD**. Post-concussion severity is associated with sleep problems and neuropsychological status. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

412. Vanuk, JR, Shane, BR, Millan, M., Bajaj, S, Grandner, MA, & **Killgore, WD**. Short-wavelength light therapy as a way of improving sleep, cognition, and functional connectivity following mild traumatic brain injury. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

413. **Killgore, WD**, Shane, BR, Vanuk, JR, Franco, J, Castellanos, A, Millan, M, Grandner, MA, & Bajaj, S. Short wavelength light therapy facilitates recovery from mild traumatic brain injury. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

414. **Killgore, WD**, Capaldi, VF, Balkin, TJ, & Kamimori, GH. The trait of introversion-extraversion contributes to sustained performance on planning and sequencing abilities during sleep deprivation. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

415. Bajaj, S, Alkozei, A, Grandner, MA, & **Killgore, WD**. Effect of bright light therapy on brain and behavioral abnormalities following a mild traumatic brain injury. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

416. Oliver, K, Gallagher, R, Hale, L, Barrett, M, Branas, C, **Killgore, WD**, Parthasarathy, S, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Development and initial validation of a brief measure of control over sleep. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

417. Grandner, MA, Athey, A, **Killgore WD**, Alfonso-Miller, P. Preliminary results of a sleep health intervention in student athletes: Changes in sleep, energy level, and mental well-being, and body weight. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

418. Yang, R, Gallagher, R, Hale, L, Perlis, M, Barrett, M, Branas, C, **Killgore, WD**, Parthasarathy, S, Alfonso-Miller, P, Gehrels, J, Grandner, MA. Would you call yourself a short or long sleeper? Perceptions of sleep category associated with reported sleep duration, insomnia, and health. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

419. Fisseha, E, Gallagher, R, Hale, L, Branas, C, Barrett, M, **Killgore, WD**, Alfonso-Miller, P, Jean-Louis, G, Seixas, A, Williams, N, Gehrels, J, & Grandner, MA. Habitual weekday sleep duration associated with multiple dimensions of socioeconomic status. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

420. Poling, K, Gallagher, R, Hale, L, Branas, C, Seixas, A, Jean-Louis, G, **Killgore, WD**, Alfonso-Miller, P, Parthasarathy, S, Gehrels, J, & Grandner, MA. Sleep partially mediates the association between food insecurity and obesity: Roles of short sleep duration, insomnia, and socioeconomic factors. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

421. Forbush, S, Fisseha, E, Gallagher, R, Hale, L, Malone, S, Patterson, F, Branas, C, Barrett, M,

Killgore, WD, Gehrels, J, Alfonso-Miller, P, & Grandner, MA. Sociodemographics, poor overall health, cardiovascular disease, depression, fatigue, and daytime sleepiness associated with social jetlag independent of sleep duration and insomnia. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

422. Till, K, Athey, A, Chakravorty, S, **Killgore, WD**, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Insomnia and daytime tiredness in student athletes associated with risky behaviors and poor decision making when under the influence of alcohol. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

423. Warlick, C, Hall, C, Athey, A, Chakravorty, S, **Killgore, WD**, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Difficulty sleeping associated with substance use among student athletes. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

424. Jaszewski, A, Athey, A, **Killgore, WD**, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Sleep duration and quality associated with mental well-being in student athletes. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

425. Athey, A, Alfonso-Miller, P, **Killgore, WD**, & Grandner, MA. Preliminary results of a sleep health intervention in student athletes: Perceived changes to sleep, performance, and mental and physical wellbeing. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

426. Goel, N, Taylor, DM, Abel, T, **Killgore, WD**, Pearson-Leary, J, & Bhatnagar, S. MicroRNAs are cross-species markers of sleep loss in humans and rats. Abstract presented at the Organization for Human Brain Mapping Conference, Boston, MA, June 3-7, 2017.

427. Meridew, C, Jaszewski, A, Athey, A, Alfonso-Miller, P, **Killgore, WD**, Gehrels, J, & Grandner, MA. Impact of time and activity demands on sleep of student athletes: It's not about reduced sleep opportunity. Abstract presented at the SLEEP Meeting, Boston, MA, June 3-7, 2017.

428. Bajaj, S, Rosso, IM, Rauch, SL, & **Killgore WD**. Impact of bright light therapy on volume and cortical thickness of the brain following mild traumatic brain injury. Abstract presented at the Organization for Human Brain Mapping Conference, Vancouver, Canada, June 25-29, 2017.***[selected for travel award]**

429. Bajaj, S, Rosso, IM, Rauch, SL, & **Killgore, WD**. Effect of bright light therapy on white matter abnormalities following mild traumatic brain injury. Abstract presented at the Organization for Human Brain Mapping Conference, Vancouver, Canada, June 25-29, June 3-7, 2017.

430. Alkozei, A, Haack, M, Smith, R, Dailey, N, Bajaj, S, & **Killgore, WD**. Chronic sleep restriction increases negative implicit attitudes toward Arab Muslims. Abstract presented at the Military Health Systems Research Symposium, Kissimmee, FL, August 27-30, 2017.

431. **Killgore WD**, Vanuk, JR, Bajaj, S. Blue wavelength light therapy increases axonal myelination in mild traumatic brain injury. Abstract presented at the Military Health Systems Research Symposium, Kissimmee, FL, August 27-30, 2017.

432. **Killgore WD**. What makes a Super-Soldier: Identifying the neural correlates of individual

differences in resilience against sleep deprivation. Abstract presented at the Military Health Systems Research Symposium, Kissimmee, FL, August 27-30, 2017.

433. Dailey, NS, Bajaj, S, Alkozei, A, & **Killgore WD**. Neural correlates of aggression during chronic and subacute stages of recovery from mild traumatic brain injury. Abstract presented at the Military Health Systems Research Symposium, Kissimmee, FL, August 27-30, 2017.

434. Bajaj, S, Alkozei, A, & **Killgore WD**. Short wavelength light therapy following mild traumatic brain injury: Can we normalize the abnormal diffusion and quantity of water within the brain? Abstract presented at the Military Health Systems Research Symposium, Kissimmee, FL, August 27-30, 2017.

435. Goel, N, Taylor, DM, Abel, T, **Killgore, WD**, Pearson-Leary, J, & Bhatnagar, S. MicroRNAs are cross-species markers of sleep loss in humans and rats. Abstract presented at the Society for Neuroscience, Washington, DC, November 11-15, 2017.

436. Dailey, NS, Bajaj, S, Alkozei, A, Smith, R, Knight, SA, & **Killgore, WD**. Neural correlates of aggression in the chronic and post-acute stages of recovery from mild traumatic brain injury: A diffusion tensor imaging study. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

437. Challener, S, Alkozei, A, Fridman, A, Dormer, A, & **Killgore, WD**. Higher depressive symptoms are associated with lower activation in the orbital frontal cortex when anticipating negative stimuli in individuals with PTSD. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

438. Alkozei, A, Smith, R, Demers, L, Divatia, S, Weber, M, Berryhill, S, & **Killgore, WD**. Emotional intelligence can be trained via an online training program and is associated with better performance on the IGT. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

439. Satterfield, B, Raikes, AC, & **Killgore, WD**. A voxel-based morphometric analysis of resilience to vigilant attention impairment during sleep deprivation. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

440. Singh, A, Thurston, MD, Gottschlich, MK, Miller, MA, & **Killgore, WD**. Trait anxiety predicts hostile tendencies post-traumatic brain injury. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

441. Raikes, AC, Satterfield, BC, Knight, SA, & **Killgore, WD**. Grey matter volumetric differences with increasing numbers of previous mild traumatic brain injuries: A voxel-based morphometric study. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

442. Bajaj, S, Dailey, N, Alkozei, A, Vanuk, JR, & **Killgore, WD**. Preservation of limbic network structure in healthy young adults. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

443. Alkozei, A, **Killgore, WD**, Smith, R, Dailey, NS, Bajaj, S, & Haack, M. Chronic sleep restriction increases negative implicit attitudes toward Arab Muslims. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

444. Skalamera, J, Alkozei, A, Haack, M, & **Killgore, WD**. Chronic sleep restriction increases racial bias and affects actual decision-making about people. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

445. Alkozei, A, Smith, R, & **Killgore, WD**. Increases in prefrontal activation after exposure to blue versus amber wavelength light during cognitive load. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

446. Knight, SA, & **Killgore, WD**. Typical sleep duration is associated with constructive thinking patterns. Abstract presented at the University of Arizona Junior Investigator Poster Forum, Tucson, AZ, November 17, 2017.

447. Nickerson, L, Li, H, Smith, S, Lukas, S, Silveri, M, Hill, K, **Killgore, WD**, & Gruber, S. Combining multi-site/study MRI data: A novel linked-ICA denoising method for removing scanner and site variability from muli-modal MRI data. Abstract presented at the American College of Neuropsychopharmacology (ACNP) 56th Annual Meeting, Palm Springs, CA, December 3-7, 2017.

448. Bajaj, S, Raikes, AC, Dailey, NS, Vanuk, JR, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Changes in cortical structure, sleep, and anxiety symptoms following blue-wavelength light therapy in individuals with mild traumatic brain injury. Abstract presented at the Big Sky Athletic Training Sports Medicine Conference, Big Sky, MT, February 4-8, 2018.

449. Dailey, NS, Raikes, AC, Smith, R, Alkozei, A, & **Killgore, WD**. The executive control network after mild traumatic brain injury: Associations between functional connectivity and aggression. Abstract presented at the Big Sky Athletic Training Sports Medicine Conference, Big Sky, MT, February 4-8, 2018.

450. Raikes, AC, Satterfield, BC, Dailey, NS, Bajaj, S, & **Killgore, WD**. Self-reported sleep quality is related to cerebellar grey matter volume after mild traumatic brain injury. Abstract presented at the Big Sky Athletic Training Sports Medicine Conference, Big Sky, MT, February 4-8, 2018.

451. Raikes, AC, Bajaj, S, Dailey, NS, Satterfield, BC, Alkozei, A, Smith, R, & **Killgore, WD**. White matter correlates of self-reported sleep quality after a mild traumatic brain injury: A DTI study. Abstract presented at the Big Sky Athletic Training Sports Medicine Conference, Big Sky, MT, February 4-8, 2018.

452. Satterfield, BC, Raikes, AC, & **Killgore, WD**. A voxel-based morphometric analysis of resilience to vigilant attention impairment during sleep deprivation. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

453. Alkozei, A, Smith, R, Dailey, NS, Bajaj, S, Knight SA, & **Killgore, WD**. Exposure to blue wavelength light during memory consolidation improves long-delay verbal memory performance.

Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

454. Alkozei, A, Smith, R, Dailey, NS, Bajaj, S, Haack, M, & **Killgore, WD**. Men, but not Women, show a decrease in implicit preferences for low-calorie food after 3 weeks of chronic sleep restriction. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

455. Alkozei, A, Smith, R, & **Killgore, WD**. A positive cognitive style mediates the relationship between trait gratitude and depressive symptoms. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

456. Bajaj, S, Dailey, NS, Alkozei, A, Vanuk, JR, & **Killgore, WD**. Preservation of limbic network structure in healthy young adults. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

457. Alkozei, A, Smith, R, Demers, LA, Divatia, S, Weber, M, Berryhill, SM, & **Killgore, WD**. Emotional intelligence can be trained via an online training program and is associated with better performance on the IGT. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

458. Dailey, NS, Bajaj, S, Alkozei, A, Smith, R, Knight, SA, & **Killgore, WD**. Neural correlates of aggression in the chronic and post-acute stages of recovery from mild traumatic brain injury: A diffusion tensor imaging study. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

459. **Killgore, WD**, Shane, BR, Vanuk, JR, Millan, M, Knight, SA, & Bajaj, S. Blue light therapy accelerates brain and cognitive recovery from mild traumatic brain injury. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

460. **Killgore, WD**. Default mode activation and the ability to resist sleep deprivation. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

461. **Killgore, WD**, Capaldi, VF, Balkin, TJ, & Kamimori, GH. Personality traits predict the ability to sustain executive function abilities during sleep deprivation. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

462. Raikes, AC, & **Killgore, WD**. Increased cerebellar grey matter in the presence of decreased subjective sleep quality following mild traumatic brain injury. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

463. Raikes, AC, Satterfield, BC, Knight, SA, & **Killgore, WD**. Gray matter volumetric differences with increasing numbers of previous mild traumatic brain injuries: A voxel-based morphometric study. Abstract presented at the 46th Annual Meeting of the International Neuropsychological

Society, Washington, DC, February 14-17, 2018.

464. Skalamera, J, Alkozei, A, Haack, M, & **Killgore, WD**. Chronic sleep restriction increases implicit racial biases and affects actual decision-making about people. Abstract presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC, February 14-17, 2018.

465. Huanjie, L, Silveri, M, Lukas, SE, Hill, K, **Killgore, WD**, Gruber, S, & Nickerson, LD. Data fusion to investigate multimodal MRI patterns associated with chronic heavy marijuana use. Abstract presented at the Harvard Psychiatry Day Poster Session, Boston, MA, April 4, 2018.

466. Bajaj, S, Dailey, NS, Vanuk, JR, Raikes, A, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Impact of blue light therapy on cortical volume, sleep and anxiety symptoms following mild traumatic brain injury. Abstract presented at the Anxiety and Depression Association of America (ADAA) Conference, Washington, DC, April 5-8, 2018.

467. Knight, SA, & **Killgore, WD**. Constructive thinking patterns correlate with typical sleep habits. Abstract presented at the Anxiety and Depression Association of America (ADAA) Conference, Washington, DC, April 5-8, 2018.

468. Raikes, AC, Dailey, NS, Bajaj, S, & **Killgore, WD**. White matter structure changes associated with depressive symptoms following recent mild traumatic brain injury. Abstract presented at the Anxiety and Depression Association of America (ADAA) Conference, Washington, DC, April 5-8, 2018.

469. Singh, A, Thurston, MD, Gottschlich, MK, Miller, MA, & **Killgore, WD**. Trait anxiety predicts hostile tendencies post-traumatic brain injury. Abstract presented at the Anxiety and Depression Association of America (ADAA) Conference, Washington, DC, April 5-8, 2018.

470. Bajaj, S, Raikes, AC, Alkozei, A, Dailey, NS, Satterfield, BC, Vanuk, JR, & **Killgore, WD**. Association between suicidal ideation and cortical volume in a sub-clinical sample of young individuals. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

471. Challener, S, Alkozei, A, Young, A, Ozcan, M, Raikes, AC, & **Killgore, WD**. Sleep problems are associated with greater default mode network activation when anticipating negative stimuli in individuals with PTSD. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

472. Dailey, NS, Smith, R, Raikes, AC, Alkozei, A, & **Killgore, WD**. Reduced functional connectivity in the executive control network following mild traumatic brain injury: Implications for emotional regulation. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

473. **Killgore, WD**, Kent, HC, Knight, SA, & Alkozei, A. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

474. **Killgore, WD**, Alkozei, A, & Weber, M. Blue light therapy improves executive function following mild traumatic brain injury. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

475. Ozcan, M, Challener, S, Yung, A, Alkozei, A, Raikes, AC, & **Killgore, WD**. Daytime sleepiness in individuals with PTSD is associated with greater activation in the right angular gyrus when viewing negative images. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

476. Smith, R, Sanova, A, Lane, RD, & **Killgore, WD**. Graph-theoretic correlates of trait differences in emotional awareness. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

477. Yung, A, Challener, S, Ozcan, M, Alkozei, A, Raikes, AC, & **Killgore, WD**. Improvements in PTSD symptom severity are associated with greater activation in the hippocampus during anticipation of negative stimuli. Abstract presented at the Society of Biological Psychiatry 73rd Annual Meeting, New York, NY, May 10-12, 2018.

478. Satterfield, BC, Silveri, M, Alkozei, A, Raikes, AC, & **Killgore, WD**. GABA: A neural marker of resilience to psychomotor vigilance impairment during sleep deprivation. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018. [*Trainee Merit Award]

479. Satterfield, BC, Alkozei, A, Raikes, AC, & **Killgore, WD**. Habitual sleep duration predicts caloric and mactronutrient intake during sleep deprivation. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

480. Bajaj, S, Raikes, A, Dailey, NS, Vanuk, JR, Satterfield, BC, Alkozei, A, Weber, M, Rosso, IM, Rauch, SL, Grandner, MA, & **Killgore, WD**. Impact of blue light therapy on cortical structure, sleep, and anxiety symptoms following mild traumatic brain injury. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

481. Challener, S, Alkozei, A, Yung, A, Ozcan, M, Raikes, AC, & **Killgore, WD**. Functional impairment due to excessive daytime sleepiness is associated with greater activation in the default mode network when anticipating negative stimuli in individuals with PDSD. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

482. **Killgore, WD**, Alkozei, A, Knight, SA, Miller, MA, Grandner, MA, & Weber, M. Daily morning blue light exposure enhances executive functioning in individuals with mild traumatic brain injury. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

483. **Killgore, WD**, & Nickerson, LA. Resistance to sleep deprivation is predicted by gray matter volume in the posterior brain stem. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

484. Alkozei, A, Kent, HC, Knight, SA, & **Killgore, WD**. Changes in morning salivary melatonin correlate with prefrontal responses during working memory performance. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

485. Ozcan, M, Alkozei, A, Raikes, A, & **Killgore, WD**. Pre-sleep cognitions partially mediate the relationship between depression and daytime energy. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

486. Raikes, AC, Dailey, NS, Satterfield, BC, Bajaj, S, & **Killgore, WD**. Self-reported sleep quality is associated with reductions in white-matter integrity following recent mild traumatic brain injury. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

487. Raikes, AC, Satterfield, BC, Dailey, NS, Bajaj, S, & **Killgore, WD**. Subjectively poor sleep quality is associated with increased cerebellar grey matter volume following mild traumatic brain injury. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

488. Skalamera, J, Alkozei, A, Haack, M, & **Killgore, WD**. The effect of chronic sleep restriction on implicit racial biases and explicit judgmental decision-making. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

489. Sanchez, C, Hale, L, Branas, C, Gallagher, R, **Killgore, WD**, Gehrels, J, Alfonso,-Miller, P, & Grandner, MA. Relationships between dietary supplement intake and sleep duration, insomnia, and fatigue. Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

490. Tubbs, A, Perlis, M, Chakravorty, S, Basner, M, **Killgore, WD**, Gehreles, J, Alfonso-Miller, P, & Grandner, MA. Does increased risk of suicide at night favor one method of suicide over another? Abstract presented at the SLEEP 2018 Annual Meeting, Baltimore, MD, June 2-6, 2018.

491. Huanjie, L, Gruber, S, Smith, SM, Lukas, SE, Silveri, M, Hill, KP, **Killgore, WD**, & Nickerson, LD. Combining multi-site/study MRI data: A novel linked-ICA denoising method for removing scanner and site variability from multi-modal MRI data. Abstract presented at the Joint Annual Meeting of ISMRM-ESMRMB, Paris, France, June 16-21, 2018. [*Trainee Stipend Award]

492. Bajaj, S, Raikes, AC, Alkozei, A, Dailey, NS, Vanuk, J, Satterfield, BC, & **Killgore, WD**. Suicidal ideation is associated with diminished cortical volume in a sub-clinical population. Abstract presented at the Organization for Human Brain Mapping (OHBM) Annual Meeting, Singapore, June 17-21, 2018.

493. Bajaj, S, Raikes, AC, Dailey, NS, Vanuk, J, Alkozei, A, Satterfield, BC, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Effect of blue light therapy on cortical volume, sleep, and anxiety symptoms following mild traumatic brain injury. Abstract presented at the Organization for Human Brain Mapping (OHBM) Annual Meeting, Singapore, June 17-21, 2018.

494. Dailey, NS, Bajaj, S, Smith, R, Raikes, AC, Alkozei, A, & **Killgore, WD**. Disrupted functional connectivity and elevated aggression in young adults with mild traumatic brain injury. Abstract presented at the Organization for Human Brain Mapping (OHBM) Annual Meeting, Singapore, June 17-21, 2018.

495. Raikes, AC, Bajaj, S, Dailey, NS, Alkozei, A, Smith, R, & **Killgore, WD**. Post-mTBI white matter correlates of self-reported sleep quality: A DTI study. Abstract presented at the

Organization for Human Brain Mapping (OHBM) Annual Meeting, Singapore, June 17-21, 2018.

496. Nickerson, LD, Li, H, , Silveri, MM, Lukas, SE, Hill, KP, **Killgore, WD**, & Gruber, SA. Multimodal MRI data fusion reveals structure-function patterns associated with chronic heavy marijuana use. Abstract presented at the Organization for Human Brain Mapping (OHBM) Annual Meeting, Singapore, June 17-21, 2018.

497. Raikes, AC, Satterfield, BC, Alkozei, A, & **Killgore, WD**. Blue light therapy improves self-reported sleep quality in individuals with a recent mild traumatic brain injury. Abstract presented at the Military Health Systems Research Symposium, Orlando, FL, August 20-23, 2018.

498. **Killgore, WD**. Executive functioning in individuals with mild traumatic brain injury is enhanced by daily morning blue light therapy. Abstract presented at the Military Health Systems Research Symposium, Orlando, FL, August, 20-23, 2018.

499. **Killgore, WD, &** Nickerson, LA. Why can't you just stay awake? Resistance to sleep deprivation is associated with measureable differences in brainstem gray matter. Abstract presented at the Military Health Systems Research Symposium, Orlando, FL, August 20-23, 2018.

500. Dailey, NS, Smith, R, Satterfield, BC, Raikes, AC, & **Killgore, WD**. Verbal fluency following mild traumatic brain injury: The strength of switching. Abstract presented at the American Speech-Language-Hearing Association Annual Convention, Boston, MA, November 15-17, 2018.

501. Forbeck, B, Dailey, NS, Esbit, S, & **Killgore, WD**. Reduced information processing speed: A dynamic deficit in mild traumatic brain injury. Abstract presented at the American Speech-Language-Hearing Association Annual Convention, Boston, MA, November 15-17, 2018.

502. Raikes, AC, Dailey, NS, & **Killgore, WD**. Neural and neurocognitive correlates of responsiveness to blue light therapy following mild traumatic brain injury. Abstract presented at the American Speech-Language-Hearing Association Annual Convention, Boston, MA, November 15-17, 2018.

503. Burns, AI, Ozcan, M, Shepard, KC, Alkozei, A, & **Killgore, WD**. The association between PTSD severity and life satisfaction is mediated by trait gratitude. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

504. Burns, AI, Shepard, KC, Ozcan, M, Alkozei, A, Vanuk, JR, & **Killgore, WD**. The association between morningness-eveningness and nightmares in PTSD. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

505. Dailey, NS, Meinhausen, C, & **Killgore, WD**. Self-initiated recall strategies in mild traumatic brain injury: Identifying the neural correlates. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

506. Esbit, S, Dailey, NS, & **Killgore, WD**. Making a list and checking it twice: Episodic verbal recall in mild traumatic brain injury. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

507. Esbit, S, LaFollette, K, Botello, R, Satterfield, BC, Alkozei, A, & **Killgore, WD**. High self-perceived adroitness: An altered perception of reality during sleep deprivation. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

508. **Killgore, WD**, Vanuk, JR, & Bajaj, S. Improving executive functioning in mild traumatic brain injury with daily morning blue light therapy. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

509. **Killgore, WD**, & Nickerson, LA. Vulnerability and resistance to sleep deprivation are associated with measurable differences in brainstem gray matter. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

510. LaFollette, K, Satterfield, BC, Lazar, M, & **Killgore, WD**. Predicting psychosocial stress reactivity from ability and trait-based emotional intelligence. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

511. LaFollette, K, Satterfield, BC, Lazar, M, & **Killgore, WD**. Stay negative? Positive affect is associated with increased psychosocial stress reactivity. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

512. Meinhausen, C, Dailey, NS, & **Killgore, WD**. Identifying memory retrieval strategies following a mild traumatic brain injury using the CVLT-II. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

513. Ozcan, M, Shepard, KC, Burns, AI, Alkozei, A, & **Killgore, WD**. Trait gratitude and the impact of daytime sleepiness on daily functioning predict PTSD severity over time. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

514. Raikes, AC, & **Killgore, WD**. Anterior cingulate gyrus volume predicts changes in post-mTBI daytime sleepiness following blue wavelength light therapy. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

515. Satterfield, BC, LaFollette, K, Lazar, M, & **Killgore, WD**. Prolonged psychosocial stress impairs cognitive flexibility. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

516. Shepard, KC, Burns, AI, Ozcan, M, Alkozei, A, & **Killgore, WD**. Racial differences regarding the effectiveness of blue light therapy in reducing PTSD severity. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY,

February 20-23, 2019.

517. Shepard, KC, Ozcan, M, Burns, AI, Alkozei, A, Vanuk, JR, & **Killgore, WD**. Differences in anxiety reduction between minority and majority racial groups participating in morning blue light exposure. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

518. Vanuk, JR., Smith, R, Raikes, AC, Alkozei, A, Skalamera, J, & **Killgore, WD**. Ability based emotional intelligence is associated with greater cardiac vagal tone. Abstract presented at the Annual Meeting of the International Neuropsychological Society (INS), New York, NY, February 20-23, 2019.

519. Vanuk, JR, Shields, S, Slavich, M, & **Killgore, WD**. Lifetime stress exposure during adulthood is associated with lower trait-based emotional intelligence. Abstract presented at the Annual Meeting of the American Psychosomatic Society, Vancouver, BC, March 6-9, 2019.

520. Raikes, AC, Satterfield, BC, Grandner, MA, & **Killgore, WD**. Daily blue light therapy reduces persistent post-mild traumatic brain injury daytime sleepiness and post-concussion. Abstract presented at the Rocky Mountain Athletic Trainer's Association Annual Meeting, Phoenix, AZ, April 12, 2019.

521. Bajaj, S, Dailey, NS, Raikes, AC, Vanuk, JR, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Effect of blue light therapy on cortical volume and reaction time following mild TBI. Abstract presented at the Organization for Human Brain Mapping Annual Meeting, June 9-13, 2019.

522. Bajaj, S, Raikes, AC, & **Killgore, WD**. Water anisotropy within the default mode network predicts mod shifts following sleep deprivation. Abstract presented at the Organization for Human Brain Mapping Annual Meeting, June 9-13, 2019.

523. Bajaj, S, Raikes, AC, Razi, A, & **Killgore, WD**. Blue-wavelength light strengthens default mode network following mild TBI: A DCM-DTI study. Abstract presented at the Organization for Human Brain Mapping Annual Meeting, June 9-13, 2019.

524. Bajaj, S, & **Killgore, WD**. Sex differences in limbic and risk-taking propensity in healthy individuals. Abstract presented at the Organization for Human Brain Mapping Annual Meeting, June 9-13, 2019.

525. Raikes, AC, Satterfield, BC, Grandner, MA, & **Killgore, WD**. Daily blue light therapy reduces persistent post-mild traumatic brain injury daytime sleepiness and post-concussion. Abstract presented at the Rocky Mountain Athletic Trainer's Association Annual Meeting, Phoenix, AZ, April 12, 2019.

526. Raikes, AC., Athey, A, Alfonso-Miller, P, **Killgore, WD**, & Grandner, MA. Self-reported insomnia and daytime sleepiness increase athletes' sports-related concussion risk. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

527. Raikes, AC, Satterfield, BC, Bajaj, S, Grandner, MA, & **Killgore, WD**. Daily blue light therapy reduces daytime sleepiness and post-concussion symptoms after mild traumatic brain injury. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

528. Burns, AI, Shepard, KC, Ozcan, M, LaFollette, K, Alkozei, A, Vanuk, JR, Raikes, AC, Grandner, MA, & **Killgore, WD**. Gratitude and frequency of naps predict resilience for individuals with PTSD. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

529. Burns, AI, Ozcan, M, Shepard, KC, LaFollette, K, Alkozei, A, Grandner, MA, & **Killgore, WD**. The association between PTSD severity and insomnia is mediated by nightmares. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

530. Bajaj, S, Dailey, NS, Raikes, AC, Vanuk, JR, Grandner, MA, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Impact of light therapy on brain structure and simple reaction time following mild traumatic brain injury. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

531. Bajaj, S, Raikes, AC, Grandner, MA, & **Killgore, WD**. Quantitative anisotropy within the default-mode network predicts mood degradation following sleep-deprivation. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

532. Dailey, NS, Satterfield, BC, Raikes, AC, Strong, MJ, Forbeck, B, Grandner, MA, & **Killgore, WD**. Disrupted thalamocortical connectivity following mild traumatic brain injury: Associations with daytime sleepiness. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

533. Shepard, KC, Ozcan, M, Burns, AI, Grandner, MA, & **Killgore, WD**. Use of anger words in trauma narratives is negatively associated with sleep quality for single individuals with PTSD. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

534. Shepard, KC, Ozcan, M, Burns, AI, Vanuk, JR, Grandner, MA, Alkozei, A, & **Killgore, WD**. The relationships between psychopathology and sleep problems differe between racial minority groups. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

535. **Killgore, WD**, & Kamimori, GH. Can caffeine sustain attention and vigilance under prolonged monotonous conditions during 77 hours of total sleep deprivation? Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

536. **Killgore, WD,** Pace-Schott, Ozcan, M, Shepard, KC, Burns, AI, Grandner, MA, Vanuk, JR, & Alkozei, A. Morning blue light exposure improves sleep and fear extinction recall in PTSD. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies

(SLEEP) Conference, San Antonio TX, June 8-12, 2019.

537. LaFollette, K, Satterfield, BC, Esbit, S, Lazar, M, Grandner, MA, & **Killgore, WD**. Negative mood and poor sleep are associated with altered moral reasoning under stress. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

538. LaFollette, KJ, Satterfield, BC, Esbit, S, Lazar, M, Grandner, MA, & **Killgore, WD**. The effects of prior at-home sleep duration on reversal-learning during a "shoot/no-shoot" task. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

539. Ozcan, M, Shepard, KC, Burns, AI, Raikes, AC, Dailey, NS, Alkozei, A, Grandner, MA, & **Killgore, WD**. Individuals with PTSD whose traumatic experiences occurred within the home have worse sleep outcomes. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

540. Ozcan, M, Shepard, KC., Burns, AI, Raikes, AC, Dailey, NS, Alkozei, A, Grandner, MA, & **Killgore, WD**. PTSD severity and use of negative emotion words in trauma narratives predict nightmares in individuals with PTSD. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

541. Satterfield, BC, Silveri, MM, Grandner, MA, & **Killgore, WD**. Baseline GABA levels predict time-on-task performance during sleep deprivation. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

542. Skalamera, J, Huang, YH, Chinkers, M, Richards, MM, & **Killgore, WDS**. The influence of habitual sleep duration on rational thinking ability. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

543. Bliznak, V, Perlis, ML, Ellis, J, Hale, L, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. What is the ideal bedtime? Data from a community sample. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

544. Lane, E, Ellis, J, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Sociodemographic, socioeconomic, and behavioral correlates of nightmare frequency in a community sample. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

545. Jajoo, A, Taylor-Pilliae, R, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Types of habitual physical activity associated with habitual sleep duration, sleep quality, and daytime sleepiness. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

546. Khader, W, Fernandez, F, Seizas, A, Knowlden, A, Ellis, J, Williams, N, Hale, L, Perlis, M, Jean-

Louis, G, **Killgore, WD**, Alfonso-Miller, P, & Grandner, MA. What makes people want to make changes to their sleep? Assessment of perceived risks of insufficient sleep as a predictor of intent to improve sleep. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

547. Pham, B, Hale, L, St-Onge, M, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Habitual dietary quality associated with habitual sleep duration, insomnia, daytime sleepiness, and fatigue in a community sample. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

548. Begay, T, Gooneratne, N, Williams, N, Seixas, A, Jean-Louis, G, Gilles, A, **Killgore, WD**, Alfonso-Miller, P, & Grandner, MA. Sleep disparities in the United States and the impact of poverty. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

549. Griffen, N, Hale, L, Jean-Louis, G, **Killgore, WD**, Warlick, C, Alfonso-Miller, & Grandner, MA. Aspects of disordered neighborhoods are associated with insomnia, sleepiness, fatigue and control over sleep. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

550. Liang, O, Seixas, A, Parthasarathy, S, Jean-Louis, G, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Healthcare financial hardship and habitual sleep duration, impact on sleep disparities, and impact on the sleep-obesity relationship. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

551. Olivier, K, Perlis, ML, Troxel, W, Basner, M, Chakravorty, S, Tubbs, A, Owens, J, Jean-Louis, G, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Influence of likely nocturnal wakefulness on 24-hour patterns of violent crime in adults and juveniles. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

552. Featherston, B, Perlis, ML, Ellis, J, Williams, N, Jean-Louis, G, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. The concept of "satisfaction with sleep: Associations with sleep continuity, sleep quality, daytime sleepiness, and related concepts of overall health, stress, depression, and anxiety. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

553. Fourte, DA, Patterson, F, Malhotra, A, Seixas, A, **Killgore, WD**, Alfonso-Miller, P, & Grandner, MA. Should habitual sleep duration be added to the American Heart Association's "Life's Simple 7?" Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

554. Wills, C, Athey, A, Robbins, R, Patterson, F, Turner, R, **Killgore, WD**, Tubbs, A, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Chronotype and social support among student athletes: Impact on depressive symptoms. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

555. Ramsey, T, Athey, A, Ellis, J, Tubbs, A, Turner, R, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Dose-response relationships between insufficient sleep and mental health symptoms I collegiate student athletes and non-athletes. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

556. Quiroz, H, Chakravorty, S, **Killgore, WD**, Warlick, C, Alfonso-Miller, P, & Grandner, MA. Sleep-related determinants of habitual cannabis use, desire to use, and problematic use: Data from a community sample. Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

557. Warlick, C, Williams, N, Hale, L, **Killgore, WD**, Alfonso-Miller, P, & Grandner, MA. Is relationship satisfaction associated with habitual sleep? Abstract presented at the 2019 Annual Meeting of the Associated Professional Sleep Societies (SLEEP) Conference, San Antonio TX, June 8-12, 2019.

558. Ozcan, M, Burns, AI, Shepard, KC, & **Killgore, WD**. The relationship between combat and non-combat trauma and risk-taking propensity in individuals with PTSD. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

559. Esbit, S, Satterfield, BC, & **Killgore, WD**. Exploration of emotional intelligence and self-perceived invincibility. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

560. LaFollette, KJ, Satterfield, BC, & **Killgore, WD**. Self-perceived invincibility is associated with greater cognitive flexibility. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

561. Strong, M, Esbit, S, LaFollette, KJ, Dailey, NS, & **Killgore, WD**. Big Five personality traits and how they relate to self-perceived invincibility. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

562. Shepard, KC, Ozcan, M, Burn, AI, Alkozei, A, & **Killgore, WD**. Blue light therapy differences in sleep quality improvement in military and civilian populations. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

563. Raikes, AC, Athey, A, Alfonso-Miller, P, **Killgore, WD**, & Grandner, MA. Moderate-to-severe self-reported insomnia and frequent daytime sleepiness increase athletes' risk for sustaining a sports-related concussion. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

564. Bajaj, S, Dailey, NS, Raikes, AC, Vanuk, JR, Weber, M, Rosso, IM, Rauch, SL, & **Killgore, WD**. Impact of blue-wavelength light therapy on cortical volume and simple reaction time following mild TBI. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

565. Raikes, AC, Satterfield, BC, Bajaj, S, Grandner, MA, & **Killgore, WD**. Daily administered blue light therapy reduces daytime sleepiness and improves somatic symptoms following mild

traumatic brain injury. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

566. Burns, AI, Ozcan, M, Shepard, KC, Alkozei, A, Vanuk, JR, & **Killgore, WD**. The relationship between sleep onset latency and gratitude. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

567. LaFollette, KJ, Satterfield, BC, Esbit, S, Lazar, M, & **Killgore, WD**. Inadequate sleep quality and duration predicts disinhibited shooting on a "shoot/no shoot" task. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

568. Bajaj, S, & **Killgore, WD**. Sex differences in risk-taking behavior and brain morphometry in healthy individuals. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

569. Satterfield, BC, Silveri, MM, & **Killgore, WD**. Baseline GABA levels are associated with time-on-task performance during sleep deprivation. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

570. **Killgore, WD**, Ozcan, M, Shepard, KC, Burns, AI, Vanuk, JR, & Alkozei, A. Blue light exposure enhances sleep and fear extinction recall in PTSD. Abstract presented at the 2019 Military Health System Research Symposium, Kissimmee, FL, August 19-2, 2019.

571. LaFollette, K, Satterfield, BC, Lazar, M., **Killgore, WDS**. Disentangling the Effects of Subjective Task Load and Performance on Neuroendocrine Stress Response. Poster presented at the 49th Annual Society for Neuroscience Meeting, Chicago, IL, October, 2019.

572. Dailey, NS, & **Killgore, WD**. Disrupted thalamocortical connectivity following mild traumatic brain injury: Associations with daytime sleepiness. Oral presentation at the American Speech-Language Hearing Association Conference, Orlando, FL, November, 2019.

573. Dailey, NS, & **Killgore, WD**. Reading fluency in mild traumatic brain injury. Poster presented at the American Speech-Language Hearing Association Conference, Orlando, FL, November, 2019.

574. Raikes, AC, Alkozei, A, Vanuk, JR, Bajaj, S, Satterfield, BC, & **Killgore, WD**. Blue light therapy reduces daytime sleepiness as well as depressive and somatic post-concussive symptoms following mild traumatic brain injury. Abstract accepted for Oral presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020. ***[*Winner of Nelson Butters Research Award for Best Paper by a Post-Doctoral Fellow]***.

575. Raikes, AC, Bajaj, S, Dailey, NS, Vanuk, JR, Alkozei, A, & **Killgore, WD**. Vestibular and emotional symptoms are associated with altered large-scale network resting stated functional connectivity after mild traumatic brain injury. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

576. Esbit, S, Satterfield, BC, LaFollette, K, Lazar, M, & **Killgore, WD**. Gender differences and

overriding misleading impulses. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

577. Esbit, S, Raygoza, D, Meinhausen, C, Dailey, NS, & **Killgore, WD.** Exploring verbal recall throughout mild traumatic brain injury recovery. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

578. Meinhausen, C, Esbit, S, Dailey, NS, & **Killgore, WD**. Self-initiated verbal recall strategies following mild traumatic brain injury. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

579. Anlap, I, Esbit, S, Alkozei, A, Satterfield, BC, & **Killgore, WD**. The effects of gratitude on wellbeing are mediated by social support. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

580. Dailey, NS, Raikes, AC, Bajaj, S, Alkozei, A, Sanasac, S, & **Killgore, WD**. Frontal cortical surface area is associated with lexical-semantic knowledge in adults with mild traumatic brain injury. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

581. **Killgore, WD**, Burns, AI, Shepard, KC, Vanuk, JR, & Alkozei, A. Enhancing fear extinction recall in PTSD using blue light therapy. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

582. **Killgore, WD**, & Kamimori, GH. The effects of caffeine under monotonous conditions during prolonged total sleep deprivation. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

583. **Killgore, WD**, & Kamimori, GH. Trait extraversion is associated with increased suicidal ideation during sleep deprivation. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

584. Bullock, A, Burns, AI, Shepard, KC, Alkozei, A, & **Killgore, WD**. Alterations in cognitive symptoms of PTSD are correlated with somatic symptoms. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

585. Taylor, E, & **Killgore, WD**. Caffeine and emotional control. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

586. Taylor, E, & **Killgore, WD**. Emotionally intelligent early birds. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

587. Alkozei, A, Dailey, NS, Bajaj, S, Vanuk, JR, Raikes, AC, & **Killgore, WD**. The effects of blue wavelength light on subsequent amygdala-DLPFC connectivity at rest. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

588. Vanuk, JR, Raikes, AC, Alkozei, A, Shields, GS, Slavich, GM, & **Killgore, WD**. Lifetime stress exposure during adulthood is associated with lower emotional intelligence. Abstract accepted for Poster presentation at the 48th Annual Meeting of the International Neuropsychological Society, Denver CO, February 5-8, 2020.

589. LaFollette, K, Satterfield, BC, Lazar, M., **Killgore, WD**. (February, 2020) The propensity for model-based control is associated with individual differences in risk behavior. Abstract submitted for presentation at the Computational and Systems Neuroscience (Cosyne) 2020 Meeting, Denver, CO, February, 2020.

590. **Killgore, WD**, Burns, AI, Bullock, A, Vanuk, J, Taylor, E, Alkozei, A. Using blue light to consolidate fear extinction memory in PTSD. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

591. **Killgore, WD**, & Kamimori, GH. Can caffeine sustain cognitive resilience during 77 hours of stressful total sleep deprivation? Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

592. **Killgore, WD**, Skalamera, J, Vanuk, J, Woods-Lubert, R, Cloonan, S, Alkozei, A, Dailey, N, Lane, R, Weihs, K, Allen, J, and Smith, R. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

593. **Killgore, WD,** & Kamimori, GH. Extraverts show increased suicidal ideation during sleep deprivation. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

594. **Killgore, WD**, Cloonan, S, Woods-Lubert, R, Taylor, E, & Skalamera, J. Political perspective is associated with differences in trait anxiety and depression. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

595. Alkozei, A, Dailey, NS, Bajaj, S, Vanuk, JR, Raikes, AC, & **Killgore, WD.** Acute blue wavelength light exposure influences functional brain connectivity. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

596. Burns, A, Shepard, KC, Bullock, A, Esbit, S, Alkozei, A, Satterfield, B, & **Killgore, WD**. The association between life history strategy and anxiety is mediated by trait gratitude. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

597. Bullock, A, Shepard, KC, Burns, A, Raikes, A, Alkozei, A, & **Killgore, WD**. Use of family words in trauma narratives predicts a higher risk of insomnia in individuals with PTSD. Abstract accepted for Poster presentation at the 40th Annual Conference of the Anxiety and Depression Association of America, San Antonio, TX, March 19-22, 2020.

598. **Killgore, WD**. Blue light therapy enhances sleep and fear extinction recall in PTSD. Symposium abstract accepted for presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

599. **Killgore, WD**, & Kamimori, GH. Extraversion and caffeine intake relate to suicidal ideation during sleep deprivation. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

600. **Killgore, WD**, Burns, AI, Bullock, A, Vanuk, JR, Taylor, E, & Alkozei, A. Morning blue light improves consolidation of fear extinction memory in PTSD. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

601. **Killgore, WD**, & Kamimori, GH. Effects of repeated dosing of caffeine on cognitive performance during prolonged sleep deprivation. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

602. Alkozei, A, Dailey, NS, Bajaj, S, Vanuk, JR, Raikes, AC, & **Killgore, WD**. Blue wavelength light and its effects on functional brain connectivity. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

603. Lucas, DA, Dailey, NS, & **Killgore, WD.** Implications for targeted interventions following mild traumatic brain injury: Post-concussion symptom severity predicts cognitive flexibility. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

604. Jecmen, D, King, R, Gould, J, Mitchell, J, Ralston, K, Alkozei, A, & **Killgore, WD**. The effect of blue light therapy on functional brain responses to masked fearful stimuli in post-traumatic stress disorder. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

605. King, R, Jecmen, D, Mitchell, J, Ralston, K, Gould, J, Burns, A, Bullock, A, Alkozei, A, & **Killgore, WD**. Co-morbid depressive symptoms are associated with reduced functional brain

responses within the insula and visual cortex in response to masked happy faces in individuals with PTSD. Abstract accepted for Poster presentation at the 75th Annual Meeting of the Society of Biological Psychiatry, New York, NY, April 30-May 2, 2020.

606. Dailey, NS, Raikes, AC, Alkozei, A, Grandner, MA, & **Killgore WD**. Reduced cortical thickness as a biomarker of daytime sleepiness in mild traumatic brain injury. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

607. Dailey, NS, Raikes, AC, Wager, ME, Grandner, MA, Alkozei, WD. The compounding impact of daytime sleepiness and brain injury on sustained vigilance. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

608. Anlap, I, Taylor, E, Grandner, MA, & **Killgore, WD**. Gray matter volume of the rostral medial prefrontal cortex is associated with resilience to mood decline during overnight sleep deprivation. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

609. Raikes, AC, Dailey, NS, Alkozei, A, Vanuk, JR, Grandner, MA, & **Killgore, WD**. Daytime sleepiness, depression, and post-concussive symptoms improve following prescribed morning exposure to blue light. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

610. Raikes, AD, Dailey, NS, Vanuk, JR, Alkozei, A, Grandner, MA, **Killgore, WD**. Improved daytime sleepiness following daily morning blue light therapy is associated with altered resting-state network connectivity. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

611. Satterfield, BC, Anlap, I, Esbit, S, & **Killgore, WD**. Corticotropin-releasing hormone receptor 1 gene polymorphism modulates cognitive flexibility following acute stress and total sleep deprivation. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

612. Jecmen, D, King, R, Gould, J, Mitchell, J, Ralston, K, Burns, AI, Bullock, A, Grandner, MA, Alkozei, A, & **Killgore, WD**. The effects of morning blue light therapy on insomnia severity and PTSD symptoms in a clinical sample. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

613. Taylor, E, Grandner, MA, & **Killgore, WD**. Later bedtime is associated with differences in prefrontal gray matter volume and executive function deficit. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

614. Taylor, E, & **Killgore, WD**. Meta-analysis on the effects of caffeine on neurodegenerative cognitive decline. Abstract submitted for Poster presentation at the 34th Annual SLEEP

Conference, Philadelphia, PA, June 13-17, 2020.

615. LaFollette, KJ, Satterfield, BC, Esbit, S, Lazar, M, Grandner, MA, & **Killgore, WD**. Emotion regulation during sleep deprivation and repeadted physiological stress: Implications for motor skill learning and production. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

616. King, R, Jecmen, D, Mitchell, J, Ralston, K, Gould, J, Burns, AI, Bullock, A, Grandner, MA, Alkozei, A, & **Killgore, WD**. Habitual sleep duration is negatively correlated with emotional reactivity within the rostral anterior cingulate cortex in individuals with PTSD. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

617. King, R, Jecmen, D, Alkozei, A, Raikes, A, Grandner, MA, & **Killgore, WD**. Hippocampal gray matter volume in healthy adult population is associated with habitual sleep duration. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

618. Burns, AI, Bullock, A, Taylor, E, Grandner, MA, Alkozei, A, & **Killgore, WD**. The association between sleep problems and risk-taking behavior differs between racial majority and minority groups. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

619. Burns, AI, Bullock, A, Raikes, AC, Dailey, NS, Grandner, MA, & **Killgore, WD**. Daytime sleepiness correlates with increased gray matter volume in the right middle temporal gyrus in healthy young individuals. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

620. **Killgore, WD**, Dailey, NS, Raikes, AC, Vanuk, John R, Taylor, E, Grandner, MA, & Alkozei, A. Blue light exposure enhances neural efficiency of the task positive network during a cognitive interference task. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

621. **Killgore, WD**, Dailey, NS, Raikes, AC, Vanuk, JR, Taylor, E, Grandner, MA, & Alkozei, A. Resilience to inhibitory deficits during sleep deprivation is predicted by gray matter volume in the ventromedial and ventrolateral prefrontal cortex. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

622. Bullock, A, Burns, A, Taylor, E, Grandner, MA, Miller, MM, Alkozei, A, & **Killgore, WD**. Self-referential language in trauma narratives predicts shorter sleep duration in women with PTSD. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

623. Vanuk, JR, Raikes, AC, Dailey, NS, Grandner, MA, & **Killgore, WD**. Grey matter volumetric differences are predictive of attentional lapses during sleep deprivation. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

624. Meinhausen, CE, Vanuk, JR, Grandner, MA, & **Killgore, WD**. Gray matter volume correlates of psychomotor vigilance speed during sleep deprivation. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

625. Kapoor, A, Perlis, M, Bastien, C, Williams, N, Hale, L, Branas, C, Barrett, M, **Killgore, WD**, Wills, CC, & Grandner, MA. Disassembling Associations between Insomnia and Anxiety Symptoms: Which Elements of Insomnia are Associated with Which Elements of Anxiety? Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

626. Ramsey, T, Athey, A, Auerbach, A, Turner, R, Williams, N, Jean-Louis, G, **Killgore, WD**, Wills, CC, & Grandner, MA. Sleep Duration and Symptoms Associated with Race/Ethnicity in Elite Collegiate Athletes. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

627. Piro, B, Garland, S, Jean-Pierre, P, Gonzalez, B, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Sleep Duration and Sleep Timing Associated with History of Breast, Prostate, and Skin Cancer: Data from a Nationally-Representative Sample. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

628. Bombarda, A, St-Onge, M, Seixas, A, Williams, N, Jean-Louis, G, **Killgore, WD**, Wills, CC, & Grandner, MA. Sleep Duration and Timing Associated with Eating Behaviors: Data from NHANES 2015-2016. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

629. Abdi, H, Athey, A, Auerbach, A, Turner, R, **Killgore, WD**, Wills, CC, & Grandner, MA. College Football Players Compared to Other Collegiate Athletes: Symptoms of Insufficient Sleep Duration, Insomnia, and Sleep Apnea. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

630. Holbert, C, Bastien, C, Chakravorty, S, **Killgore, WD**, Wills, CC, & Grandner, MA. Hallucinogen Use Among College and University Students: Associations with Insufficient Sleep and Insomnia. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

631. Onyeonwu, C, Nowakowski, S, Hale, L, Branas, C, Barrett, M, **Killgore, WD**. Wills, CC, & Grandner, MA. Menstrual Regularity and Bleeding Associated with Sleep Duration, Sleep Quality, and Daytime Sleepiness in a Community Sample. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

632. Ghani, S, Delgadillo, ME, **Killgore, WD**, Wills, CC, & Grandner, MA. Culturally Consistent Diet Among Individuals of Mexican Descent at the US-Mexico Border Is Associated with Sleep Duration and Quality. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

633. Mason, B, Tubbs, A, Hale, L, Branas, C, Barrett, M, **Killgore, WD**, Wills, CC, & Grandner, MA. Use of Mobile Devices at Night Associated with Mental Health in Young Adults. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

634. Gozar, A, Seixas, A, Hale, L, Branas, C, Barrett, M, **Killgore, WD**, Wills, CC, Grandner, MA. Mobile Device Use in Bed and Relationships to Work Productivity: Impact of Anxiety. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

635. Barker, M, St-Onge, M, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Dietary Macronutrients and Sleep Duration, Sleep Disturbance, and Daytime Fatigue. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

636. Phan, S, Perlis, ML, Hale, L, Branas, C, **Killgore, WD**, Wills, CC, & Grandner, MA. Reconsidering Stimulus Control: Activities in Bed Differentially Associated with Sleep-Related Outcomes. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

637. Grandner, MA, Tubbs, A, Jean-Louis, G, Seixas, A, Hale, L, Branas, C, **Killgore, WD**, & Wills, CC. Daytime Sleepiness in the Community: Implications for Sleep Health, Circadian Health, and Overall Physical Health. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

638. Begay, T, Tubbs, A, Jean-Louis, G, Hale, L, Branas, C, **Killgore, WD**, Wills, CC, & Grandner, MA. Demographic and Socioeconomic Implications of Excessive Daytime Sleepiness in the Community. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

639. Khader, WS, Tubbs, A, Fernandez, F, Chakravorty, S, Hale, L, Branas, C, Barrett, M, **Killgore, WD**, Wills, CC, & Grandner, MA. Community-Level Daytime Sleepiness and Substance Use: Implications of Sleep Time and Mental Health. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

640. Jajoo, A, Tubbs, A, Perlis, ML, Chakravorty, S, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Population-Level Suicide Ideation: Impact of Combined Roles of Sleep Duration, Sleep Disturbance, and Daytime Sleepiness. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

641. Clay, MA, Athey, A, Charest, J, Auerbach, A, Turner, R, **Killgore, WD**, Wills, CC, & Grandner, MA. Team-Based Athletes Sleep Less than Individual Athletes, But Do Not Report More Insomnia or Fatigue. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

642. Grandner, MA, Fernandez, F, Khader, S, Jean-Louis, G, Seixas, A, Williams, N, **Killgore, WD**, & Wills, CC. Decline in Habitual Sleep Duration over 10 Years and Worsening Sleep Disparities: Data From NHIS 2006-2015. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

643. Villalobos, KM, Seixas, A, Williams, N, Jean-Louis, G, **Killgore, WD**, Wills, CC, & Grandner, MA. Disparities in Sleep Timing in the US: Data from the National Health and Nutrition Examination Survey 2015-2016. Abstract submitted for Poster presentation at the 34th Annual SLEEP Conference, Philadelphia, PA, June 13-17, 2020.

AWARDED GRANTS AND CONTRACTS

Completed

2001-2003 fMRI of Unconscious Affect Processing in Adolescence.
NIH, 1R03HD41542-01
PI: **Killgore** ($79,000.)

2003-2006 The Effects of Sleep-Loss and Stimulant Countermeasures on Judgment and Decision Making.
U.S. Army Medical Research and Materiel Command (USAMRMC) Competitive Medical Research Proposal Program (CMRP); Intramural Funding,
PI: **Killgore** (Total Award: $1,345,000.)

2004-2005 Sleep/wake Schedules in 3ID Aviation Brigade Soldiers.
Defense Advanced Research Projects Agency (DARPA)
PI: **Killgore** (Total Award: $60,000.)

2005-2006 Functional Neuroimaging Studies of Neural Processing Changes with Sleep and Sleep Deprivation.
U.S. Army Medical Research and Materiel Command (USAMRMC); Intramural Funding
Task Area C (Warfighter Judgment and Decision Making) Program Funding
PI: **Killgore** (Total Award: $219,400.)

2006-2007 Establishing Normative Data Sets for a Series of Tasks to Measure the Cognitive Effects of Operationally Relevant Stressors.
U.S. Army Medical Research and Materiel Command (USAMRMC); Intramural Funding
Task Area C (Warfighter Judgment and Decision Making) Program Funding,

PI: **Killgore** (Total Award: $154,000.)

2006-2007 Military Operational Medicine Research Program (MOM-RP), Development of the Sleep History and Readiness Predictor (SHARP).
U.S. Army Medical Research and Materiel Command (USAMRMC); Intramural Funding
PI: **Killgore** (Total Award:$291,000.)

2009-2014 The Neurobiological Basis and Potential Modification of Emotional Intelligence through Affective Behavioral Training (W81XWH-09-1-0730).
U.S. Army Medical Research and Materiel Command (USAMRMC),
PI: **Killgore** (Total Award: $551,961.)
Major Goal: To identify the neurobiological basis of cognitive and emotional intelligence using functional and structural magnetic resonance imaging.

2011-2016 Effects of Bright Light Therapy on Sleep, Cognition, and Brain Function following Mild Traumatic Brain Injury (W81XWH-11-1-0056).
U.S. Army Medical Research and Materiel Command (USAMRMC),
PI: **Killgore** (Total Award: $941,924)
Major Goal: To evaluate the effectiveness of morning exposure to bright light as a treatment for improving in sleep patterns among individuals with post-concussive syndrome. Effects of improved sleep on recovery due to this treatment will be evaluated using neurocognitive testing as well as functional and structural neuroimaging.

2012-2014 Neural Mechanisms of Fear Extinction Across Anxiety Disorders
NIH NIMH
PI: Milad, M. Site Subcontract PI: **Killgore** (Subcontract Award: $505,065)
Major Goal: To examine the neurocircuitry involved in fear conditioning, extinction, and extinction recall across several major anxiety disorders.

2012-2014 Multimodal Neuroimaging to Predict Cognitive Resilience Against Sleep Loss
Defense Advance Research Projects Agency (DARPA) Young Faculty Award in Neuroscience (D12AP00241)
PI: **Killgore** (Total Award: $445,531)
Major Goal: To combine several neuroimaging techniques, including functional and structural magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy to predict individual resilience to 24 hours of sleep deprivation.

2012-2015 Internet Based Cognitive Behavioral Therapy Effects on Depressive Cognitions and Brain function (W81XWH-12-1-0109).
U.S. Army Medical Research and Materiel Command (USAMRMC),
PI: Rauch, SL; Co-PI: **Killgore** (Total Award: $1,646,045)
Major Goal: To evaluate the effectiveness of an internet-based cognitive behavioral therapy treatment program on improving depressive symptoms, coping and resilience skills, cognitive processing and functional brain activation patterns within the prefrontal cortex.

2015 Effects of Blue Light on Melatonin Levels and EEG Power Density Spectrum
Arizona Area Health Education Centers (AHEC) Program
Co-PI: Alkozei, A.; Co-PI: **Killgore** (Total Award: $4,373)

Percent Effort: 0%
Major Goal: Adjunctive intramural funding to add a melatonin collection to an ongoing study of the effects of blue wavelength light on alertness and brain function.

Current

2012-2020 A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry following Traumatic Brain Injury (W81WH-12-0386)
Congressionally Directed Medical Research Program (CDMRP), Psychological Health/Traumatic Brain Injury (PH/TBI) Research Program: Applied Neurotrauma Research Award.
PI: **Killgore** (Total Award: $2,272,098)
Percent Effort: 25%
Major Goal: To evaluate the relation between axonal damage and neurocognitive performance in patients with traumatic brain injury at multiple points over the recovery trajectory, in order to predict recovery.

2014-2019 Bright Light Therapy for Treatment of Sleep Problems following Mild TBI (W81XWH-14-1-0571).
Psychological Health and Traumatic Brain Injury Research Program (PH/TBI RP) Traumatic Brain Injury Research Award-Clinical Trial.
PI: **Killgore** (Total Award: $1,853,921)
Percent Effort: 40%
Major Goal: To verify the effectiveness of morning exposure to bright light as a treatment for improving in sleep patterns, neurocognitive performance, brain function, and brain structure among individuals with a recent mild traumatic brain injury.

2014-2020 A Non-pharmacologic Method for Enhancing Sleep in PTSD (W81XWH-14-1-0570)
Military Operational Medicine Research Program (MOMRP) Joint Program Committee 5 (JPC-5), FY13 Basic and Applied Psychological Health Award (BAPHA)
PI: **Killgore** (Total Award: $3,821,415)
Percent Effort: 35%
Major Goal: To evaluate the effectiveness of blue light exposure to modify sleep in PTSD and its effects on fear conditioning/extinction, symptom expression, and brain functioning.

2016-2020 Refinement and Validation of a Military Emotional Intelligence Training Program (JW150005)
Joint Warfighter Medical Research Program 2015
PI: **Killgore** (Total Award: $5,977,570)
Percent Effort: 45%
Major Goal: To develop and validate a new internet-based training program to enhance emotional intelligence capacities in military Service Members.

2017-2019 Emotional State and Personality: A Proof-of-Concept Model for Predicting Performance Under Stress (DM160347)
USAMRMC 2015
PI: **Killgore** (Total Award: $1,247,290)
Percent Effort: 20%
Major Goal: To develop a statistical model to predict effective cognitive performance under stress using personality and state emotion metrics.

2018-2020 Understanding the Mechanisms of Blue Light Exposure on Cognitive Performance
USAMRDC
PI: Alkozei **Co-I: Killgore** (Total Award: $306,903)
Percent Effort: 4%
Major Goal: To identify the subcortical systems responsible for acute cognitive improvement associated with blue light exposure in the scanner.

2019-2022 Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep
USAMRDC
PI: **Killgore** (Total Award: $TBD)
Percent Effort: 5%
Major Goal: Determine whether continuous theta burst stimulation of the default mode network can improve sleep among individuals with insomnia.