AWARD NUMBER: W81XWH-12-1-0386

TITLE: A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry Following Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Dr. William D. “Scott” Killgore

CONTRACTING ORGANIZATION: University of Arizona, Tucson, AZ

REPORT DATE: February 2021

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

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
February 2021	Final Report	15 SEP 2012 – 14 OCT 2020

4. TITLE AND SUBTITLE

A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry Following Traumatic Brain Injury

5a. CONTRACT NUMBER
W81XWH-12-1-0386

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Dr. William D. S. Killgore
E-Mail: killgore@psychiatry.arizona.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Arizona
888 N. Euclid Ave.
Tucson, AZ 85719-4824

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

Mild traumatic brain injury (mTBI) is one of the major health problems facing military servicemembers returning from deployments. White matter axonal damage, as measured by neuroimaging techniques like Diffusion Weighted Imaging (DWI), is one of the hypothesized mechanisms contributing to the cognitive and affective sequalae of mTBI. Presently, many of the findings in the literature examining the association between DWI and neuropsychological outcome are contradictory, possibly due to differences in stage of recovery at the time of assessment. This study addresses this problem by collecting measures of white matter integrity and concomitant neuropsychological status at five time points in the first year following an mTBI. The findings suggest that neurocognitive status is significantly worse at 2 weeks post-injury and improves thereafter. However, neurocognitive status was effective at determining time-since-injury status. Additionally, among the neuroimaging metrics used, resting state connectivity demonstrated better discrimination of injured from healthy individuals than structural measures based on DWI or cortical volumetrics. Results from neuroimaging and neurocognitive testing suggest that time since injury is an important factor to consider when assessing structural and functional outcomes following mild traumatic brain injury.

15. SUBJECT TERMS

TBI, traumatic brain injury, concussion, DWI, Diffusion Weighted Imaging, white matter, brain imaging, neuropsychological performance, neurocognitive performance, structural connectivity

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	600	19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified			(520) 621-0605

Table of Contents

1. INTRODUCTION 4

2. KEYWORDS 5

3. ACCOMPLISHMENTS 5

4. IMPACT 173

5. CHANGES/PROBLEMS 174

6. PRODUCTS 177

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS 182

8. SPECIAL REPORTING REQUIREMENTS 189

1. INTRODUCTION

Since the year 2000, military personnel have sustained over 413,000 traumatic brain injuries (TBIs) (DVBIC Report, November 8, 2019). Of these injuries, the vast majority, exceeding 82% of all TBIs, are in the mild category. In addition to the impact on military readiness, mild traumatic brain injury (mTBI) represents a major health concern and economic burden in the United States (Humphreys, Wood, Phillips, & Macey, 2013). While most individuals who sustain an mTBI will recover fully within a matter of days (McCrea et al., 2003), a significant proportion of individuals with mild TBI will experience a prolonged recovery with persistent post-concussive symptoms, and it is yet unclear why some individuals will show a good injury outcome, whereas other will not (Bogdanova & Verfaellie, 2012; Lange et al., 2012; Lange, Brickell, Ivins, Vanderploeg, & French, 2013; Leong, Mazlan, Abd Rahim, & Ganesan, 2013). Structural damage to white matter axonal tracts has been suggested to underlie many of these persistent behavioral changes (Arenth, Russell, Scanlon, Kessler, & Ricker, 2013; Jorge et al., 2012; Morey et al., 2012; Spitz, Maller, O'Sullivan, & Ponsford, 2013; Yeh et al., 2013). Yet due to differences in brain imaging methods, neuropsychological testing approaches, and sample characteristics, this has not been consistently demonstrated at different recovery stages. Furthermore, the relationship between structural connectivity, functional connectivity and neuropsychological performance remains unclear.

The present study aims to systematically assess structural connectivity, functional connectivity and neuropsychological functioning at five recovery stages (i.e., two weeks, one month, three months, six months and 12 months) following mild TBI relative to healthy controls. We hypothesize that structural white matter tract disintegrity will underlie abnormalities in functional connectivity, neurocognitive performance and post-concussion symptom severity, but that these metrics will vary with time since injury. The primary aim of the proposed study is therefore to investigate whether measures of white matter disintegrity following mild TBI would explain abnormalities in functional connectivity of the brain, cognition and emotional disturbance, and whether white matter integrity (or lack thereof) could serve as a reliable biomarker of mild TBI. This will allow conclusions on the utility of measures of white matter integrity in the diagnosis of mild TBI. As the study incorporates five time points of measurement to represent different recovery stages of mild TBI, this will allow conclusions on the natural recovery course of mild TBI and the utility of white matter integrity measures in the prediction of injury outcome.



Figure 1. The goal of the study was to enroll 180 participants. This included 150 participants with mild traumatic brain injury (mTBI), and 30 healthy controls (HC). The cross-sectional study included 5 mTBI groups, of 30 subjects each, enrolled based on time since injury (2 weeks, 2W; 1 month,1M; 3 months, 3M; 6 months, 6M; 12 months, 12M).

2. KEYWORDS

TBI, traumatic brain injury, mTBI, mild traumatic brain injury, concussion, DWI, Diffusion Weighted Imaging, white matter, brain imaging, neuropsychological performance, neurocognitive performance, structural connectivity, brain injury, head injury

3. ACCOMPLISHMENTS

a. **What were the major goals and objectives of the project?**

i. **Major Task 1: Study Preparation, Staff Hiring, and Materials Acquisition – Completed**

- *Milestone Achieved:* Research staff hired and trained (as needed)
- *Milestone Achieved:* All materials and tasks ready for data collection – 16 JULY 2014

ii. **Major Task 2: Human Subjects Approval – Completed**

- *Milestone achieved:* Local IRB approval at University of Arizona – 16 JULY 2014
- *Milestone achieved:* HRPO and local UA IRB approval for all protocols – 16 JULY 2014

iii. **Major Task 3: Advertisement and Subject Recruitment – Complete**

- *Milestone Achieved*: All subjects recruited – 9 JAN 2020

iv. **Major Task 4: Data Collection – Complete**

- *Milestone Achieved:* Data collected – 9 JAN 2020

v. **Major Task 5: Quality Control Checks – Complete**

- *Milestone Achieved:* Data reliability verified for analysis – 23 APR 2020

vi. **Major Task 6: Preliminary Analysis – Complete**

- *Milestone Achieved:* Data analysis procedures created and validated (as needed).

vii. **Major Task 7: Extensive Data Analysis – Complete**

- *Milestone Achieved:* Data analyzed – 01 OCT 2020

viii. **Major Task 8: Manuscript Preparation and Submission for Publication – Complete**

- *Milestone Achieved:* Study complete and final report submitted – 11 FEB 2021

b. **What was accomplished under these goals?**

i. **Major Activities:**

Recruitment

Figure 2 summarizes the recruitment process for participants included in the study. Cumulatively, 1,950 individuals completed a telephone screen or online interest form to indicate their interest in the study. Of these, 433 individuals were eligible to participate and 1,517 were deemed ineligible to participate. Of the 433 eligible participants, 219 were enrolled to participant and 190 successfully completed the study. In total 29 participants were deemed ineligible after enrollment. The remaining 214 individuals either did not show up for scheduled study visits (i.e., not enrolled) or did not return our phone calls (i.e., lost to follow-up).

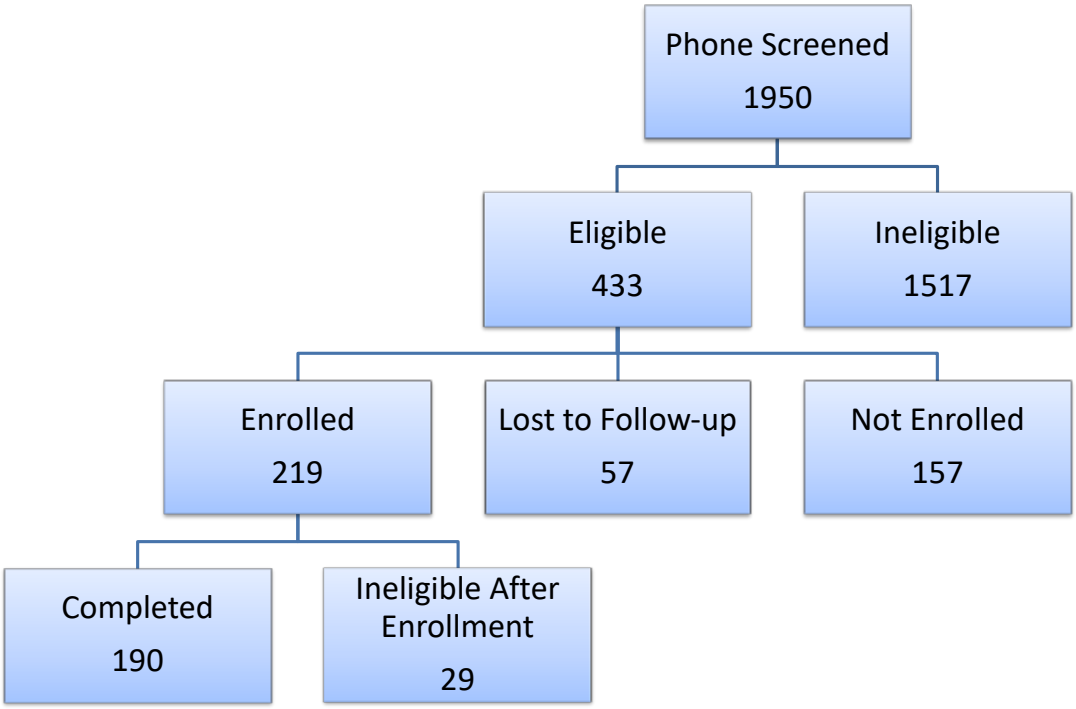


Figure 2. Consort diagram of the present study. The final sample size included 190 completed participants

Although 219 individuals were initially enrolled, 29 were subsequently excluded from study participation due to exclusion criteria. The reasons participants were deemed ineligible following enrollment are summarized in Figure 3. Three exclusion criteria accounted for ~60% of all participants deemed ineligible after enrollment. Despite diligent phone screening, individuals were removed from the study who later indicated non-removable metal in the body (28.6%), depression prior to head injury (21.4%), and past suicide attempts (10.7%).

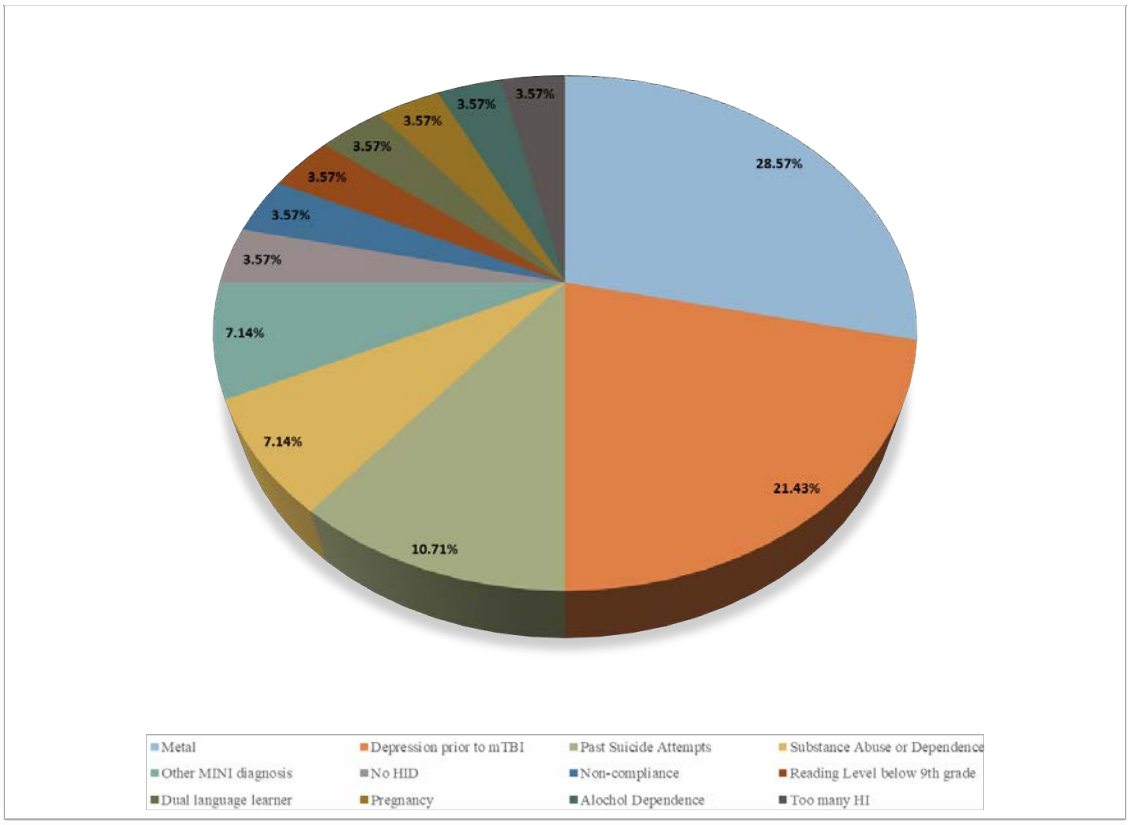


Figure 3. Percentage of individuals meeting exclusion criteria after enrollment.

Data Collection

- The final sample included N = 190 participants, 39 healthy controls (HC) and 151 participants with a documented mild traumatic brain injury (MTBI).

Data Management

- Study staff utilized REDCap, a HIPAA compliant digital storage database to compile the final dataset for the study.

Statistical Analysis

- *Behavioral data*: neuropsychological assessments and self-report questionnaires resulted in over 1,400 variables of interest. These data were imported to IBM SPSS v. 26 for statistical analysis.
- *Neuroimaging data:* Multimodal imaging data included high-resolution anatomical (T1w), diffusion tensor imaging (DTI), and resting state functional connectivity (FC). Imaging data were analyzed using SPM, CONN, FSL, and DSI Studio.

ii. **Specific Objectives:**

- The stated objective of this proposal was to assess the associations between structural connectivity, functional connectivity, and neuropsychological functioning at two weeks (2W), one month (1M), three months (3M), six months (6M), and 12 months (12M) post-injury relative to HCs.
- This objective was accomplished, as described in detail in the following section, Significant Results/Key Outcomes.

iii. **Significant Results/Key Outcomes:**

3.A. Overview

As shown above in Figure 1, the cross-sectional study design included 30 healthy controls and five separate samples of 30 participants at various time points post-injury, ranging from 2 weeks to 1 year (2W, 1M, 3M, 6M, 12M). Participants attended a single visit at the University of Arizona (or McLean Hospital during the first year of the project) comprised of a neuroimaging session and comprehensive neuropsychological assessment battery. The neuroimaging session included the collection of a high-resolution structural scan, diffusion tensor imaging (DTI), and resting state functional connectivity (FC). During the neuropsychological assessment, participants completed tests that measured attention, speed of information processing, learning and memory, and executive function. The following three aims were included in the initial grant proposal.

> **Specific Aim 1**: The proposed study will evaluate DTI metrics across multiple stages of recovery in mild TBI relative to healthy controls.
>
> **Specific Aim 2**: The proposed study will examine the relationship between DTI metrics and neurocognitive performance across multiple stages of recovery in mild TBI and relative the healthy controls.
>
> **Specific Aim 3**: The proposed study will examine resting state FC in the Default Mode Network (DMN) and Task Positive Network (TPN), and its concordance with DTI metrics, across multiple stages of recovery in mild TBI and relative to healthy controls.

In the following sections, we will present summary data regarding differences in structural and functional connectivity across the various stages of recovery, as well as associated differences in neurocognitive performance and symptom expression. We will first present the primary outcome and study data related to our Specific Aims and hypotheses. Then, in a subsequent section, we will present supplementary analyses of interest based on outcome measures collected. During the study visit, we collected the following primary measures:

Neuroimaging on 3T scanner

- High resolution structural (MPRAGE)
- Diffusion Tensor Imaging (DTI)
- Resting State Function Connectivity (FC)

Measures of Attention

- Psychomotor Vigilance Test (PVT)

Measures of Information Processing Speed

- Go/No Go (GNG)
- Automated Neuropsychological Assessment Metrics (ANAM)

Measures of Learning and Memory

- California Verbal Learning Test (CVLT)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Brief Visuospatial Memory Test – Revised (BVMT-R)

Measures of Executive Function

- Delis-Kaplan Executive Function System (D-KEFS)

The study was initially proposed to be completed over a four-year period. However, during the second year of the study, the PI (Dr. Killgore) changed primary institutions. Specifically, Dr. Killgore moved his laboratory and research operations from McLean Hospital/Harvard Medical School to the Department of Psychiatry, College of Medicine at the University of Arizona. Requests were made to USAMRMC on 24 MAR 2014 to permit the transfer of the project to the new institution. The laboratory was successfully relocated to the University of Arizona on 1 JUL 2014. However, the transfer of funding to the University of Arizona was not completed until 15 APR 2015. Consequently, research operations on this project were suspended between 21 MAY 2014 and 15 APR 2015. Upon approval, the project was re-initiated at the University of Arizona on 15 APR 2015 at that time. A NCE for 12 months was submitted 1 JAN 2019 and approved, extending the project to 14 APR 2020. With the disruption from COVID-19, a final NCE for 6 months was requested 15 JUNE 2020 and approved, with a final project completion date of 14 OCT 2020.

3.B. Sample Characteristics

Data collection for the project is complete. A total of N = 219 participants enrolled in the study. Of those enrolled, 29 were excluded, resulting in a final sample of N = 190. Of those included in the final sample, n = 29 were collected while laboratory was located at McLean, while the remaining n = 161 were collected after the laboratory relocated to the University of Arizona. Inclusion criteria for all individuals included the following: (1) age 18-45 years of age, (2) English as the primary language and (3) the ability to provide written informed consent. Individuals reported a mild TBI were also required to provide head injury documentation. Individuals were excluded from the study for the following reasons: (1) contraindicators to MRI including non-removable metal in the body and claustrophobia, (2) history of neurological conditions, (3) less than 9^{th} grade education, or (4) pregnancy as assessed by urine β-HCG. Additionally, healthy control individuals were excluded for reporting a history of brain injury or a history of psychological disorder, individuals with mild TBI were excluded for a history of psychological disorder prior to the injury. Enrolled participants were assigned to one of six groups depending on brain injury status and time since injury. Although the initial study design was to enroll equal number participants per group, enrollment of individuals in the acute phase

(i.e., 2W post-injury) proved challenging. To address this challenge and reach our proposed goal of enrolling a total of 150 individuals with mild TBI, we increased enrollment numbers in sub-acute and chronic groups. Therefore, the final enrollment numbers by group include a healthy control group (**HC**, n = 39), and five mild TBI groups based on time post-injury include 2-weeks (**2W**, n=12), 1-month (**1M**, n = 30), 3-months (**3M**, n = 34), 6-months (**6M**, n = 33), and 12-months (**12M**, n = 42) post-injury.

Basic demographic characteristics for the groups are reported in Table 1. The ratio of males to females between the six groups did not differ significantly ($\chi^2 = 2.50$, $p = .78$). The majority of participants enrolled in the study were right-handed, although 7 participants reported being left-handed (HC, n = 2; 2W, n = 1; 1M, n = 1; 3M, n = 2; 6M, n = 1) and 2 participants reported being ambidextrous (1M, n = 1; 3M, n = 1). The ratio of handedness in the groups did not differ significantly ($\chi^2 = 7.27$, $p = 0.70$). In addition, groups did not differ significantly on basic demographic variables including age ($F(5, 184) = 1.03$, $p = .40$, partial $\eta^2 = .03$), years of education ($F(5, 183) = 2.18$, $p = .06$, $\eta^2 = .06$), body mass index (BMI) ($F(5, 184) = 0.96$, $p = .40$, $\eta^2 = .03$) or full scale IQ as measured by the Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-II) ($F(5, 184) = 0.81$, $p = .55$, $\eta^2 = .02$).

Table 1. Demographic characteristics

	HC n = 39	**2W n = 12**	**1M n = 30**	**3M n = 34**	**6M n = 33**	**12M n = 42**
Age	24.33 ± 5.69	25.58 ± 7.81	25.90± 8.60	25.62 ± 7.41	22.85 ± 4.91	23.64 ± 6.75
Sex (% F)	61.54	50.00	63.33	58.82	72.73	61.90
Hand (%R)	94.87	91.67	93.33	91.18	96.97	100.00
Education	14.77 ± 2.36	14.50 ± 2.75	14.27 ± 1.82	14.24 ± 1.97	13.91 ± 1.77[a]	13.43 ± 1.31
BMI	24.83 ± 5.14	27.48 ± 8.17	25.14 ± 4.58	24.18 ± 4.28	25.93 ± 7.22	24.44 ± 4.20
IQ	111.23 ± 9.25	109.92 ± 19.70	108.83 ± 11.38	107.24 ± 10.54	108.76 ± 12.63	106.36 ± 11.91
[a] = one missing value.						

In addition to demographic information, all participants completed psychological questionnaires to assess depression, anxiety, resilience, pleasure, and life satisfaction. Summary statistics for psychological characteristics are presented in Table 2.

Depression, as measured by the 21-item Beck Depression Inventory (BDI-II), was significantly different between the group ($F(5, 182) = 7.13$, $p < .001$, $\eta^2 = .16$). Specifically, those in the healthy control group exhibited significantly lower depression scores compared to all mTBI groups (2W, $p < .001$; 1M, $p = .002$; 3M, $p < .001$; 6M, $p = .03$; 12M, p = .008; Bonferroni corrected). Snaith Hamilton Pleasure Scale (SHAPS) is a 14-item scale used to measure anhedonia, the inability to experience pleasure, where scores of 2 or less are defined as normal. Groups differed significantly on the SHAPS ($F(5, 183) = 4.01$, $p = .002$, $\eta^2 = .10$), with participants in the 2W group scoring higher than HCs ($p = .001$), 3M ($p = .04$), 6M ($p = .002$), and 12M groups ($p = .009$) (Bonferroni corrected for multiple comparisons). Furthermore, the 2W MTBI group was the only group to score, on average, in the abnormal rage, indicating an inability to experience pleasure within their life.

No significant between-group differences were found for the following psychological assessments: State Trait Anxiety Inventory (STAI) ($F(5,182) = 2.10$, $p = .07$, $\eta^2 = .05$), Connor-Davidson Resilience Scale (CD-RISC) ($F(5, 183) = 2.03$, $p = .08$, $\eta^2 = .05$), or Satisfaction With Life Scale (SWLS) ($F(5, 184) = 1.17$, $p = .33$, $\eta^2 = .03$).

Table 2. Psychological characteristics

	HC n = 39	**2W n = 12**	**1M n = 30**	**3M n = 34**	**6M n = 33**	**12M n = 42**	**p-value**
BDI-II	1.79 ± 2.68	12.42 ± 8.67	8.43 ± 7.1	9.88 ± 8.83	7.13 ± 8.21[b]	7.29 ± 6.59	***<.001***
STAI	57.74 ± 11.05[a]	70.42 ± 19.02	67.03 ± 12.5[a]	65.74 ± 19.1	66.33 ± 17.6	64.43 ± 14.48	.07
CD-RISC	80.44 ± 10.77	72.75 ± 10.26	73.40 ± 11.31	75.56 ±11.67	76.73 ± 9.91	78.63 ± 11.79[a]	.08
SHAPS	0.44 ± 0.85	2.50 ± 2.11	1.00 ± 1.74	0.97 ± 1.82	0.53 ± 1.55[a]	0.81 ± 1.13	***.002***
SWLS	28.13 ± 5.31	24.17 ± 7.76	25.77 ± 5.87	25.91 ± 6.76	26.91 ± 5.60	27.00 ± 5.69	.33
[a] = one missing value. [b] = two missing values.							

Participants included in the mild TBI groups provided written head injury documentation from a physician or third-party witness. Based on documentation submitted prior to study enrollment, these individuals met Defense and Veterans Brain injury Center (DVBIC) and VA/DoD Clinical Practice Guidelines injury criteria for a mild TBI (i.e. Glasgow Coma Scale = 13-15; alteration of consciousness ≤ 24 hrs.; loss of consciousness 0-30 min.; post-traumatic amnesia ≤ 24 hrs.; standard structural imaging = negative). Group assignment was based on the number of days since the most recent, documented mild TBI. On average, groups were similar on the total number of TBIs sustained ($F(4, 146) = 0.42$, $p = .79$, $\eta^2 = .01$), as reported on the Ohio State University TBI Identification Method Short Form.

With regard to symptom severity, the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) was administered to rate degree to which 16 symptoms were more of a problem compared to before the injury. In accordance with scoring by Eyres and colleagues (Eyres, Carey, Gilworth, Neumann, & Tennant, 2016), we analyzed the initial 3 and remaining 13 items, separately. Mild TBI groups differed significantly on the presentation of early symptoms (RPQ-3; $F(4, 146) = 5.13$, $p = .001$, $\eta^2 = .12$). Post-hoc analyses revealed that individuals in the acute phase of injury (2W) experienced significantly higher early symptoms compared to individuals in sub-acute and chronic phases of recovery (3M, $p = .006$; 6M, $p = .001$; and 12M, $p = .03$; Bonferroni corrected). In contrast, there was no significant difference between the groups on late symptoms (RPQ-13; $F(4, 144) = 1.44$, $p = .22$, $\eta^2 = .04$).

In addition to differentiating between early and late symptom presentation, the RPQ can be analyzed for somatic, cognitive, and emotional symptom presentation (Potter, Leigh, Wade, & Fleminger, 2006). Significant between-group differences were found on the RPQ-Somatic subscale ($F(4, 144) = 3.54$, $p = .009$, $\eta^2 = .09$), which included fatigue, headache, dizziness, nausea, noise, sleep, blurred vision and light sensitivity. More specifically, individuals at 2W exhibited significantly higher somatic symptoms compared to individuals at 3M ($p = .03$) and 6M ($p = .02$) post-injury. No significant differences were found for cognitive ($F(4, 146) = 1.50$, $p = .21$, $\eta^2 = .04$) or emotional ($F(4, 146) = 0.87$, $p = .48$, $\eta^2 = .02$) symptom subscales.

Table 3. Injury characteristics

	2W n = 12	1M n = 30	3M n = 34	6M n = 33	12M n = 42	p-value
Days since injury	14.67 ± 1.83	29.87 ± 3.42	92. 74 ± 8.25	183.61 ± 16.64	364.60 ± 4.37	N/A
Total TBIs	2.67 ± 1.72	2.60 ± 1.71	2.21 ± 1.25	2.39 ± 1.44	2.52 ± 1.35	.79
RPQ-3	4.83 ± 3.61	3.00 ± 2.57	1.91 ± 1.94	1.36 ± 1.98	2.36 ± 2.73	***.001***
RPQ-13	13.67 ± 10.87	10.87 ± 10.08	7.82 ± 9.01[a]	7.22 9.60[a]	8.45 ± 9.16	.22
PRQ-Cognitive	4.58 ± 4.89	4.10 ± 3.93	2.76 ± 3.64	2.52 ± 3.50	2.64 ± 3.20	.21
PRQ-Somatic	10.92 ± 7.96	7.63 ± 6.38	4.61 ± 4.74 [a]	4.34 ± 5.29 [a]	6.83 ± 7.00	***.009***
PRQ-Emotional	3.00 ± 3.10	2.13 ± 3.04	2.24 ± 3.53	1.88 ± 3.29	1.33 ± 2.53	.48
[a] = one missing value.						

Changes in sleep quality and duration have been reported following mild TBI and were therefore, assessed in the present cross-sectional study. We administered the Pittsburg Sleep Quality Index (PSQI), a standardized measure of sleep quality, the Epworth Sleepiness Scale (ESS), the most widely used scale of excessive daytime sleepiness, and the Automated Neuropsychological Assessment Metrics TBI (ANAM4 TBI) Sleepiness Scale, a measure of fatigue. Summary statistics for sleep characteristics are included in Table 4.

Based on the PSQI, we found significant between-group differences in overall sleep quality (PSQI Total; $F(5, 179) = 6.84$, $p < .001$, $\eta^2 = .16$). Individuals 2W ($p = .04$), 1M ($p = .04$), 3M ($p = .009$), and 12M ($p < .001$) post-injury reported significantly worse sleep quality compared to HCs. The 6M mild TBI group was the only group that did not differ significantly from healthy controls ($p = .09$). It is important, however, to note that all mild TBI groups, including the 6M group, had PSQI Total scores greater than 5, indicating poor sleep quality.

On the ESS, we found significant differences between the groups ($F(5, 181) = 5.86$, $p < .001$, $\eta^2 = .14$). Post-hoc analyses were calculated and indicated that 1M ($p = .002$), 3M ($p < .001$), 6M ($p = .001$) and 12M ($p < .001$) post-injury exhibited significantly higher levels of daytime sleepiness when compared to HC (Bonferroni corrected for multiple comparisons). This suggests that nearly all individuals who have experience a mild TBI report suffering from daytime sleepiness, above and beyond that which is typically experienced by healthy adults. Interestingly, MTBI participants in the acute phase of recovery (2W) did not report significantly greater daytime sleepiness compared to HC ($p = .36$). One interpretation of this finding is that daytime sleepiness is a symptom that arises at least a month after the injury and is a more persistent symptom, present in sub-acute and chronic recovery stages. It is also possible that small sample size (n=12) and large within-sample variance made it difficult accurately quantify daytime sleepiness in the acute MTBI recovery stage.

The Sleepiness Scale is a 7-item measure of fatigue, ranging from 1 (feeling very alert, wide awake, and energetic) to 7 (very sleepy and cannot stay awake much longer). Participants were instructed to select the number of the statement that best described how they were felling at that moment. Groups differed significantly on the Sleepiness Scale ($F(5, 179) = 5.06$, $p < .001$, η^2

= .12). Post-hoc analyses (Bonferroni-corrected for multiple comparisons) indicated high levels of fatigue among individuals with a mild TBI. Specifically, participants 2W (p = .003), 1M (p = .004) and 6M (p = .003) post-injury were significantly more fatigued, compared to health controls. The Sleepiness Scale was administered halfway through the 8-hour study visit, at roughly 1:00 pm. These finding suggest a majority of individuals with a history of mild TBI experience fatigue, especially during a cognitively taxing day, which may have significant implications in academic and vocational settings.

Table 4. Sleep characteristics

	HC n = 39	**2W n = 12**	**1M n = 30**	**3M n = 34**	**6M n = 33**	**12M n = 42**	**p-value**
ESS	5.05 ± 3.29[a]	7.75 ± 4.18	8.43 ± 3.88	8.70 ± 3.86[a]	8.59 ± 4.23[a]	8.64 ± 2.52	***<.001***
PSQI Total	3.82 ± 2.25	7.00 ± 3.49	6.14 ± 2.91[a]	6.38 ± 2.70	5.90 ± 2.94[b]	7.80 ± 4.16[b]	***<.001***
Sleepiness Scale	1.76 ± .76[b]	3.17 ± 1.34	2.79 ± 1.29[a]	2.27 ± .76[a]	2.78 ± 1.50[a]	2.43 ± 1.12	***<.001***
[a] = one missing value [b] = two missing values							

3.C. Neuroimaging Data

Multimodal neuroimaging data were collected to examine structural integrity and functional connectivity in the brain at various stages of TBI recovery, as well as to explore the relationship between neurological measures and neuropsychological performance. This report will provide findings from diffusion tensor imaging (DTI), resting state functional connectivity (FC), and voxel-based morphometry (VBM).

Data Collection: Neuroimaging data were collected using a 3T Siemens MAGNETOM Skyra using a 32-channel head coil. Head movement was restricted using foam cushions during all image acquisition. We collected a high-resolution anatomical T1-weighted (T1w) MPRAGE (TR/TE/flip angle = 2100 msec., 2.33 msec., 12°) that consisted of 176 slices (256 x 256 matrix) with a slice thickness of 1mm and voxel size of 1mm x 1mm x 1mm. Diffusion data were acquired along 72 directions with a b-value of 1000 s/mm^2 and the following parameters: voxel size = 2mm x 2mm x 2mm, TR = 9600 msec., TE = 88 msec., and 74 slices with a slice thickness = 2mm. Functional images were acquired using a gradient echo T2*-weighted sequence (TR/TE/flip angle = 2000 msec., 25 msec., 90°). Resting state functional images were collected with 32 slices and a voxel size of 2.5mm x 2.5mm x 2.5mm, in an interleaved excitation order, with anterior-posterior phase encoding. During the collection of the resting state functional data, participants were instructed to remain awake, but keep their eyes closed and let their "mind wander".

Image Processing: Neuroimaging data were processed using standard preprocessing pipelines. DTI data were preprocessed using QSIPrep 0.12.2, which is based on Nipype 1.5.1. A detailed description QSIPrep pipeline can be found at https://qsiprep.readthedocs.io/en/latest.html. rsFC data were preprocessed using fMRIPrep 20.2.1. For a detailed description of the preprocessing pipeline used on the functional data, see https://fmriprep.org/en/stable/workflows.html.

C.I. Diffusion Tensor Imaging (DIT)

Anatomical data preprocessing

The T1w image was corrected for intensity non-uniformity using N4BiasFieldCorrection (Tustison et al. 2010,), and subsequently used as the T1w-reference. The T1w-reference was then skull-stripped using antsBrainExtraction.sh (ANTs 2.3.1). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al. 2009) was performed through nonlinear registration with antsRegistration (Avants et al. 2008), 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 6.0.3; Zhang, Brady, and Smith 2001).

Diffusion data preprocessing

Several confounding time-series were calculated based on the preprocessed DWI: framewise displacement (FD) using the implementation in Nipype. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. Slice-wise cross correlation was also calculated. The DWI time-series were resampled to AC-PC orientation, generating a preprocessed DWI run in AC-PC space. The FMRIB Diffusion Toolbox was used for brain extraction (Smith, 2002), and fitting of the diffusion tensor model (DTIFIT), which calculates fractional anisotropy (FA) and mean diffusivity (MD) and provides outputs for the calculation of axial diffusivity (AD = λ_1) and radial diffusivity (RD = $[\lambda_2 + \lambda_3]/2$).

Tract Based Spatial Statistics (TBSS)

Voxel-wise statistical analysis of FA data was carried out using TBSS (Tract-Based Spatial Statistics, [Smith 2006]), part of FSL [Smith 2004]. First, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET [Smith 2002]. A study specific T1 template was created from preprocessed T1w images using antsMultivariateTemplateConstruction2.sh, which produced warps from the T1w image to the study T1 template for each subject. All subjects' FA data were then aligned to a study specific template using the nonlinear registration tool FNIRT [Andersson 2007a, 2007b], which uses a b-spline representation of the registration warp field [Rueckert 1999]. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the center of all tracts. Each subject's aligned FA data was then projected onto the skeletonized image and resulting data fed into voxel-wise cross-subject statistics, for whole-brain analyses.

To conduct ROI-based analyses, binary template masks were created 13 white matter pathways outlined in the initial grant proposal. Targeted pathways included the bilateral cingulum bundle (CING L, CING R), bilateral internal capsule (anterior: aIC L, aIC R; posterior pIC L, pIC R), bilateral external capsule (EC L, EC R), bilateral anterior corona radiata (aCR L, aCR R), bilateral superior longitudinal fasciculus (SLF L, SLF R), and the corpus callosum (CC). Template masks were based on the JHU ICBM-DTI 81 white-matter atlas in MNI space. FA images were registered to standard FMRIB58_FA_1mm space with FSL FLIRT for affine transformation, FSL FNIRT for non-linear registration, and applywarp to apply transformation

warps to map FA images to FMRIB58_FA_1mm. MD, RD, and AD images were transferred to standard space by apply the same transformation warps. Voxels that overlapped a given white matter mask were included in subsequent analyses for that tract. Mean values for each tract were obtained by averaging all values from voxels extracted from the white matter mask. By extracting values from the warped FA data and targeting specific tracts of interest a-priori, the ROI approach eliminates superfluous comparisons and provides higher detection power of white matter differences between the groups of interest. The same process was applied to the other DTI metric images including MD, RD, and AD.

Table 5. Targeted white matter pathways

JHU ICBM Name	X	Y	Z	Label
Cingulum (cingulate gyrus) L	-7	-16	36	CING.L
Cingulum (cingulate gyrus) R	7	6	33	CING.R
Corpus callosum	-5	-26	25	CC
Anterior limb of internal capsule L	-14	3	7	aIC.L
Anterior limb of internal capsule R	15	3	7	aIC.R
Posterior limb of internal capsule L	-23	-18	13	pIC.L
Posterior limb of internal capsule R	24	-18	13	pIC.R
External capsule L	-31	5	-8	EC.L
External capsule R	32	5	-8	EC.R
Anterior corona radiata L	-20	37	1	aCR.L
Anterior corona radiata R	21	37	1	aCR.R
Superior longitudinal fasciculus L	-36	-23	30	SLF.L
Superior longitudinal fasciculus R	37	-23	30	SLF.R

C.II Resting State Functional Connectivity (FC)

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008), and used as the T1w-reference. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh (ANTs). Brain tissue segmentation of cerebrospinal fluid, white-matter, and gray-matter was performed on the brain-extracted T1w image using fast (FSL 5.0.9; Zhang, Brady, and Smith 2001). Next, brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1; Dale, Fischl, and Sereno 1999). Finally, volume-based spatial normalization to standard, MNI space was performed through nonlinear registration with antsRegistration, using brain-extracted versions of both T1w-reference and the T1w template.

Functional data preprocessing

For the resting state BOLD run, the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. The BOLD reference was co-registered to the T1w-reference image using bbregister (FreeSurfer). Head-motion parameters (transformation matrices, and six corresponding rotation and translation parameters) were estimated before spatiotemporal filtering using mcflirt (FSL 5.0.9; Jenkinson et al. 2002). The BOLD run was then slice-time corrected and resampled into standard, MNI space (MNI152NLin2009cAsym, MNI152NLin6Asym). Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al. 2015) was

performed on the preprocessed BOLD in MNI space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Several confounding time-series were calculated including, framewise displacement, DVARS, and three region-wise global signals. 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 et al. 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99. The head-motion estimates calculated in the correction step were also placed in the corresponding confounds file. Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers.

Functional connectivity: CONN

Post-processing and functional connectivity estimations from the preprocessed BOLD time series was accomplished for each subject using CONN (v.20.b.; https://web.conn-toolbox.org). The default denoising pipeline in CONN was implemented, which combines linear regression of potential confounding effects in the BOLD signal, and temporal band-pass filtering. Confound regressors from fMRIPrep were entered including 1) noise components from WM and CSF, 2) estimated subject motion parameters, and 3) outlier scans. Temporal band-pass filtering was implemented using a discrete cosine transformation windowing operation to remove frequencies below 0.01 Hz or above 0.1 Hz from the BOLD signal. Following denoising, individual subject seed-to-voxel whole-brain connectivity maps were calculated with the mean time series from each seed used as a predictor in a general linear model (GLM). The resulting individual bivariate correlation coefficients were Fisher transformed into z-scores for subsequent second-level analysis.

Prior studies suggest mild TBI is associated with decreased functional connectivity in the Default Mode Network (DMN), but hyperconnectivity between regions associated with the Task Positive Network (TPN), relative to healthy controls (Johnson et al., 2012; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011). Therefore, a seed-driven analyses were conducted in CONN using 7 seed regions. Regions of interest (ROIs) included the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), left and right lateral parietal cortices (LP L, LP R), anterior cingulate cortex (ACC), and left and right lateral prefrontal cortices (LPFC L, LPFC R). Seed regions used in connectivity analyses are outlined in Figure 4.

Seed Region	X	Y	Z	Label
Medial prefrontal cortex	1	55	-3	mPFC
Lateral parietal cortex (L)	-39	-77	33	LP.L
Lateral parietal cortex (R)	47	-67	29	LP.R
Posterior cingulate cortex	1	-61	38	PCC
Anterior cingulate cortex	0	22	35	ACC
Lateral prefrontal cortex (L)	-43	33	28	LPFC.L
Lateral prefrontal cortex (R)	41	38	30	LPFC.R

Note: Seed locations based on Montreal neurological institute (MNI) coordinates. L, left; R, right.

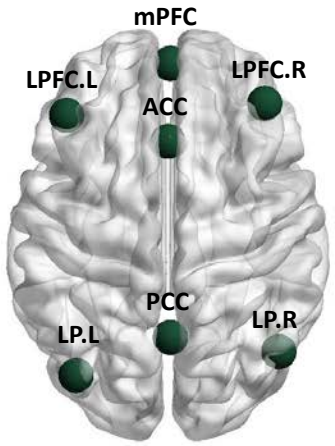


Figure 4. Seed regions used in structural and functional connectivity analyses covered regions of the default mode network (DMN) and task positive network (TPN).

Tractography (DSI Studio)

A total of 145 diffusion MRI scans were included in the connectometry database. A DTI diffusion scheme was used, and a total of 72 diffusion sampling directions were acquired. The b-value was 1000 s/mm2. The in-plane resolution was 1 mm. The slice thickness was 1 mm. The b-table was checked by an automatic quality control routine to ensure its accuracy (Schilling et al. MRI, 2019). The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction (Yeh et al., Neuroimage, 58(1):91-9, 2011) to obtain the spin distribution function (Yeh et al., IEEE TMI, ;29(9):1626-35, 2010). A diffusion sampling length ratio of 1.25 was used. The output resolution of is 1 mm isotropic. The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., MRM, 77:603–612 (2017)). The quantitative anisotropy was extracted as the local connectome fingerprint (LCF, Yeh et al. PLoS Comput Biol 12(11): e1005203) and used in the connectometry analysis. A deterministic fiber tracking algorithm (Yeh et al., PLoS ONE 8(11): e80713, 2013) was used with augmented tracking strategies (Yeh, Neuroimage, 2020) to improve reproducibility.

The seven seed regions outlined above (mPFC, LPFC L, LPFC R, ACC, PCC, LP L and LP R) were placed as seeding regions for fiber tracking. Outcomes from seed-to-voxel functional connectivity analyses were then imported to DSI Studio and used as end regions for fiber tracking. Standard parameters included: anisotropy threshold randomly selected, change threshold was 20%, angular threshold was randomly selected from 15 degrees to 90 degrees. The step size was randomly selected from 0.5 voxel to 1.5 voxels. Tracks with length shorter than 15 or longer than 150 mm were discarded. A total of 500000 seeds were placed.

C.III Voxel Based Morphometry

The proposed project did not specify structural gray matter correlates of time-since-injury (TSI). However, our standard anatomical neuroimaging data collection included T1-weighted structural images. Therefore, it was possible to also examine gray matter volume differences between groups as part of exploratory analyses. Because those analyses were not part of the initial project

proposal, we will present such data separately in the Supplementary Analyses section at the end of the discussion of the primary hypothesized analyses.

3.D. Neuropsychological/Behavioral Data Collection and Formal Reduction

As shown in Table 6, each participant completed a comprehensive assessment battery that covered neuropsychological and emotional functioning, intellectual capacity, post-concussive symptoms, and activities of daily living.

Table 6. List of assessments administered during the study.

Assessment Title	What it measures
Rivermead Post Concussion Symptoms Questionnaire (RPCSQ)	Post-concussion symptomology
Alcohol Use Disorder Identification Test (AUDIT)	Hazardous alcohol consumption behavior
Day of Scan Questionnaire (DSIQ)	Details related to relevant demographics, most recent mild traumatic brain injury sustained, sleep habits, caffeine consumption
Weschler Abbreviated Scale of Intelligence (WASI II)	Verbal, nonverbal and general cognitive functioning
MINI International Psychiatric Interview	Past and current psychopathology
Epworth Sleepiness Scale (ESS)	Sleep quality
OSU TBI Interview	lifetime mild traumatic brain injuries and symptomology
Glasgow Outcome Scale – Extended (GOS-E)	Measure of injury outcome
California Verbal Learning Task (CVLT)	Verbal memory – the ability to learn, retain, recall, and recognize verbal information
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Attention, processing speed, and executive control
Delis-Kaplan Executive Function System (D-KEFS)	Executive function, attention
Go/No-Go	Sustained attention and response inhibition
Brief Visual Memory Test-Revised (BVMT-R)	Visuospatial memory
Personality Assessment Inventory (PAI)	Psychopathological syndromes
Buss Perry Aggression Questionnaire (BPAQ)	Aggression
Psychomotor Vigilance Task (PVT)	Sustained vigilance and attention
Pittsburgh Sleep Quality Index (PSQI)	Sleep quality over the past 30 days
State Trait Anxiety Inventory (STAI)	State and Trait Anxiety
Automated Neuropsychological Assessment Metrics (ANAM)	visual search, sustained attention, concentration, spatial processing, visuo-spatial working memory, processing speed, visuomotor reaction time
(CHART-SF)	Extent to which impairments and disabilities result in participation restriction in the WHO domains: physical independence, cognitive independence, mobility, occupation, social integration, and economic self-sufficiency
Beck Depression Inventory (BDI-II)	Severity of depression symptoms
Connor-Davidson Resilience Scale (CD-RISC)	Resilience
Snaith Hamilton Pleasure Scale (SHAPS)	Hedonic tone
Satisfaction With Life Scale (SWLS)	Subjective well-being: Quality of life

During the initial submission of the grant proposal, we proposed a set of neurocognitive and behavioral measures that we expected to account for at least four primary domains that are often affected by mTBI (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Vanderploeg, Curtiss, & Belanger, 2005), including attention, speed of information processing, learning and memory, and executive function, although more domains were expected. Upon completion of data collection, we scored each assessment instrument according to the instructions provided by the test manuals or other published literature. To reduce the large number of test scores to a manageable set of neurocognitive domains for subsequent analyses, we conducted a principal component analysis (PCA) on the obtained test scores, as described below.

First, each raw outcome measure was scored by two separate individuals according to published criteria, and converted to standardized scaled scores based on the published normative criteria available for the specific instrument. The final set included 110 standardized scaled scores from the various psychometric instruments. To ensure that the PCA was conducted on scores in the same format, all scaled scores were then converted to z-scores based on the performance of the current sample. These normalized z-scores were then entered into a PCA in IBM SPSS version 26 on the entire sample of 190 participants who provided complete data. Most variables had few, if any, missing values, and if they occurred, they were replaced with the column mean for the entire sample. The scree plot for the initial PCA is shown in Figure 5.

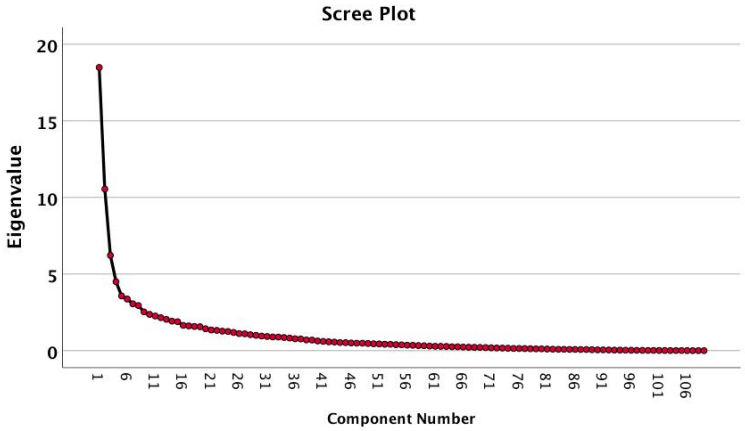


Figure 5. The principal-component analysis (PCA) revealed a gradual slope with 110 components. A conservative threshold for component inclusion was set at an eigenvalue of 2.0, which provided conservative restriction of components, while still ensuring that there was adequate sampling of the various neurocognitive domains.

Initial assessment of the component structure suggested that using a conservative threshold for including components in the solution was appropriate for these data. The threshold for inclusion was set at an eigenvalue of 2.0, which insured that each selected component accounted for much more variance in the data than individual test scores. This threshold resulted in a final selection of 13 components that accounted for 58.731% of the cumulative variance in the data. Table 7 shows the variance parameters from this selection for the first 20 components. These 13 components account for the majority of the data and effectively reduce a large dataset down to a manageable number of neurocognitive, behavioral, and emotional domains.

Table 7. Component extraction was set to an eigenvalue of 2.0, which yielded a final 13-component solution, accounting for 58.95% of the cumulative variance.

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	18.480	16.954	16.954	18.480	16.954	16.954	9.557	8.768	8.768
2	10.544	9.673	26.628	10.544	9.673	26.628	8.980	8.238	17.007
3	6.217	5.704	32.331	6.217	5.704	32.331	8.742	8.020	25.027
4	4.498	4.127	36.458	4.498	4.127	36.458	6.881	6.313	31.340
5	3.568	3.274	39.732	3.568	3.274	39.732	4.554	4.178	35.518
6	3.368	3.090	42.821	3.368	3.090	42.821	3.955	3.629	39.146
7	3.056	2.804	45.625	3.056	2.804	45.625	3.811	3.496	42.643
8	2.942	2.699	48.324	2.942	2.699	48.324	3.095	2.840	45.483
9	2.528	2.319	50.643	2.528	2.319	50.643	3.072	2.819	48.301
10	2.366	2.171	52.814	2.366	2.171	52.814	3.057	2.805	51.106
11	2.259	2.072	54.886	2.259	2.072	54.886	2.784	2.554	53.660
12	2.151	1.973	56.859	2.151	1.973	56.859	2.771	2.542	56.203
13	2.041	1.872	58.731	2.041	1.872	58.731	2.756	2.529	58.731
14	1.924	1.766	60.497						
15	1.891	1.735	62.232						
16	1.650	1.514	63.746						
17	1.614	1.481	65.226						
18	1.580	1.450	66.676						
19	1.558	1.429	68.105						
20	1.426	1.308	69.414						

The component matrix was rotated using a Varimax rotation to ensure orthogonality of components and facilitate ease of interpretation. The rotated matrix converged in 13 iterations. Component scores were then extracted and saved for each participant using standard regression options in the PCA module of SPSS. The rotated component matrix is presented in Table 8 and shows the component loadings for each variable on the 13 extracted principal components (loadings below 0.40 are suppressed for ease of interpretation). Table 8 provides a list of the 13 principal components and a quick interpretive summary. As evident in Table 8, the component solution includes all of the major cognitive domains that are most commonly affected by mTBI (i.e., attention, speed of information processing, verbal and visuospatial learning and memory, and several aspects of executive function (Belanger et al., 2005; Vanderploeg et al., 2005)), as well as additional domains assessing emotional functioning, post-concussive complaints, and sleep quality.

The 13 components were extracted to provide a conceptual framework for assessing the effects of concussion on various neurocognitive domains, but these components are by no means exhaustive and are not meant to represent the entire range of possible human capacities. Rather, these components provide an initial starting point for analysis. In the sections that follow, we begin with the components as primary outcome variables, but in various instances we also move beyond the broad components to examine specific cognitive, behavioral, social, and emotional capacities in greater detail.

Table 8. Principal Components Analysis (PCA) of cognitive, behavioral, social, and emotional variables.

Rotated Component Matrix[a]

	Component												
	1	2	3	4	5	6	7	8	9	10	11	12	13
CVLT Trial 1-5 FR	0.904												
CVLT Long Delay CR	0.873												
CVLT Short Delay FR	0.857												
CVLT Short Delay CR	0.854												
CVLT Long Delay FR	0.842												
CVLT Trial 5 FR	0.829												
CVLT Trial 3 FR	0.809												
CVLT Trial 4 FR	0.796												
CVLT Trial 2 FR	0.786												
CVLT Trial 1 FR	0.633												
CVLT LD Recog Hits	0.587												
CVLT List B FR	0.532												
CVLT LD Recog FP													
DKEFS Tower Total Achv													
ANAM M2S %Corr													
ANAM Composite		0.732					0.459						
RBANS Attention Index		0.704											
ANAM CS Delayed Mn RT		0.696											
DKEFS CW Inhib/Switch		0.675											
ANAM CS Mn RT		0.652											
DKEFS DF Switch		0.642											
DKEFS Trails Switch		0.626											
ANAM M2S Mn RT		0.611											
ANAM CS Delayed Throughput		0.607										0.446	
ANAM CS Throughput		0.604										0.475	
DKEFS DF Tot Cor		0.597											
ANAM Proc RT Throughput		0.596											
ANAM Proc RT Mn RT		0.593					0.423						
RBANS Coding		0.591											
ANAM Math Proc Mn RT		0.582											
ANAM M2S Throughput		0.567											
ANAM Math Proc Throughput		0.534											
RBANS Digit Span		0.464											
DKEFS Lett Fluen Cor		0.435											
DKEFS Cat Switch Cor													
CVLT Total Repetitions													
DKEFS Des Fluen Set Loss													
BDI Total			0.792										
PAI Depression			0.749										
STAI Trait Anxiety			0.699	0.442									
PAI Somatic Complaints			0.689										
PAI Schizophrenia			0.680	0.473									
RPCSQ Cognitive			0.673										
STAI State Anxiety			0.667										
PAI Anxiety			0.644	0.415									
RPCSQ Emotional			0.619										
RPCSQ Somatic			0.611										
PAI Anxiety Related Disorders			0.607	0.439									
ANAM Sleepiness Scale			0.604										
PSQI Daytime Dysfunction			0.568										
Satisfaction With Life Scale			-0.528										
ESS Daytime Sleepiness			0.523										
CD-RISC Total Resilience			-0.492										
BPAQ Total Aggression				0.874									
PAI Aggression				0.744									
BPAQ Anger				0.720									
BPAQ Hostility				0.705									
BPAQ Physical Aggression				0.699									
PAI Antisocial Features				0.698									
PAI Borderline Features			0.582	0.664									
BPAQ Verbal Aggression				0.663									
PAI Paranoia			0.401	0.660									
PAI Mania				0.564									
BVMT Total FR					0.868								
BVMT Trial 1 FR					0.782								
BVMT Trial 2 FR					0.766								
BVMT Trial 3 FR					0.706								
BVMT Delayed FR					0.635								
BVMT Learning					-0.477								
GNG Go Accuracy													
GNG No-Go Accuracy													
DKEFS Tower Move Accuracy													
PSQI Total						0.847							
PSQI Sleep Efficiency						0.655							
PSQI Sleep Quality			0.407			0.647							
PSQI Sleep Latency						0.612							
PSQI Sleep Duration						0.549							
PSQI Sleep Meds						0.454							
PSQI Sleep Disturbance													
CHARTS Self-Sufficiency													
ANAM SRT Delay Mn RT							0.855						
ANAM SRT Mn RT							0.834						
ANAM SRT Throughput							0.749						
ANAM SRT Delay Throughput							0.687						
PVT Mn Speed								0.828					
PVT Mn RT w/o False Starts								-0.827					
PVT Total Lapses								-0.597					
GNG Go RT		-0.447						-0.471					
CVLT Total Intrusions									0.899				
CVLT FR Intrusions									0.828				
CVLT CR Intrusions									0.755				
DKEFS Trails Total Errors													
CHARTS Physical Independence										0.826			
CHARTS Cog Independence										0.771			
CHARTS Mobility										0.677			
CHARTS Social Function										0.556			
PVT False Starts											0.817		
PVT Too Early											0.801		
ANAM Math Proc Correct													
PVT Too Fast													
CHARTS Occupational Funct													
ANAM CS Correct												0.673	
ANAM CS Delay Correct												0.534	
DKEFS CW Inhib/Swit Total Errors													
ANAM Proc RT Correct													
DKEFS Conf Cor Card Sorts													0.800
DKEFS Free Sorting Description													0.798
DKEFS Sort Recog Description													0.696
PSQI Minutes of Sleep													

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
a. Rotation converged in 13 iterations.

Description

1. Verbal Memory
Assesses the ability to learn, retain, recall, and recognize verbal information.

2. Attention & Executive Control
A global metric of neurocognitive functioning. Assesses the ability to attend to and maintain relevant information in working memory, rapidly process and manipulate information, and shift mental set when appropriate.

3. PCS & Emotional Disturbance
Assesses general mood and psychiatric disturbance, including common emotional and somatic concerns associated with post-concussion syndrome.

4. Aggression
Assesses aggressive tendencies.

5. Visuospatial Memory
Assesses the ability to learn, retain, and recall visual information.

6. Sleep Quality
Assesses sleep disruption and other sleep problems.

7. Motor Speed
Assesses simple reaction time and motor responses.

8. Sustained Vigilance/Attention
Assesses to maintain vigilance and mental focus for extended time.

9. Cognitive Errors
Assesses intrusions and errors in cognitive processing.

10. Daily Functioning
Assesses physical, cognitive, and social independence and function.

11. Impulsivity
Assesses the tendency to respond too quickly and make impulsive errors.

12. Processing Speed
Assesses general speed of processing complex information.

13. Concept Formation
Assesses the ability to learn and form abstract concepts and rules.

Additionally, while it is acknowledged that no single value can represent the complexity of human neurocognitive performance, we endeavored to calculate a global score that would encapsulate the general level of functioning of each individual. This Global Neurocognitive Function (GNF) score was calculated by constraining the PCA to extract a single factor that accounted for the maximum variance. This analysis accounted for 16.954% of the common variance and yielded a single component score for each individual, which was assumed to comprise a global estimate of functioning based on performance across all neurocognitive, emotional, PCS, and daily functioning tasks. Higher scores on the GNF indicate greater neurocognitive functioning relative to lower scores. This GNF score will be used as a general global estimate of neurocognitive function in some subsequent analyses.

3.E. Key Outcomes Related to the Specific Aims and Hypotheses

The proposed project included three Specific Aims comprising 14 hypotheses. In the sections below, each aim will be presented. Subsumed within each Specific Aim, the associated hypotheses will be presented along with the corresponding specific statistical analyses and results.

Specific Aim 1: Previous research reported abnormalities in DTI metrics following mild TBI at the acute, subacute and chronic recovery stage. However, the literature is characterized by marked inconsistencies and, more importantly, contradictory findings that do not allow inferences on the directionality of these at different recovery stages following mild TBI. We will evaluate DTI metrics across multiple stages of recovery. The specific hypotheses tested are:

Hypothesis 1: Independent of recovery stage, mild TBI will be associated with greater white matter abnormalities than healthy controls.

Our analysis of study data revealed no discoveries in white matter abnormalities among participants. Neuroimaging data was used, however, to conducted analyses on diffusion metrics, which quantify fiber characteristics and provide a measure of axonal integrity. As outlined in section 3.C.I, standard processing pipelines were used to calculate FA, MD, RD, and AD in TBSS, using whole-brain and ROI-based approaches. Due to differences in acquisition parameters, the present sample only included participants collected at the UA. To assess white matter characteristics, the sample (n = 145) was divided into two groups based on concussion status (HC: n = 32 total [15 male, 17 female], age M = 24.56, SD = 6.15; mTBI: n = 113 total [41 male; 72 female], age M = 24.91, SD = 7.63).

Group Differences: Voxel-wise statistics were calculated to compare white matter integrity between HC and MTBI groups. General linear models (GLMs) were fit with group as the categorical independent variable (HC, MTBI) and DTI metric (FA, MD, RD, AD) as the dependent variable, controlling for participant age and sex. Results were corrected for multiple comparisons at $p < .05$ FWE corrected, based on the threshold-free cluster-enhanced (TFCE) statistic image using default parameters (H=2, E=0.5; 500 permutations). Diffusion metrics were calculated for the 13 targeted pathways (CING L, CING R, aIC L, aIC R, pIC L, pIC R, EC L, EC R, aCR L, aCR R, SLF L, SLF R, CC). A multivariate analysis of covariance (MANCOVA)

was conducted comparing injury status group as the independent variable (HC or MTBI) and DTI metric in 13 targeted pathways as the dependent variable. Covariates included participant age and sex.

Whole-brain analysis

White matter integrity was calculated and compared between HC and mild TBI groups using whole brain, voxel-wise statistics. Contrary to *Hypothesis 1*, there were no statistically significant differences between HC and MTBI groups when comparing whole-brain DTI metrics (FA, MD, RD, AD; p < .05 TFCE corrected). As shown in Table 9, HC and MTBI group exhibited similar diffusion values.

Table 9. Diffusion metrics by group

Descriptive Statistics

	FA		MD		RD		AD	
Injury Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HC	.22668919	.006909668	.00103387	.000048637	.00092553	.000049106	.00125041	.000047813
MTBI	.22581406	.006760145	.00103439	.000045673	.00092652	.000046110	.00125011	.000045170

Region-of-interest analysis

White matter characteristics for the 13 targeted pathways were compared between HC and MTBI groups. Similar to results from the whole-brain analyses, we found no statistically significant differences on measures of anisotropy or diffusion in the targeted pathways (see Figure 6). Among targeted pathways, participant age accounted for significant variance in FA ($p < .01$), however, there was no significant difference between HC and MTBI groups ($F(13, 144) = 0.34$, $p = .99$; Wilk's $\Lambda = 0.97$, partial $\eta^2 = .03$). Age also accounted for significant variance in MD ($p < .001$), although there was no significant between-group difference in MD ($F(13, 144) = 0.43$, $p = .95$; Wilk's $\Lambda = 0.96$, partial $\eta^2 = .04$). Both covariates accounted for significant variance in RD (age: $p = .02$; sex: $p = .04$), however there was no significant difference between groups ($F(13, 144) = 0.31$, $p = .99$; Wilk's $\Lambda = 0.97$, partial $\eta^2 = .03$). Finally, when comparing AD, age accounted for a significant amount of variance ($p < .01$). As with the other DTI metrics, we did not find significant between-group differences in AD for the 13 targeted pathways ($F(13, 144) = 0.56$, $p = .88$; Wilk's $\Lambda = 0.95$, partial $\eta^2 = .05$).

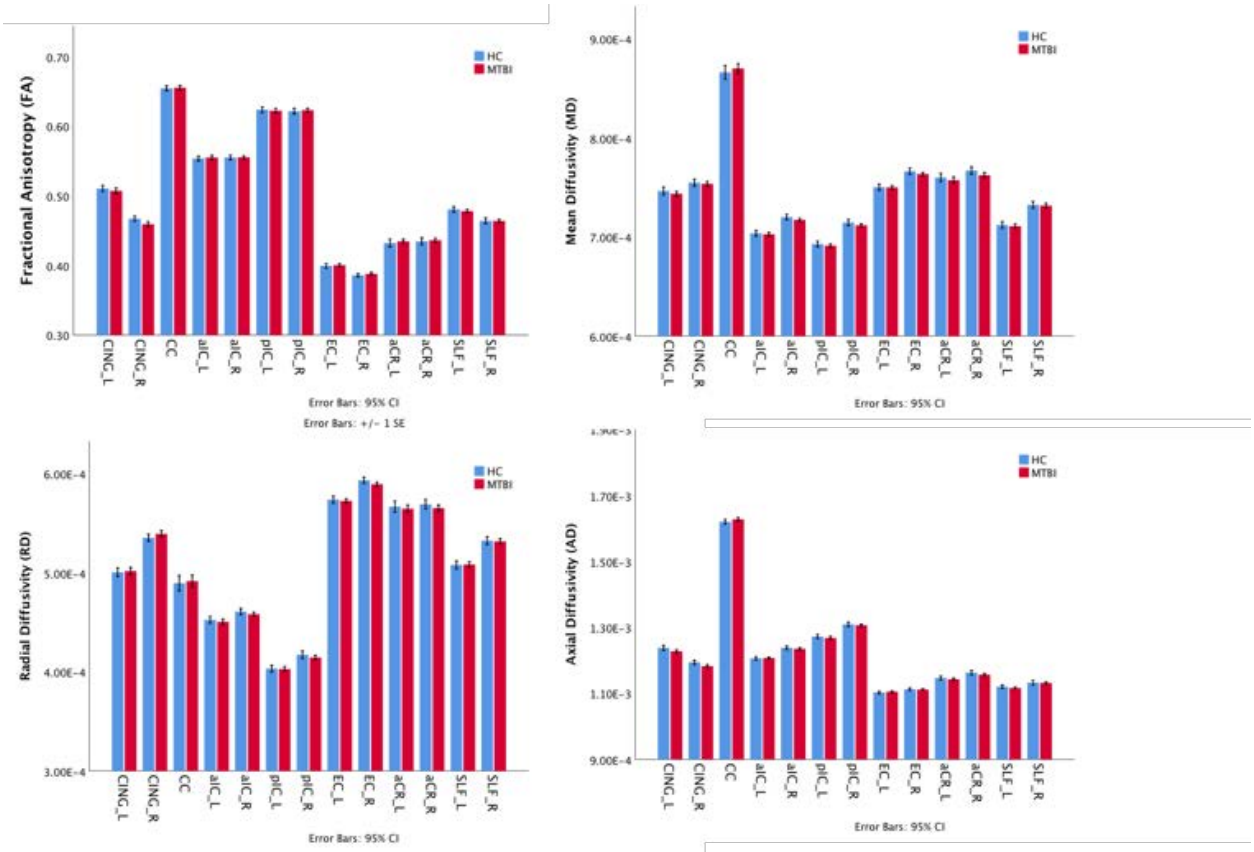


Figure 6. Diffusion metrics of targeted pathways. Healthy controls (HC, blue) and mild traumatic brain injury (MTBI, red) groups exhibited similar FA, MD, RD, and AD across 13 targeted white matter pathways.

Conclusion. *Findings from the present analyses did not lead to the discovery of white matter abnormalities in MTBI participants. Fiber characteristics, as measured by traditional diffusion metrics (FA, MD, RD, and AD) did not differ between the HC group and MTBI group (irrespective of time since injury). However, time since injury may be a critical factor in the characterizing white matter integrity following MTBI, and is addressed in subsequent analyses.*

Hypothesis 2: Independent of recovery stage, RD, AD, number of fibers and number of voxels with abnormal RD/ AD will be more sensitive markers of white matter abnormalities than FA and MD.

Traditional diffusion metrics (FA, MD, RD, AD) were similar between HC and MTBI groups and no abnormalities in white matter were discovered from the analyses conducted for the present study. Normalized quantitative anisotropy (NQA) is an additional measure of diffusion that was calculated using DSI Studio (see section 3.C.II above). NQA provides a measure of diffusion density, or the *amount* of diffusion along a fiber pathway. Given this difference in diffusion measurement, NQA may be more sensitive to structural connectivity differences after a mild TBI.

To address the use of NQA as a more sensitive diffusion metric after mild TBI, the analyses in this section were restricted to the MTBI group. Diffusion data were reviewed for normality and outliers values. Six participants exhibited NQA values ≤ 3 SD and were, therefore, excluded

from further analysis. Results in this section are based on a sample of n =108 (**2W**: n = 10, **1M**: n = 20; **3M**: n = 25; **6M**: n = 20, **12M**: n = 33)

Group differences: Whole-brain tractography was conducted in DSI Studio and used to quantify NQA, while TBSS was used to calculate whole-brain FA, MD, RD, and AD. An analysis of covariance (ANCOVA) was conducted with MTBI group (2W, 1M, 3M, 6M, 12M) as the independent variable and NQA as the dependent variable. Covariates in the analysis included participant age and sex. The test of between-subject effects revealed a statistically significant difference in NQA between MTBI groups ($F(4,101) = 4.32$, $p = .003$, partial $\eta^2 = 0.14$). In post-hoc comparisons, we found that participants in the chronic phase of recovery (12M) exhibited significantly lower NQA compared to 2W ($p = .02$), 1M ($p < .0001$), and 6M ($p = .005$) MTBI groups (see Figure 7).

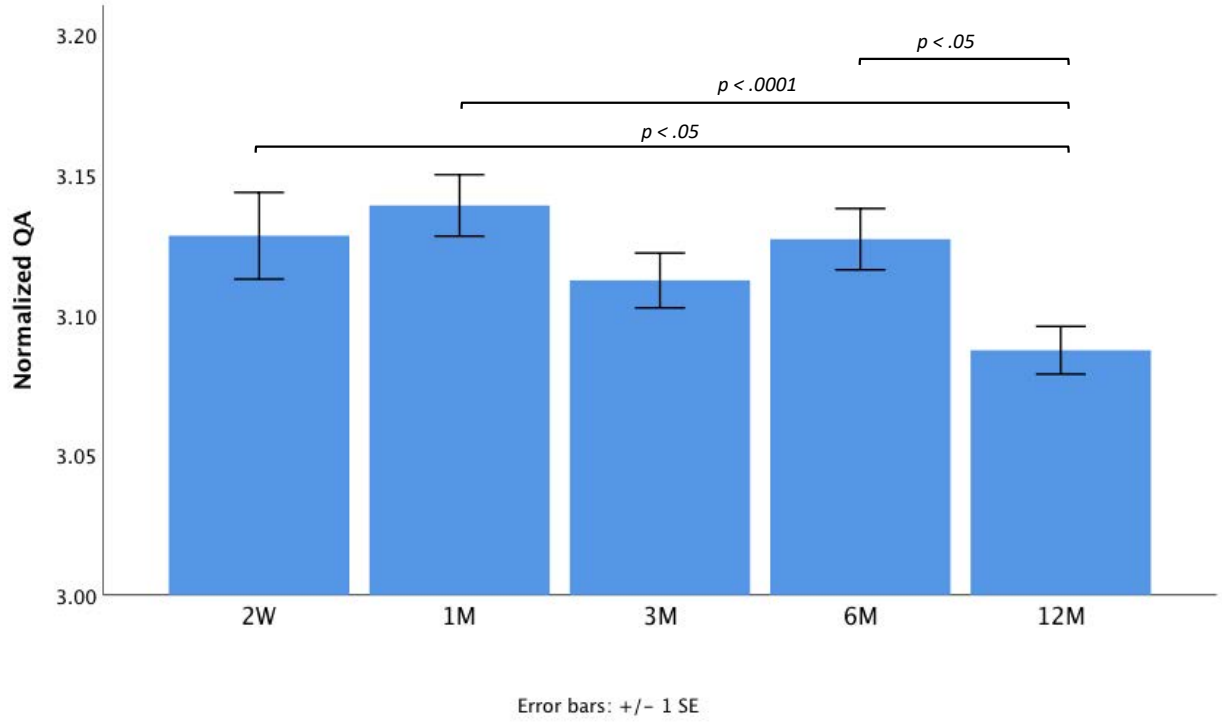


Figure 7. Whole-brain normalized quantitative anisotropy (NQA) by time since injury. NQA was significantly lower in the 12M compared to 2W, 1M, and 6M MTBI groups.

ANCOVAs were also calculated to compare MTBI groups on traditional measures of diffusion outlined in the initial grant (FA, MD, RD, and AD). We found no significant between-group differences on measures of FA ($F(4,101) = 0.20$, $p = .94$, partial $\eta^2 = 0.01$), MD ($F(4,101) = 0.69$, $p = .60$, partial $\eta^2 = 0.03$), RD ($F(4,101) = 0.62$, $p = .65$, partial $\eta^2 = 0.02$), or AD ($F(4,101) = 0.77$, $p = .55$, partial $\eta^2 = 0.03$).

Conclusion. *Findings from the current analysis indicate that NQA, as opposed to FA, MD, RD, or AD, may be a more sensitive in detecting fluctuations in white matter integrity at discrete stages of MTBI recovery.*

Hypothesis 3: Independent of recovery stage, RD, AD, number of fibers and number of voxels with abnormal RD/ AD will be a better predictor of group membership than FA and MD.

Extracted values from the DTI analyses were summarized for each of the five methods (RD, AD, FA, MD, and NQA). To minimize small values that occur from extraction of DTI values, each variable was normalized to a z-score for further analysis. To test this hypothesis, we first entered each of the five types of DTI metrics into a series of five separate binomial logistic regression analyses to predict injury status (HC versus mTBI). All extracted regions were entered simultaneously into the equation to assess combined effects.

Radial Diffusivity (RD): Prior to variable entry, the best guess classification for all participants was that they had a mTBI, since there were $n = 113$ mTBIs and $n = 32$ HCs with RD data. Therefore, the baseline accuracy prior to entry of any variables was 77.9%. Simultaneous entry of all 13 DTI region values did not result in a significant model χ^2 (13) = 5.085, $p = .973$, Nagelkerke $R^2 = .053$. Overall, the model led to a nonsignificant increase in prediction to 78.6% accuracy. Thus, we conclude that, RD in the tracts assessed here, was not a significant discriminator of injury status. Table 10 presents the variables and their associated statistics.

Table 10. Results of the simultaneous entry of all RD values into the binomial logistic regression to predict mTBI status. Overall, no RD values predicted injury status.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	ZCING L RD Mean	-.201	.510	.155	1	.693	.818	.301	2.221
	ZCING R RD Mean	.636	.483	1.730	1	.188	1.888	.732	4.868
	ZCC RD Mean	.182	.305	.356	1	.551	1.199	.660	2.178
	ZaIC L RD Mean	.100	.467	.046	1	.830	1.105	.442	2.763
	ZaIC R RD Mean	-.128	.373	.118	1	.732	.880	.424	1.828
	ZpIC L RD Mean	.038	.481	.006	1	.937	1.039	.405	2.664
	ZpIC R RD Mean	-.083	.424	.039	1	.844	.920	.401	2.110
	ZEC L RD Mean	.207	.316	.430	1	.512	1.231	.662	2.287
	ZEC R RD Mean	-.411	.373	1.210	1	.271	.663	.319	1.379
	ZaCR L RD Mean	-.006	.630	.000	1	.993	.994	.289	3.417
	ZaCR R RD Mean	-.363	.521	.485	1	.486	.696	.250	1.932
	ZSLF L RD Mean	.065	.438	.022	1	.883	1.067	.452	2.516
	ZSLF R RD Mean	-.014	.440	.001	1	.975	.986	.417	2.334
	Constant	1.319	.210	39.390	1	.000	3.742		

a. Variable(s) entered on step 1: ZCING_L_RD_Mean, ZCING_R_RD_Mean, ZCC_RD_Mean, ZaIC_L_RD_Mean, ZaIC_R_RD_Mean, ZpIC_L_RD_Mean, ZpIC_R_RD_Mean, ZEC_L_RD_Mean, ZEC_R_RD_Mean, ZaCR_L_RD_Mean, ZaCR_R_RD_Mean, ZSLF_L_RD_Mean, ZSLF_R_RD_Mean.

Axial Diffusivity (AD): As above, prior to variable entry, the best guess classification for all participants was that they had a mTBI, since there were n = 113 mTBIs and n = 32 HCs with AD data. Therefore, the baseline accuracy prior to entry of any variables was 77.9%. Simultaneous entry of all 13 DTI region values did not result in a significant model χ^2 (13) = 8.173, p = .832, Nagelkerke R^2 = .084. Overall, the model led to no discernable change in classification accuracy, which remained at 77.9%. Thus, we conclude that, RD in the tracts assessed here, was not a significant discriminator of injury status. Table 11 presents the variables and their associated statistics.

Table 11. Results of the simultaneous entry of all AD values into the binomial logistic regression to predict mTBI status. Overall, no AD values predicted injury status.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	ZCING L AD Mean	-.229	.369	.383	1	.536	.796	.386	1.641
	ZCING R AD Mean	-.220	.325	.457	1	.499	.803	.424	1.518
	ZCC AD Mean	.406	.274	2.201	1	.138	1.501	.878	2.566
	ZaIC L AD Mean	.687	.467	2.165	1	.141	1.988	.796	4.964
	ZaIC R AD Mean	-.555	.418	1.762	1	.184	.574	.253	1.303
	ZpIC L AD Mean	-.441	.442	.997	1	.318	.644	.271	1.529
	ZpIC R AD Mean	.218	.373	.341	1	.559	1.243	.599	2.583
	ZEC L AD Mean	.362	.376	.927	1	.336	1.437	.687	3.003
	ZEC R AD Mean	-.082	.368	.050	1	.823	.921	.448	1.893
	ZaCR L AD Mean	-.086	.343	.063	1	.802	.917	.468	1.798
	ZaCR R AD Mean	-.170	.348	.240	1	.624	.843	.427	1.667
	ZSLF L AD Mean	-.123	.351	.123	1	.725	.884	.444	1.760
	ZSLF R AD Mean	.070	.385	.033	1	.855	1.073	.505	2.280
	Constant	1.353	.216	39.274	1	.000	3.871		

a. Variable(s) entered on step 1: ZCING_L_AD_Mean, ZCING_R_AD_Mean, ZCC_AD_Mean, ZaIC_L_AD_Mean, ZaIC_R_AD_Mean, ZpIC_L_AD_Mean, ZpIC_R_AD_Mean, ZEC_L_AD_Mean, ZEC_R_AD_Mean, ZaCR_L_AD_Mean, ZaCR_R_AD_Mean, ZSLF_L_AD_Mean, ZSLF_R_AD_Mean.

Fractional Anisotropy (FA): Again, prior to variable entry, the best guess classification for all participants was that they had a mTBI, since there were n = 113 mTBIs and n = 32 HCs with FA data. Therefore, the baseline accuracy prior to entry of any variables was 77.9%. Simultaneous entry of all 13 DTI region values did not result in a significant model χ^2 (13) = 4.506, p = .985, Nagelkerke R^2 = .047. Overall, the model led to no change in the accuracy of prediction, remaining at 77.9% correct after all variables were entered. Thus, we conclude that, FA, in the tracts assessed here, was not a significant discriminator of injury status. Table 12 presents the variables and their associated statistics.

Table 12. Results of the simultaneous entry of all FA values into the binomial logistic regression to predict mTBI status. Overall, no FA values predicted injury status.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	ZCING L FA Mean	.126	.411	.094	1	.759	1.134	.507	2.539
	ZCING R FA Mean	-.452	.376	1.451	1	.228	.636	.305	1.328
	ZCC FA Mean	.052	.311	.028	1	.867	1.053	.572	1.939
	ZaIC L FA Mean	.176	.453	.151	1	.697	1.192	.491	2.896
	ZaIC R FA Mean	-.099	.358	.077	1	.781	.905	.449	1.825
	ZpIC L FA Mean	-.397	.442	.807	1	.369	.673	.283	1.598
	ZpIC R FA Mean	.296	.361	.674	1	.412	1.345	.663	2.728
	ZEC L FA Mean	-.108	.324	.112	1	.738	.897	.475	1.694
	ZEC R FA Mean	.243	.367	.437	1	.508	1.275	.621	2.619
	ZaCR L FA Mean	.220	.409	.288	1	.591	1.246	.559	2.778
	ZaCR R FA Mean	-.089	.386	.054	1	.817	.915	.429	1.949
	ZSLF L FA Mean	-.221	.346	.406	1	.524	.802	.407	1.581
	ZSLF R FA Mean	.183	.347	.280	1	.597	1.201	.609	2.370
	Constant	1.315	.210	39.373	1	.000	3.724		

a. Variable(s) entered on step 1: ZCING_L_FA_Mean, ZCING_R_FA_Mean, ZCC_FA_Mean, ZaIC_L_FA_Mean, ZaIC_R_FA_Mean, ZpIC_L_FA_Mean, ZpIC_R_FA_Mean, ZEC_L_FA_Mean, ZEC_R_FA_Mean, ZaCR_L_FA_Mean, ZaCR_R_FA_Mean, ZSLF_L_FA_Mean, ZSLF_R_FA_Mean.

Mean Diffusivity (MD): Again, prior to variable entry, the best guess classification for all participants was that they had a mTBI, since there were $n = 113$ mTBIs and $n = 32$ HCs with MD data. Therefore, the baseline accuracy prior to entry of any variables was 77.9%. Simultaneous

Table 13. Results of the simultaneous entry of all MD values into the binomial logistic regression to predict mTBI status. Overall, no MD values predicted injury status.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	ZCING L MD Mean	-.512	.597	.736	1	.391	.599	.186	1.931
	ZCING R MD Mean	.396	.548	.521	1	.470	1.485	.507	4.348
	ZCC MD Mean	.290	.353	.675	1	.411	1.337	.669	2.669
	ZaIC L MD Mean	.392	.466	.708	1	.400	1.480	.594	3.689
	ZaIC R MD Mean	-.177	.450	.156	1	.693	.837	.347	2.023
	ZpIC L MD Mean	-.208	.492	.179	1	.673	.812	.309	2.131
	ZpIC R MD Mean	-.131	.515	.065	1	.799	.877	.320	2.407
	ZEC L MD Mean	.321	.385	.696	1	.404	1.379	.648	2.935
	ZEC R MD Mean	-.336	.408	.679	1	.410	.715	.321	1.589
	ZaCR L MD Mean	.103	.810	.016	1	.899	1.109	.227	5.418
	ZaCR R MD Mean	-.607	.678	.802	1	.371	.545	.144	2.059
	ZSLF L MD Mean	-.009	.600	.000	1	.988	.991	.306	3.214
	ZSLF R MD Mean	.506	.607	.693	1	.405	1.658	.504	5.455
	Constant	1.335	.213	39.132	1	.000	3.798		

a. Variable(s) entered on step 1: ZCING_L_MD_Mean, ZCING_R_MD_Mean, ZCC_MD_Mean, ZaIC_L_MD_Mean, ZaIC_R_MD_Mean, ZpIC_L_MD_Mean, ZpIC_R_MD_Mean, ZEC_L_MD_Mean, ZEC_R_MD_Mean, ZaCR_L_MD_Mean, ZaCR_R_MD_Mean, ZSLF_L_MD_Mean, ZSLF_R_MD_Mean.

entry of all 13 DTI region values did not result in a significant model χ^2 (13) = 5.902, p = .950, Nagelkerke R^2 = .061. Overall, the model led to only a small nonsignificant increase in prediction to 79.3% after all variables were entered. Thus, we conclude that, MD, in the tracts assessed here, was not a significant discriminator of injury status. Table 13 presents the variables and their associated statistics.

Normalized Quantitative Anisotropy (NQA): At the time the original proposal was written, NQA procedures had not been developed. However, we have now also been able to extract NQA metrics to analyze in the same way as the other metrics described above. NQA could not be extracted from all participants, so there were n = 102 mTBIs and n = 32 HCs with usable NQA data. As in the preceding sections, without additional information, the best guess was that all participants had an mTBI. Therefore, the baseline accuracy prior to entry of any variables was 76.1%. Simultaneous entry of all 15 NQA region values did not result in a significant model χ^2 (15) = 19.249, p = .203, Nagelkerke R^2 = .201. Overall the model led to a nonsignificant decline in the accuracy of classification, resulting in 73.9% correct classifications after all variables were entered. Thus, we conclude that, NQA, in the tracts assessed here, was not a significant discriminator of injury status. Table 14 presents the variables and their associated statistics.

Table 14. Results of the simultaneous entry of all NQA values into the binomial logistic regression to predict mTBI status. Overall, only the corpus collosum was predictive of injury status.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	ZMPFC NQA	-.537	.332	2.620	1	.106	.585	.305	1.120
	ZACC NQA	.200	.250	.644	1	.422	1.222	.749	1.993
	ZaCR L NQA	.083	1.538	.003	1	.957	1.086	.053	22.140
	ZaCR R NQA	-1.772	1.737	1.041	1	.308	.170	.006	5.118
	ZaIC L NQA	-.026	.844	.001	1	.975	.974	.186	5.088
	ZaIC R NQA	1.423	1.106	1.654	1	.198	4.149	.474	36.285
	ZCC NQA	1.347	.662	4.134	1	.042	3.845	1.050	14.081
	ZCING L NQA	.645	.451	2.042	1	.153	1.906	.787	4.615
	ZCING R NQA	-.812	.451	3.238	1	.072	.444	.184	1.075
	ZEC L NQA	.711	.809	.774	1	.379	2.037	.418	9.937
	ZEC R NQA	-.512	.647	.626	1	.429	.599	.169	2.129
	ZpIC L NQA	-.466	.644	.524	1	.469	.627	.178	2.216
	ZpIC R NQA	-.108	.694	.024	1	.876	.897	.230	3.498
	ZSLF L NQA	-.741	.475	2.434	1	.119	.477	.188	1.209
	ZSLF R NQA	.445	.388	1.316	1	.251	1.561	.729	3.341
	Constant	1.406	.248	32.181	1	.000	4.081		

a. Variable(s) entered on step 1: ZMPFC_seed_3_NQA, ZACC_seed_NQA, ZaCR_L_NQA, ZaCR_R_NQA, ZaIC_L_NQA, ZaIC_R_NQA, ZCC_NQA, ZCING_L_NQA, ZCING_R_NQA, ZEC_L_NQA, ZEC_R_NQA, ZpIC_L_NQA, ZpIC_R_NQA, ZSLF_L_NQA, ZSLF_R_NQA.

Conclusion: *The present analyses do not support the hypothesis that RD and AD are superior to FA and MD at predicting injury status. In fact, none of the traditional DTI metrics, as well as*

the newer NQA metric, were effective at discriminating between HC and mTBI participants. This finding raises doubts about the potential utility of DTI metrics as global indicators of mild forms of traumatic brain injury.

<u>Specific Aim 2</u>: Previous research has suggested associations between DTI metrics and neuropsychological performance following mild TBI. Inconsistencies in the literature do not allow inferences on the cognitive and behavioral significance of white matter abnormalities at different recovery stages following mild TBI to behavior. We will examine the relationship between DTI metrics and neurocognitive performance across multiple stages of recovery. The specific hypotheses tested are:

Hypothesis 4: Independent of recovery stage, mapped white matter abnormalities will be predictive of neuropsychological performance.

Based on the obtained structural imaging data, no white matter abnormalities were noted for any of the participants. Therefore, this hypothesis was not able to be directly tested.

Hypothesis 5: Independent of recovery stage, RD, AD, number of fibers and number of voxels with abnormal RD/ AD will be better predictors of neuropsychological performance than FA and MD.

As described above in section 3.C.I, we first extracted the values for the primary DTI metrics from each of the 13 major brain tracts in Table 15. The extracted values from each tract included the four DTI values of RD, AD, FA, and MD, yielding 52 values. For the initial test of this hypothesis, these 52 DTI values were entered into a stepwise multiple linear regression analysis to predict neurocognitive performance. For this first analysis, the dependent variable was the single metric of Global Neurocognitive Function (GNF) based on the extraction of a single component from the PCA described in Section 3.D above.

Table 15. Diffusion Tensor Imaging (DTI) tracts identified earlier as differentiating HC from mTBI groups. The diffusion metrics of Radial Diffusivity (RD), Axial Diffusivity (AD), Fractional Anisotropy (FA), and Mean Diffusivity (MD), were extracted from each.

JHU ICBM Name	X	Y	Z	Label
Cingulum (cingulate gyrus) L	-7	-16	36	CING.L
Cingulum (cingulate gyrus) R	7	6	33	CING.R
Corpus callosum	-5	-26	25	CC
Anterior limb of internal capsule L	-14	3	7	aIC.L
Anterior limb of internal capsule R	15	3	7	aIC.R
Posterior limb of internal capsule L	-23	-18	13	pIC.L
Posterior limb of internal capsule R	24	-18	13	pIC.R
External capsule L	-31	5	-8	EC.L
External capsule R	32	5	-8	EC.R
Anterior corona radiata L	-20	37	1	aCR.L
Anterior corona radiata R	21	37	1	aCR.R
Superior longitudinal fasciculus L	-36	-23	30	SLF.L
Superior longitudinal fasciculus R	37	-23	30	SLF.R

The best fit model retained only two predictors, $R^2 = .141$, $F(2,142) = 11.62$, $p = .00002$. As hypothesized, the two best predictors of GNF included a <u>metric of RD</u> (i.e., External Capsule mean RD, $\beta = -.221$, $t = -2.78$, $p = .006$), and a <u>metric of AD</u> (i.e., Right Cingulate Gyrus, $\beta = .349$, $t = 4.40$, $p = .00002$). After these two predictors were entered into the equation, no other variables added significantly to the prediction. Better general neuropsychological performance was predicted by a linear

combination of reduced RD within the external capsule and greater AD within the right cingulate gyrus. The partial regression plots for these two variables are presented in Figure 8. The full regression equation table is presented in Table 16. Thus, the hypothesis was supported, suggesting that RD and AD were better predictors of overall neuropsychological performance than MD or FA.

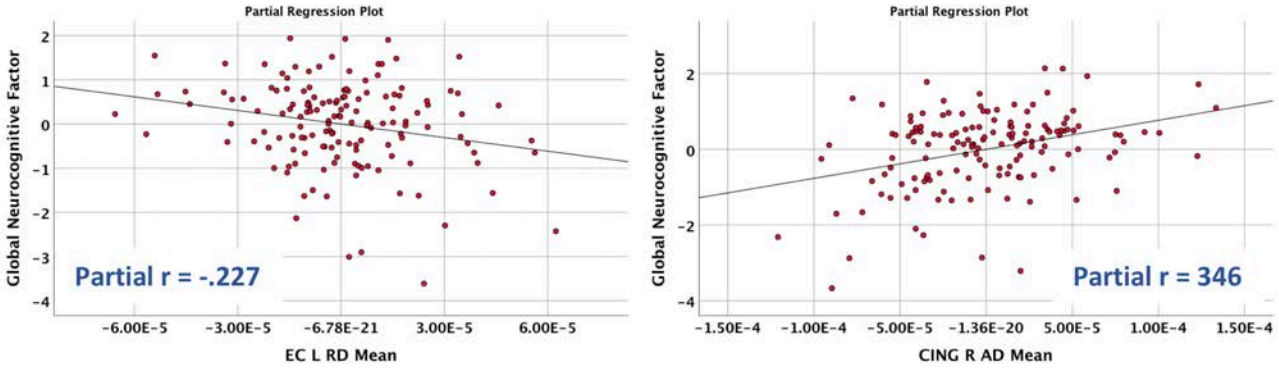


Figure 8. The figure shows the partial regression plot for predicting Global Neurocognitive Factor (GNF) performance from DTI metrics. Two predictors contributed significantly to prediction. Greater radial diffusivity (RD) within the left external capsule (EC) was associated with worse GNF performance (Left), while greater axial diffusivity (AD) within the right cingulate (R Cing) was associated with better GNF scores.

Table 16. The table presents the regression scores for the two variables that were retained in the regression equation for predicting Global Neurocognitive Factor (GNF) performance from diffusion tensor imaging (DTI) metrics.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Correlations		
		B	Std. Error	Beta	t	Sig.	Zero-order	Partial	Part
1	(Constant)	-8.094	2.076		-3.899	.000			
	CING R AD Mean	6730.407	1750.567	.306	3.845	.000	.306	.306	.306
2	(Constant)	-3.335	2.653		-1.257	.211			
	EC L RD Mean	-10244.308	3679.815	-.221	-2.784	.006	-.153	-.227	-.217
	CING R AD Mean	7668.823	1743.552	.349	4.398	.000	.306	.346	.342

a. Dependent Variable: Global_NP_Factor

Additionally, it was of interest to determine whether the DTI metrics were predictive of each of the 13 individual neurocognitive factors. To examine this, we conducted a series of 13 stepwise linear regression analyses, each entering the 52 DTI tract measures as independent variables to predict each of the 13 individual neurocognitive factor scores. The outcomes are summarized in Table 17. Whereas the data for the GNF scores suggested that RD and AD were more predictive of overall neuropsychological status, the individual factor scores paint a more complex picture. Higher RD in specific pathways tended to be associated with fewer cognitive errors overall, while higher AD in specific pathways was associated with better attention/executive control, better sleep quality, faster processing speed, but lower overall quality of daily functioning. Higher FA within particular tracts was associated with better verbal memory and lower impulsivity, while higher MD in specific pathways was associated with worse emotional disturbance and symptoms of PCS, as well as complex effects on visual memory.

Table 17. The table presents the resulting models from the 13 stepwise regression analyses to predict individual neurocognitive factor performance. For each analysis, 52 diffusion metrics were entered in a stepwise fashion to identify the optimal model. This was repeated for each of the 13 neurocognitive factor scores.

Neurocognitive Factor	*R*	R^2	*F*	p-value	Predictor Variable	β	t	p-value	partial *r*
F1 Verbal Memory	0.182	0.033	4.927	0.0280	FA Left post IC	0.182	2.22	0.0280	0.182
F2 Atten/Exec Control	0.194	0.038	5.614	0.0190	AD Right EC	0.194	2.369	0.0190	0.194
F3 PCS/Emotional Disturbance	0.175	0.031	4.541	0.0350	MD Left ant IC	0.175	2.131	0.0350	0.175
F4 Aggression	0.213	0.045	6.776	0.0100	MD Right SLF	0.213	2.603	0.0100	0.213
F5 Visual Memory	0.295	0.087	6.787	0.0020	MD Right ant IC	0.347	3.64	0.0004	0.292
					MD Right SLF	-0.234	-2.454	0.0150	-0.202
F6 Sleep Quality (Disturbance)	0.192	0.037	5.451	0.0210	AD Right Cing	-0.192	-2.335	0.0210	-0.192
F7 Motor Speed	0.272	0.074	11.388	0.0010	AD Right post IC	0.272	3.375	0.0010	0.272
F8 Vigilance	--								
F9 Cognitive Errors	0.374	0.14	5.683	0.0003	FA Right ant CR	-0.406	-3.494	0.0010	-0.283
					RD Left ant CR	-0.404	-2.81	0.0060	-0.231
					RD Left SLF	0.513	3.265	0.0010	0.266
					RD Right SLF	-0.328	-2.091	0.0380	-0.174
F10 Daily Functioning	0.196	0.039	5.741	0.0180	AD Right post IC	-0.196	-2.396	0.0180	-0.196
F11 Concept Formation	--								
F12 Impulsivity	0.231	0.054	8.086	0.0050	FA Right ant CR	-0.231	-2.844	0.0050	-0.231
F13 Processing Speed	0.321	0.053	8.024	0.0050	AD Right Cing	0.231	2.833	0.0050	0.231

Conclusion: *Based on the preceding analyses, the primary hypothesis is supported for general neurocognitive performance, as RD and AD appear to be the most significant predictors of global performance across groups. However, the specific DTI metrics may add valuable information to understanding specific neurocognitive outcomes and should be explored further for their individual predictive capacity.*

Hypothesis 6: Independent of recovery stage, RD, AD, number of fibers and number of voxels with abnormal RD/ AD in conjunction with neuropsychological performance will be better predictors of group membership than FA, MD and neuropsychological performance.

To test this hypothesis, we conducted two hierarchical binary logistic regression analyses. In both analyses, the 13 neurocognitive factor scores were forced into the regression in the first block. Then in the second block, we used a forward conditional entry of DTI metrics. In Model A, we entered the RD and AD metrics at Block 2 and the FA and MD metrics in Block 3. In Model B, this was reversed, so that FA and MD metrics were entered in Block 2 while RD and AD metrics were entered in Block 3. This permitted a direct test in each Model of the additive effect of the type of metric. The outcome of these two models is summarized below:

Model A (Neurocognitive Factors + RD/AD + FA/MD): As described earlier, prior to variable entry, the best guess classification for all participants was that they had an mTBI, since there were $n = 113$ mTBIs and $n = 32$ HCs with usable data. Therefore, the baseline accuracy prior to entry of any variables was 77.9%. Simultaneous entry of the 13 Neurocognitive Factors at **Block 1** resulted in a significant model, χ^2 (13) = 64.923, $p < .0000001$, Nagelkerke $R^2 = .554$. This led to 85.5% classification accuracy. At **Block 2**, forward conditional stepwise entry of RD and AD

did not lead to any additional improvement in the model. However, at **Block 3**, forward conditional stepwise entry of FA and MD variables led to the further inclusion of the MD within the right anterior internal capsule in the final model, leading to a significant improvement in the model, (Block: $\chi 2$ (13) = 4.362, p =.037, Model: $\chi 2$ (13) = 69.285, p < .0000001, Nagelkerke R^2 = .583). This suggests that RD and AD did not improve the initial model, but the addition of one metric of MD did lead to improvement in the model.

Model B (Neurocognitive Factors +FA/MD + RD/AD): This model essentially reversed the order of Block 2 and Block 3. As before, simultaneous entry of the 13 Neurocognitive Factors at **Block 1** resulted in a significant model, χ^2 (13) = 64.923, p < .0000001, Nagelkerke R^2 = .554. This led to 85.5% classification accuracy. At **Block 2**, forward conditional stepwise entry of FA and MD led to significant improvement in the model, (Block: $\chi 2$ (13) = 4.362, p =.037, Model: $\chi 2$ (13) = 69.285, p < .0000001, Nagelkerke R2 = .583). However, at **Block 3**, forward conditional stepwise entry of FA and MD variables did not significantly improve the model.

Conclusion: *The present analyses do not support the hypothesis that RD and AD are superior to FA and MD at predicting injury status when added to neurocognitive performance metrics. In fact, the opposite effect was observed. In this case, we see that FA and MD added a very small improvement to prediction of injury status, while RD and AD did not.*

Hypothesis 7: Independent of recovery stage, neuropsychological performance will be worse in participants with mild TBI relative to healthy controls.

As described in section 3.D above, the neuropsychological outcome measures were initially reduced to 13 neurocognitive component scores using PCA. For continuity with the neuroimaging data, the present sample only included participants collected at the UA. To test this hypothesis, the sample was divided into two groups based on concussion status (HC: n = 36 total [15 male, 21 female], age M = 24.3, SD = 5.9; mTBI: n = 125 total [45 male; 80 female], age M = 24.8, SD = 7.4).

Group Differences: First, a multivariate analysis of covariance (MANCOVA) was conducted comparing the injury status groups as the independent variable (HC or mTBI) for the 13 neurocognitive component scores as dependent variables. Covariates included participant sex, age, and full scale WASI IQ. All three covariates accounted for significant variance (p < .001). There was a statistically significant difference between HC and mTBI groups in the combined dependent variables, F(13, 144) = 4.23, p = .000006; Wilk's Λ = 0.724, partial η^2 = .276, suggesting a large effect size. Univariate analysis of covariance (ANCOVA) showed that two of the neurocognitive components were significantly different between injury groups. As shown in Table 18, this included Component 3, PCS & Emotional Disturbance, and Component 6, Sleep Quality (Disturbance).

Table 18. The table shows the univariate differences between HC and mTBI groups for each of the 13 neurocognitive component scores.

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Injury Group	F1_Verbal_Memory	.156	1	.156	.171	.680	.001
	F2_Atten_Exec_Control	.269	1	.269	.289	.592	.002
	F3_PCS_Emotion	**20.887**	**1**	**20.887**	**24.855**	**.000**	**.137**
	F4_Aggression	2.903	1	2.903	3.177	.077	.020
	F5_Visual_Memory	.226	1	.226	.232	.631	.001
	F6_Sleep_Quality	**14.209**	**1**	**14.209**	**14.881**	**.000**	**.087**
	F7_Motor_Speed	.347	1	.347	.355	.552	.002
	F8_Vigilance	.314	1	.314	.321	.572	.002
	F9_Cognitive_Errors	3.943	1	3.943	3.825	.052	.024
	F10_Daily_Functioning	.088	1	.088	.076	.783	.000
	F11_Concept_Formation	.199	1	.199	.208	.649	.001
	F12_Impulsivity	1.301	1	1.301	1.363	.245	.009
	F13_Processing_Speed	.168	1	.168	.188	.665	.001

Figure 9 shows the mean scores (adjusted for covariates) for the HC and mTBI groups for each of the 13 neurocognitive components extracted from the comprehensive assessment battery. Contrary to *Hypothesis 7*, when time-since-injury was not considered, most neurocognitive domains did not differ significantly between the HC and mTBI groups. This suggests that without consideration for recovery stage, individuals with a concussion did not show worse performance than HCs on verbal memory, attention and executive control, visual memory, motor speed, vigilance, cognitive errors, daily functioning, concept formation, impulsivity, or processing speed.

On the other hand, we did find that the mTBI group overall showed significantly higher scores on the domain assessing post-concussion symptoms and general emotional dysfunction and the domain assessing general disturbance in sleep. Additionally, we found that the mTBI group showed a nonsignificant trend toward greater aggression and fewer cognitive intrusions and errors on timed tasks. Overall, this suggests that, in aggregate, most individuals who have sustained an mTBI in the preceding year do not demonstrate measurable deficits in a wide range of neuropsychological performance measures relative to healthy individuals, and if anything, tend to be a bit more careful than non-concussed persons when completing certain tasks. However, our data strongly show that mTBI is associated with significant elevation in emotional problems and symptoms of post-concussion syndrome, including increased complaints of depression, anxiety, somatic concerns, and worry about unusual cognitive issues, and potential increase in aggressive tendencies. These emotional, somatic, and cognitive complaints also occur in conjunction with significant sleep disturbance within those recovering from an mTBI.

Because of the close connection between sleep

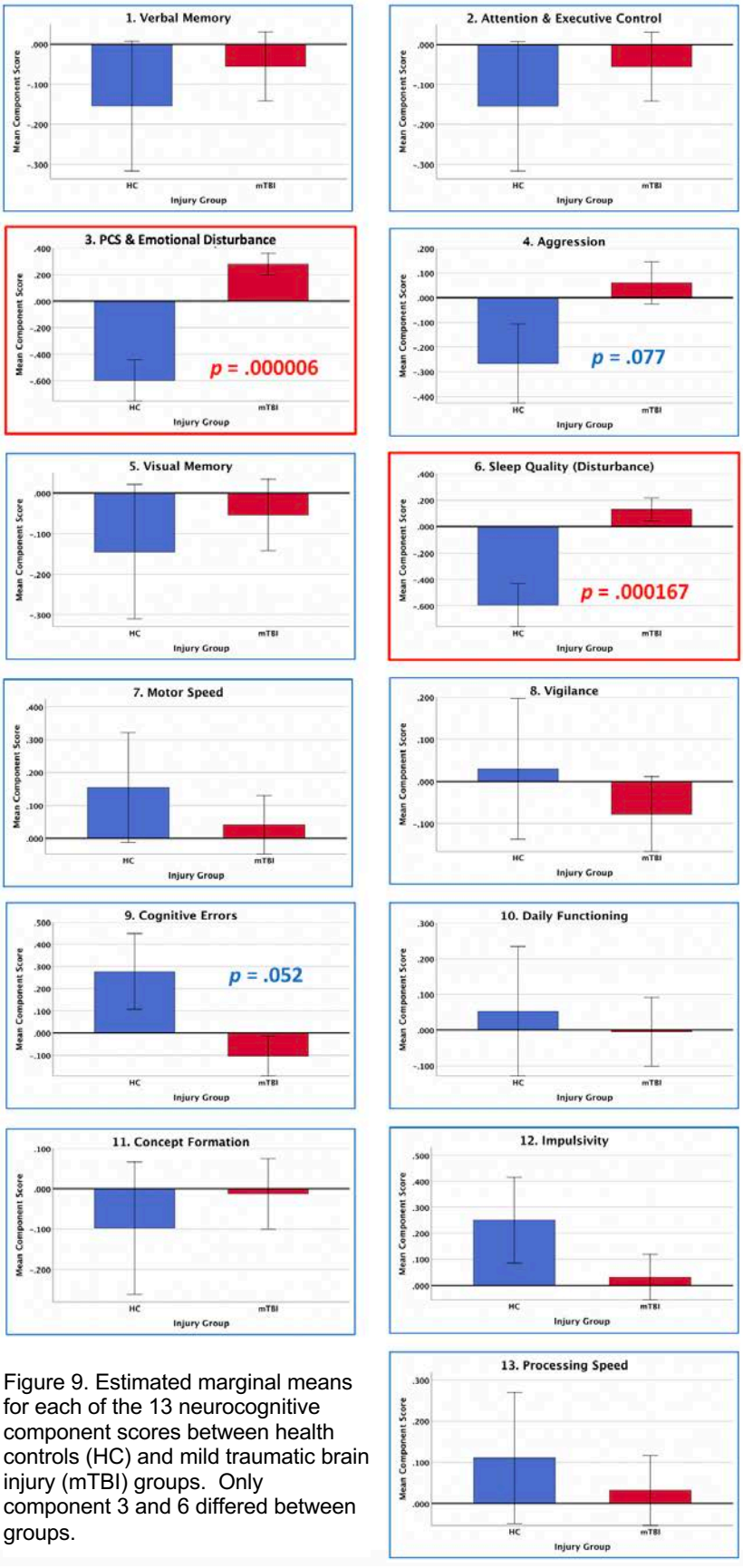


Figure 9. Estimated marginal means for each of the 13 neurocognitive component scores between health controls (HC) and mild traumatic brain injury (mTBI) groups. Only component 3 and 6 differed between groups.

disruption and problems with emotional regulation, these findings raise the possibility that many of the complaints associated with mTBI may be secondary to the emotional dysregulation produced by prolonged reductions in the quality and quantity of sleep. This is strongly recommended as an area for further research.

Group Prediction: Next, to further understand the association between the various neurocognitive components and mTBI, we conducted a binary logistic regression, using the 13 component scores as independent variables to predict injury group status (i.e., HC vs. mTBI). At the first step, demographic covariates including age, sex, and WASI IQ scores were forced into the equation. Then, the component scores were entered using a stepwise forward conditional entry ($p = .05$ for entry, $p \geq .10$ for removal). The initial entry of the demographic covariates did not significantly add to prediction of injury group membership (Nagelkerke $R^2 = .039$, p = .246). However, stepwise entry of the neurocognitive component scores led to progressive increases in the proportion of variance accounted for. The optimal prediction was achieved upon entry of four neurocognitive component scores (Nagelkerke $R^2 = .524$, $p < .0000001$). Table 19 shows the results of the logistic regression at each step. As evident in Table 19, after accounting for demographic factors of age, sex, and IQ, the most effective model included 1) higher scores on the component assessing PCS symptoms and emotional disturbance, 2) higher aggression, 3) higher sleep disturbance (i.e., labeled as "sleep quality), and fewer cognitive errors. The best

Table 19. Results of stepwise logistic regression predicting injury group status (HC vs. mTBI) from the 13 component scores. Left: After including demographics, model selection showed that injury group was predicted most effectively by a combination of four component scores, including post-concussive emotional symptoms, aggression, sleep disruption, and cognitive errors. Right Top: all models were significant. Right Middle: pseudo R-square values are provided for each model. Right Bottom: The classification table shows that the model in Step 4 correctly classified 87% of cases (88% true positives; 83.3% true negatives).

Stepwise Logistic Regression

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Age	.000	.032	.000	1	.994	1.000	.940	1.064
	Sex	-.222	.450	.243	1	.622	.801	.332	1.934
	IQ	-.045	.020	4.774	1	.029	.956	.919	.995
	F3 PCS Emotion	1.809	.401	20.361	1	.000	6.103	2.782	13.389
	Constant	6.935	2.725	6.477	1	.011	1028.077		
Step 2[b]	Age	-.012	.037	.105	1	.746	.988	.919	1.063
	Sex	-.402	.509	.622	1	.430	.669	.247	1.816
	IQ	-.048	.023	4.314	1	.038	.953	.910	.997
	F3 PCS Emotion	2.187	.488	20.080	1	.000	8.911	3.423	23.194
	F6 Sleep Quality	1.366	.352	15.039	1	.000	3.919	1.965	7.816
	Constant	8.497	3.156	7.248	1	.007	4898.079		
Step 3[c]	Age	.012	.038	.103	1	.748	1.012	.939	1.092
	Sex	.106	.560	.036	1	.849	1.112	.371	3.332
	IQ	-.047	.024	3.861	1	.049	.955	.911	1.000
	F3 PCS Emotion	2.489	.562	19.627	1	.000	12.054	4.007	36.261
	F4 Aggression	.717	.336	4.549	1	.033	2.049	1.060	3.962
	F6 Sleep_Quality	1.296	.348	13.876	1	.000	3.655	1.848	7.229
	Constant	7.051	3.253	4.700	1	.030	1154.024		
Step 4[d]	Age	.008	.039	.044	1	.834	1.008	.934	1.088
	Sex	.013	.579	.000	1	.982	1.013	.326	3.148
	IQ	-.054	.025	4.752	1	.029	.948	.903	.995
	F3 PCS Emotion	2.685	.600	20.030	1	.000	14.656	4.522	47.497
	F4 Aggression	.689	.342	4.065	1	.044	1.992	1.019	3.892
	F6 Sleep Quality	1.277	.347	13.548	1	.000	3.585	1.816	7.076
	F9 Cognitive Errors	-.600	.299	4.027	1	.045	.549	.305	.986
	Constant	8.100	3.418	5.616	1	.018	3293.761		

a. Variable(s) entered on step 1: F3 PCS Emotion.
b. Variable(s) entered on step 2: F6 Sleep Quality.
c. Variable(s) entered on step 3: F4 Aggression.
d. Variable(s) entered on step 4: F9 Cognitive Errors.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	33.304	1	.000
	Block	33.304	1	.000
	Model	37.455	4	.000
Step 2	Step	21.585	1	.000
	Block	54.889	2	.000
	Model	59.040	5	.000
Step 3	Step	5.212	1	.022
	Block	60.101	3	.000
	Model	64.252	6	.000
Step 4	Step	4.977	1	.026
	Block	65.078	4	.000
	Model	69.229	7	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	133.665[a]	.208	.317
2	112.080[b]	.307	.469
3	106.868[b]	.329	.503
4	101.891[b]	.349	.534

Classification Table[a]

			Predicted is_mTBI 0	1	Percentage Correct
Step 1	Observed is_mTBI	0	26	10	72.2
		1	23	102	81.6
	Overall Percentage				79.5
Step 2	is_mTBI	0	28	8	77.8
		1	21	104	83.2
	Overall Percentage				82.0
Step 3	is_mTBI	0	29	7	80.6
		1	18	107	85.6
	Overall Percentage				84.5
Step 4	is_mTBI	0	30	6	83.3
		1	15	110	88.0
	Overall Percentage				87.0

a. The cut value is .700

model correctly classified 87% of participants, with 88% sensitivity and 83.3% specificity. The positive predictive value was 94.8% and the negative predictive value was 66.7%.

Finally, as described above in Section 3D, we also extracted a single component from the PCA of all neurocognitive summary measures. This Global Neurocognitive Factor (GNF) is used as an overall assessment of general functioning across all assessed domains. First we compared the HC and mTBI participants directly and found that the HC group was significantly higher on this global factor, $F(1,156) = 12.98$, $p = .0004$. To explore this further, we carried out a one-way ANOVA showing that scores on this global factor were significantly higher among the HC group and were significantly reduced among those with mTBI in all TSI groups separately, $F(5,152) = 3.80$, $p = .003$ (see Figure 10). Overall, the HC group far out performed the mTBI group (left side of Figure 10) and when all groups were compared, it is clear that the HC group was superior to each of the TSI groups. Further, the worst performance was evident in the 2W group compared to all other TSI groups (see right side of Figure 10).

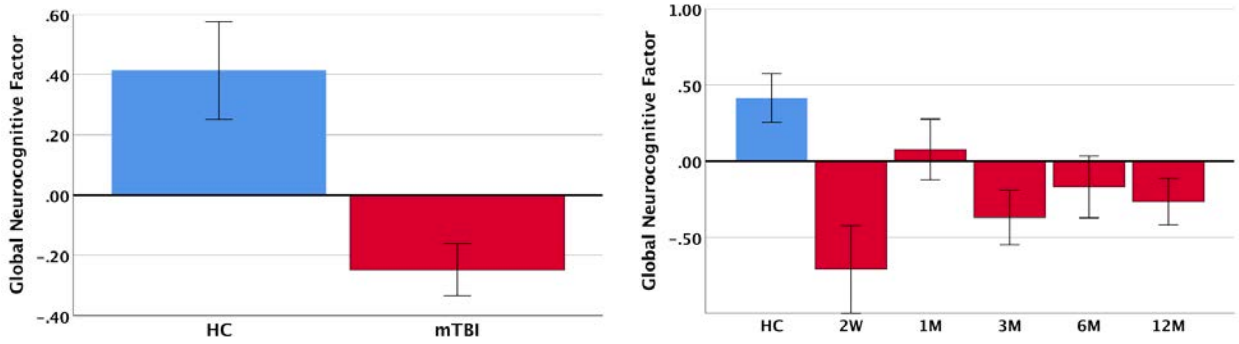


Figure 10. Comparison of the General Neurocognitive Function (GNF) score between healthy controls (HC) and all mild traumatic brain injury (mTBI) participants (left) and a group-wise ANOVA showing mean performance on the GNF across all time-since-injury groups.

Conclusion: *Based on the preceding analyses, the primary hypothesis is supported. Individuals with a history of mTBI at any stage generally performed more poorly on neuropsychological outcomes compared to the HC group.*

Hypothesis 8: Time since injury will be associated with neuropsychological performance such that neuropsychological deficits will be more pronounced at earlier than later mild TBI recovery stages.

As described in section 3.D above, the neuropsychological outcome measures were initially reduced to 13 neurocognitive component scores using PCA. For continuity with the neuroimaging data, the present sample only included participants collected at the UA. Independent variables for this set of analyses included the number of months since the index mTBI, and time-since-injury (TSI) group status (**HC**: $n = 36$; [15 male, 21 female], age $M = 24.3$, $SD = 5.9$; **2W**: $n = 11$; [5 male, 6 female], age $M = 25.6$, $SD = 8.2$; **1M**: $n = 24$; [8 male, 16 female], age $M = 25.2$, $SD = 8.5$; **3M**: $n = 29$; [12 male, 17 female], age $M = 26.3$, $SD = 7.8$; **6M**:

n = 22; [5 male, 17 female], age M = 23.4, SD = 5.9; **12M**: n = 39; [15 male, 24 female], age M = 23.9, SD = 6.9).

Group Differences: First, a multivariate analysis of covariance (MANCOVA) was conducted comparing the injury status groups as the independent variable (HC + 5 TSI groups) for the 13 neurocognitive component scores as dependent variables. Covariates included participant sex, age, and full scale WASI IQ. All three covariates accounted for significant variance ($p < .001$). There was a statistically significant main effect of HC/TSI group for the combined dependent variables, $F(65, 665.56) = 1.89$, $p = .00007$; Wilk's $\Lambda = 0.449$, partial $\eta^2 = .148$, suggesting a large effect size. Univariate analysis of covariance (ANCOVA) showed that three of the neurocognitive components were significantly different across TSI groups. As shown in Table 20, this included Component 3, PCS & Emotional Disturbance, Component 6, Sleep Quality (Disturbance), and Component 10, Daily Functioning (p-values < .001).

Table 20. The table shows the univariate main effect of time-since-injury for each of the 13 neurocognitive component scores.

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
TSI_group	F1_Verbal_Memory	1.882	5	.376	.409	.842	.013
	F2_Atten_Exec_Control	1.987	5	.397	.421	.833	.014
	F3_PCS_Emotion	**26.453**	**5**	**5.291**	**6.406**	**.000**	**.174**
	F4_Aggression	8.074	5	1.615	1.787	.119	.056
	F5_Visual_Memory	5.358	5	1.072	1.108	.359	.035
	F6_Sleep_Quality	**25.802**	**5**	**5.160**	**5.711**	**.000**	**.158**
	F7_Motor_Speed	3.309	5	.662	.672	.645	.022
	F8_Vigilance	2.719	5	.544	.550	.738	.018
	F9_Cognitive_Errors	4.339	5	.868	.822	.536	.026
	F10_Daily_Functioning	**27.768**	**5**	**5.554**	**5.517**	**.000**	**.154**
	F11_Concept_Formation	2.932	5	.586	.609	.693	.020
	F12_Impulsivity	3.236	5	.647	.670	.647	.022
	F13_Processing_Speed	4.411	5	.882	.991	.425	.032

Figure 11 shows the mean scores (adjusted for covariates) for the HC and five TSI groups for each of the 13 neurocognitive components extracted from the comprehensive assessment battery.

This analysis suggested that the pattern of results was more complex than initially hypothesized. Most component scores did not differ significantly across TSI groups, with the exception of emotional disturbance, sleep disturbance, and daily functioning. For emotional disturbance, the pattern was generally consistent with the hypothesis, suggesting that PCS symptoms and emotional/psychiatric symptoms were most pronounced during the first four weeks following the injury and were less at later time points. However, in contrast to the hypothesis, we found that sleep disturbance was present for all mTBI groups compared to HCs, but was particularly worse for the 12M post-injury group relative to all others. Finally, for daily functioning, we found that the only group to show significant differences from the others was the 2W post-injury group. Our data suggest that individuals are still experiencing some difficulty in independent daily functioning that leads to perceptions of physical, cognitive, mobility, and/or occupational limitations. However, individuals assessed at 1M and beyond did not differ from the HC group.

Overall, this set of analyses suggests that most neurocognitive symptom components are not significantly impaired by mTBI, but that many

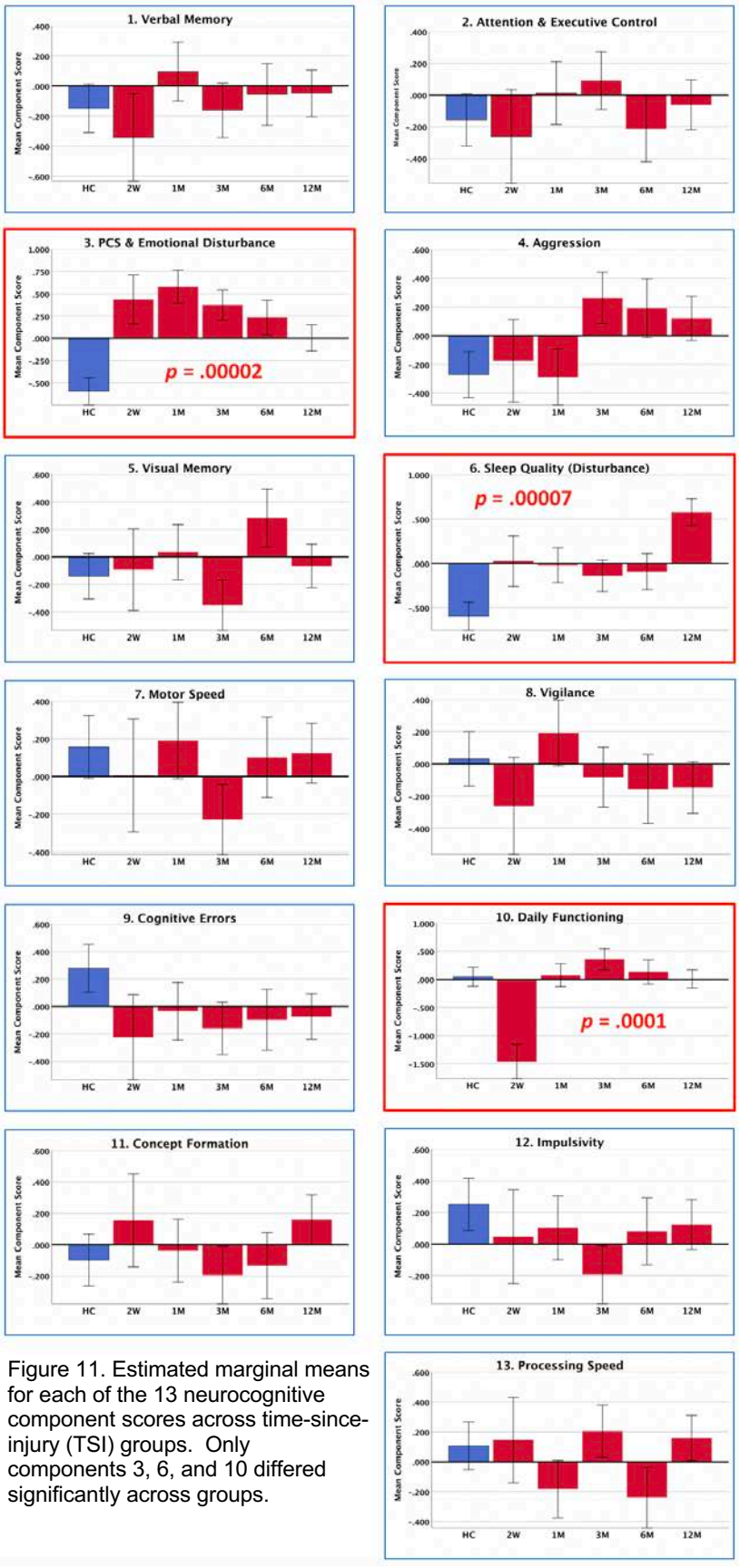


Figure 11. Estimated marginal means for each of the 13 neurocognitive component scores across time-since-injury (TSI) groups. Only components 3, 6, and 10 differed significantly across groups.

individuals may experience limitations on normal daily functioning during the first two weeks after an injury, which may be accompanied by more prolonged increase in self-perceived post-concussive symptoms and emotional disturbances that may be present for several months following the injury. On the other hand, all mTBI groups showed some evidence of sleep disruption relative to HCs, but this was particularly evident among individuals at chronic stage of the injury (i.e., 12 months post-injury).

Conclusion: *The preceding analyses support the hypothesis that globally, neuropsychological performance tends to be worse in the first two weeks following the injury and is less severe when assessed thereafter. Nonetheless, there is evidence of increased sleep-related problems when injured individuals are assessed at 12-months post-injury.*

Hypothesis 9: Time since injury will be associated with DTI metrics with more pronounced abnormalities at earlier than later mild TBI recovery stages.

As described in section 3.C.I, diffusion metrics were calculated using standard processing procedures in FSL. Whole-brain and ROI approaches were used to compare FA, MD, RD, and AD at discreet times in the recovery trajectory. As mentioned previously, the analyses outlined in this section only included participants collected at the University of Arizona. Furthermore, to address the association between DTI metrics and time since injury, the analyses in this section focused only on participants with a reported mild TBI. Diffusion data were reviewed for normality and the presence of outliers. Five participants exhibited DTI metrics at least 3 SD outside the mean and were excluded from further analysis. Results in this section are based on a sample of n =108 (**2W**: n = 11 total [5 male; 6 female], age M = 25.64, SD = 8.19; **1M**: n = 19 total [6 male; 13 female], age M = 25.89, SD = 9.19; **3M**: n = 25 total [10 male; 15 female], age M = 25.88, SD = 7.33; **6M**: n = 20 total [5 male; 15 female], age M = 23.05, SD = 7.30; **12M**: n = 33 total [15 male; 18 female], age M = 23.85, SD = 7.30).

Time since injury and DTI: Partial correlations were conducted to identify the association between time since injury (measured in days) and white matter integrity (FA, MD, RD, AS). Participant age and sex were entered as covariates in the correlations. Given the directionality of the hypothesis, analyses were conducted and deemed statistically significant at $p < .05$, 1-tailed. Mean FA, MD, RD, and AD from whole-brain processing was included in the analysis, as well as diffusion metrics from the 13 axonal pathways selected *a-priori*, (CING L, CING R, aIC L, aIC R, pIC L, pIC R, EC L, EC R, aCR L, aCR R, SLF L, SLF R, CC).

Whole-brain analysis

Summary statistics for whole-brain diffusion metrics are reported for the five MTBI groups in Table 21. Using this approach, we found no significant associations between time since injury and whole-brain diffusion metrics (FA: r = -0.001, p = .49; MD: r = -0.08, p = .20; RD: r = -07, p = .23; AD: r = -0.10, p = .16).

Table 21. Whole-brain diffusion metrics

Descriptive Statistics

	FA		MD		RD		AD	
TSI_group	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
2W	.22640009	.008020269	.00102864	.000044376	.00092082	.000045677	.00124464	.000041984
1M	.22611784	.005433208	.00103384	.000034967	.00092589	.000034657	.00124979	.000036035
3M	.22579676	.005681075	.00104676	.000048198	.00093832	.000048285	.00126312	.000048255
6M	.22654290	.007775491	.00102865	.000044140	.00092065	.000045296	.00124475	.000041916
12M	.22629652	.005781849	.00102545	.000042622	.00091803	.000042580	.00124033	.000043396

Region-of-interest

When comparing the association between TSI and FA, there was only one significant association. Lower FA in the right cingulum bundle was associated with earlier recovery, whereas higher FA was associated with later recovery stage (r = 0.17, p = .04). This finding, however, did not remain statistically significant after correcting for multiple comparisons.

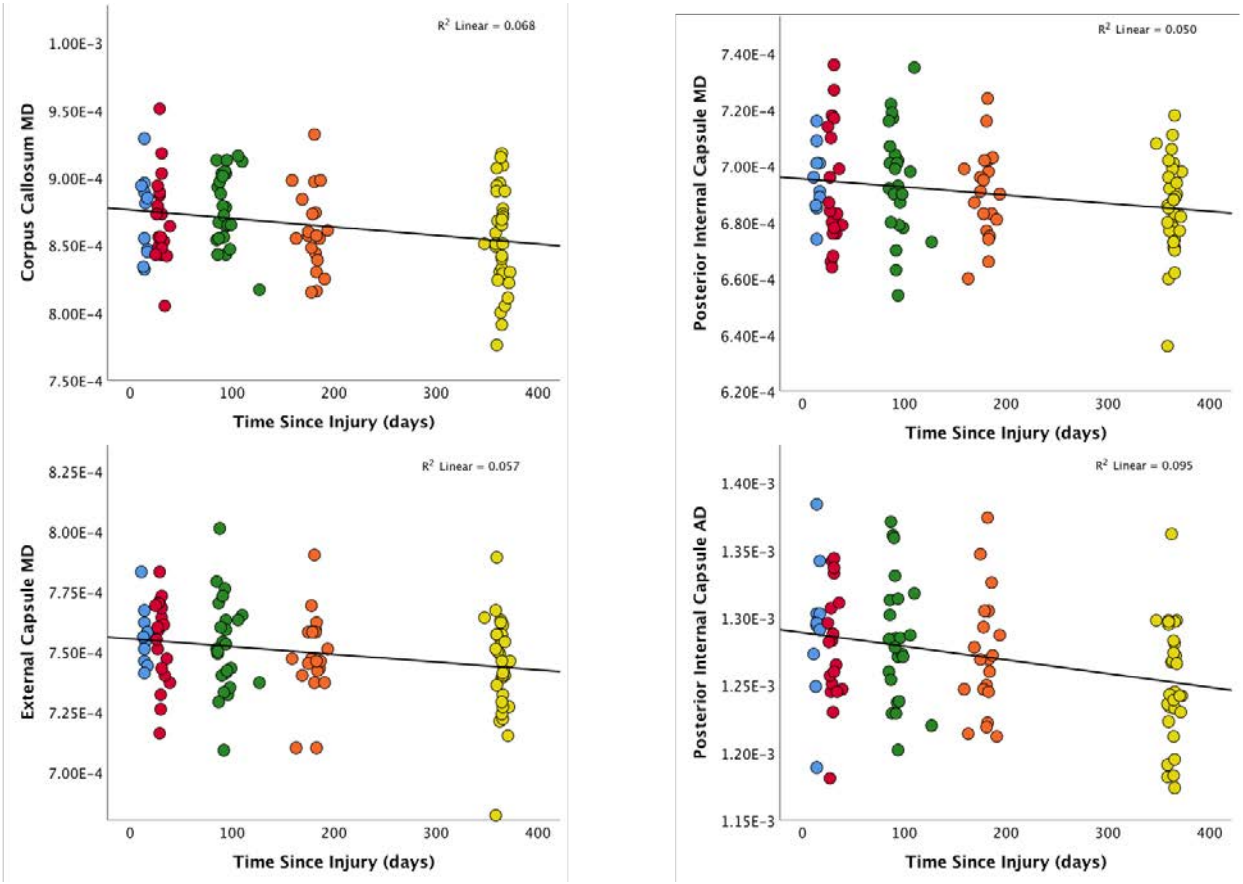


Figure 12. Associations between DTI metrics and time since injury for participants with MTBI. Early stages post-injury were associated with higher MD and AD, whereas later stages post injury were associated with lower MD and AD in targeted white mater pathways.

As shown in Figure 12, significant associations between time since injury and measures of MD or AD were found for a select number of pathways. After controlling for multiple comparisons,

time since injury was associated with MD in the CC, left pIC, and left EC. In particular, we found that higher MD in the corpus callosum (r = -0.29, p = .001; Bonferroni-corrected), left posterior internal capsule (left: r = -0.27, p = .003; Bonferroni-corrected), and left external capsule (r = -0.27, p = .003; Bonferroni-corrected) were all significantly correlated with earlier recovery times and lower MD in those pathways was associated with more chronic recovery stages. Time since injury was associated with AD of the left pIC (r = -0.34, p < .0001), with higher AD found at earlier recovery stages and lower AD found in sub-acute and chronic stages. Associations between RD of targeted pathways and time since injury were not significant after correcting for multiple comparisons.

Conclusion. *The hypothesis is supported by findings from the present analyses. Time since injury was associated with white matter characteristics, as measured by MD and AD, which higher values found during earlier stages post-injury and lower values found during later stages post injury.*

Specific Aim 3: Previous research has reported mild TBI to disturb both the number and strength of connections of the Default Mode Network (DMN) and the Task Positive Network (TPN) at the acute and subacute recovery stages (i.e., less than four weeks post-injury) relative to controls. However, no research has been conducted at more than four weeks post-injury, and little research has related functional connectivity to neuropsychological performance and DTI metrics. We will examine resting state functional connectivity, and its concordance with DTI findings, across multiple stages of recovery.

Hypothesis 10: Independent of recovery stage, mild TBI will be associated with fewer and less strong connectivity in the DMN, but more and stronger connectivity TPN relative to healthy controls.

As described in section 3.C.II, neuroimaging data were preprocessed and imported to CONN to compare resting state functional connectivity between the groups. To test this hypothesis, the sample was divided into two groups based on concussion status (HC: n = 35 total [15 male, 20 female], age M = 24.40, SD = 5.95; mTBI: n = 121 total [43 male; 78 female], age M = 24.76, SD = 7.48).

Group Differences: Second-level, seed-to-voxel analyses were performed to create statistical parametric maps representing functional connectivity between a seed ROI and the rest of the brain. Seed-to-voxel analyses were conducted for the 7 ROIs shown in Figure 13. One-way analyses of covariate (ANCOVAs) were used to investigate the main effect of group on functional connectivity, with participant age and sex included as covariates in the models. Statistical parametric maps for each seed ROI were defined using thresholds of two-tailed, voxel-wise p < .01 and cluster-level p < .05, false discovery rate (FDR) corrected, to identify clusters associated with significantly stronger functional

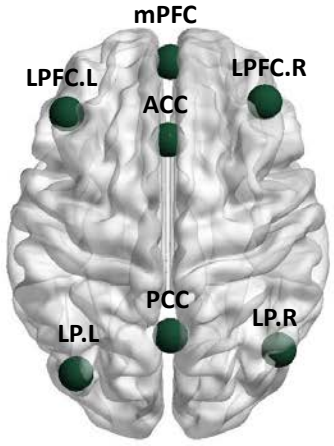


Figure 13. Seed regions used in seed-to voxel analyses.

connectivity (positive or negative) to each seed region for HCs compared to mild TBI participants.

Medial prefrontal cortex (mPFC): Using the mPFC as the seed region, statistically significant differences in functional connectivity were found in anterior and posterior regions HC and mTBI groups. HCs exhibited significantly greater positive functional connectivity between the mPFC and voxels in bilateral frontal poles, and significantly greater negative functional connectivity (i.e. anticorrelated) between the mPFC and voxels of the right lateral occipital cortex and right precuneus, compared to mTBI participants (see Figure 14).

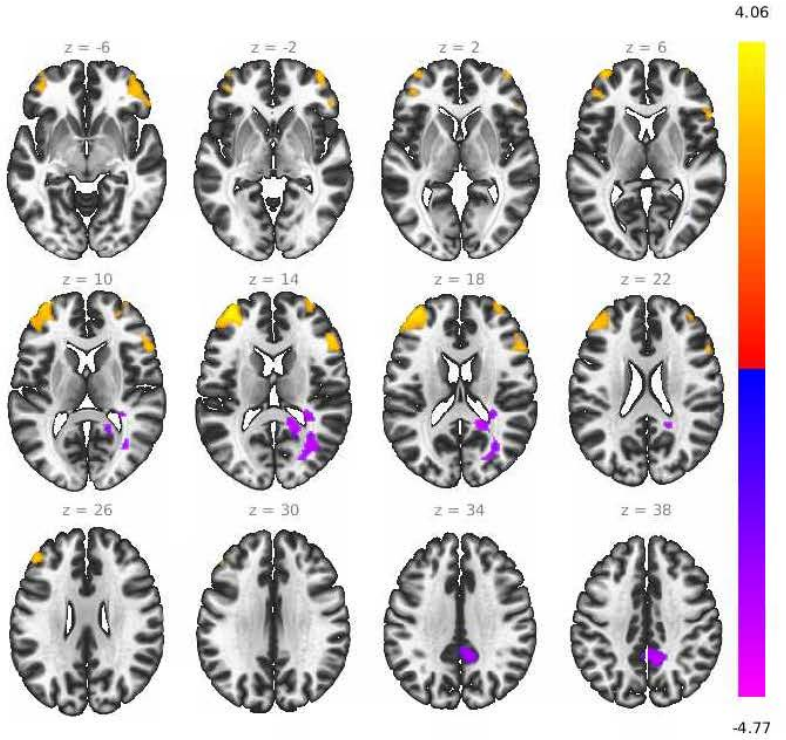


Figure 14. mPFC seed-to-voxel connectivity for contrast healthy controls > mild TBI. Overlay shows significant clusters at thresholds of two-tailed, voxel-wise $p < .01$ and cluster-level $p < .05$, false discovery rate (FDR) corrected.

Posterior Cingulate Cortex (PCC): When the PCC was used as the seed region, HCs, compared to the MTBI group, exhibited significantly greater positive functional connectivity between the PCC and 4 regions including the left lateral occipital cortex, right inferior frontal gyrus (pars triangularis), right middle temporal gyrus, and right lateral occipital cortex (Figure 15A).

Anterior Cingulate Cortex (ACC): Seed-to-voxel connectivity from the ACC seed region to the right frontal pole was significantly higher in HCs, compared to the MTBI group (Figure 15B).

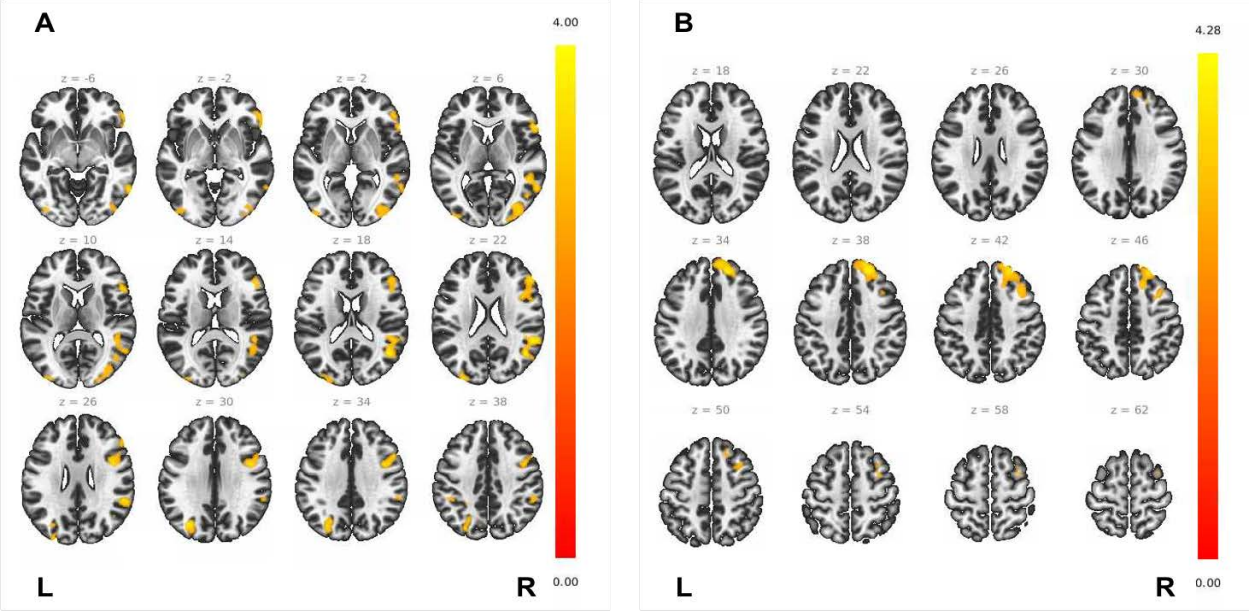


Figure 15. Seed-to-voxel connectivity with PCC (left panel A) and ACC (right panel B) seed regions for contrast HC > mild TBI. Overlay shows significant clusters at thresholds of two-tailed, voxel-wise p < .01 and cluster-level p < .05, false discovery rate (FDR) corrected.

Lateral Prefrontal Cortex (LPFC): Differences in seed-to-voxel functional connectivity were found between HC and MTBI groups when using left and right LPFC as seed regions. HCs showed significantly greater positive functional connectivity between the left LPFC and the left paracingulate gyrus (Figure 16A), as well as between the right LPFC and the frontal medial cortex (Figure 16B), in contrast to the MTBI group.

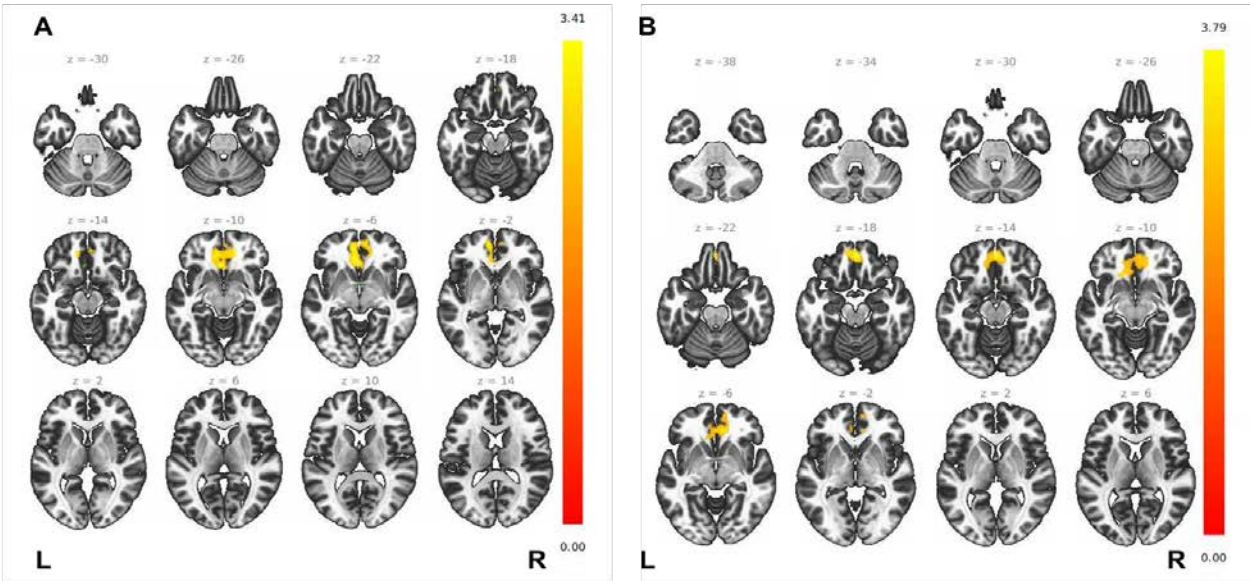


Figure 16. Seed-to-voxel connectivity with seed regions LPFC L (panel A) and LPFC R (panel B) for contrast HC > mild TBI. Overlay shows significant clusters at thresholds of two-tailed, voxel-wise p < .01 and cluster-level p < .05, false discovery rate (FDR) corrected.

Lateral Parietal Cortex (LP): There were no significant between-group differences in seed-to-voxel connectivity when using the left or right LP as a seed region.

As shown in Table 22, differences in seed-to-voxel connectivity between HC and MTBI groups was found when using seed regions spanning the default mode network (DMN) and task positivity network (TPN).

Table 22. Functional connectivity differences between HC and mild TBI participants.

Brain regions of peak coordinates	**Peak MNI Coordinates**			**Cluster size**	**p-FDR**
	X	**Y**	**Z**		
mPFC seed					
Frontal pole L	-36	54	16	913	0.002
Frontal pole R	42	44	-10	906	0.002
Inferior Precuneus R	18	-46	16	538	0.03
Superior Precuneus R	06	-50	44	434	0.04
PCC seed					
Lateral occipital cortex L	-48	-38	48	1170	0.0003
Inferior frontal gyrus R	44	04	28	1153	0.0003
Middle temporal gyrus R	46	-60	20	1106	0.0003
Lateral occipital cortex R	32	-78	06	509	0.02
ACC seed					
Frontal pole R	18	46	36	1200	0.0006
LPFC.L seed					
Paracingulate gyrus L	-08	50	-04	809	0.006
LPFC.R seed					
Frontal medial cortex	02	48	-16	865	0.007

Conclusion: *Results from the analyses conducted in the present study partially support the hypothesis. In support of the hypothesis, MTBI was associated with weaker functional connectivity in the DMN compared to HC. Contrary to the hypothesis, we also found weaker functional connectivity in the TPN for MTBI compared to HCs. These findings suggest widespread reduction in functional connectivity following mTBI.*

Hypothesis 11: Time since injury will be associated with functional connectivity in DMN and TPN in such that connectivity abnormalities relative to controls will be more pronounced at earlier than later recovery stages following mild TBI.

As described in section 3.C.II, neuroimaging data were preprocessed and imported to CONN to compare resting state functional connectivity between the groups and included only participants collected at the UA. To test this hypothesis, the sample was divided into one HC group, and five mild TBI groups based on time-since-injury (HC: n = 35 total [15 male, 20 female], age M = 24.40, SD = 5.95; **2W**: n = 10 total [4 male; 6 female], age M = 25.50, SD = 8.62; **1M**: n = 23

total [7 male; 16 female], age *M* = 25.30, *SD* = 8.70; **3M**: *n* = 28 total [12 male; 16 female], age *M* = 26.54, *SD* = 7.86; **6M**: *n* = 22 total [5 male; 17 female], age *M* = 23.36, *SD* = 5.89 **12M**: *n* = 38 total [15 male; 23 female], age *M* = 23.74, *SD* = 6.97).

Group Differences: Second-level, seed-to-voxel analyses were performed to create statistical parametric maps representing functional connectivity between a seed ROI and the rest of the brain. Seed-to-voxel analyses were conducted using the same 7 ROIs mentioned above (see Figure 13 above). One-way analyses of covariate (ANCOVAs) were used to investigate the main effect of group on functional connectivity, with participant age and sex included as covariates in the models. Statistical parametric maps for each seed ROI were defined using thresholds of two-tailed, voxel-wise $p < .01$ and cluster-level $p < .05$, false discovery rate (FDR) corrected, to identify areas of the brain associated with significantly stronger functional connectivity (positive or negative) to each seed region for HCs compared to mild TBI groups (2W, 1M, 3M, 6M and 12M).

2-Week Mild TBI (2W). We found significant differences in functional connectivity between HCs and mild TBI participants in the acute recovery stage (i.e. 2W). As shown in Figure 17A, HCs had significantly stronger negative connectivity (i.e., anticorrelated) between the ACC and right precentral/postcentral gyrus, compared to the 2W MTBI group. In addition, HCs had significantly stronger positive functional connectivity between the left LPFC and regions of the subcallosal cortex, left paracingulate gyrus, and posterior cingulate gyrus (Figure 17B), and between the right LPFC and bilateral putamen (Figure 17C).

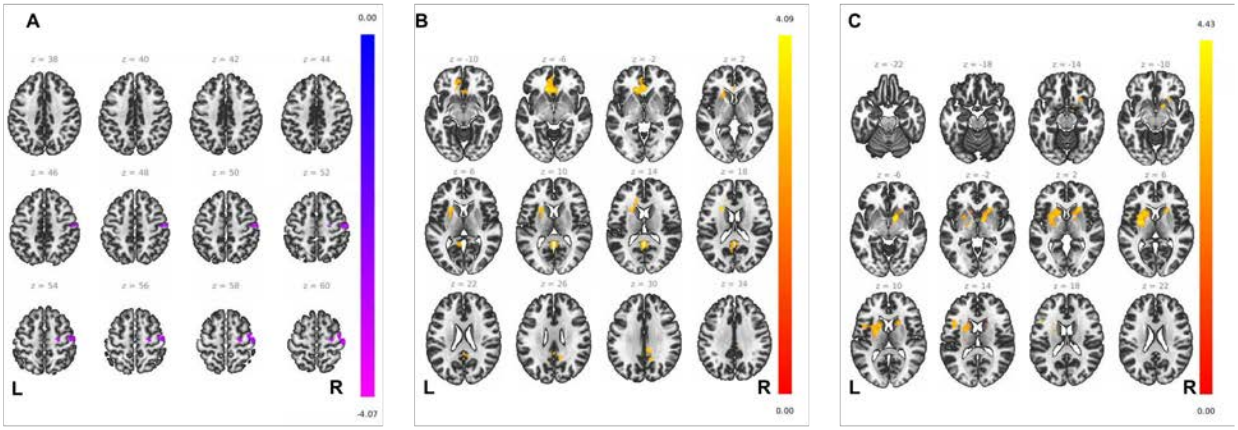


Figure 17. Differences in functional connectivity between HC and 2W mild TBI groups. Seed-to-voxel connectivity with seed regions ACC (panel A), LPFC L (panel B) and LPFC R (panel C) for contrast HC > 2W TBI. Overlay shows significant clusters at thresholds of two-tailed, voxel-wise $p < .01$ and cluster-level $p < .05$, false discovery rate (FDR) corrected

1-Month Mild TBI (1M). When comparing HCs and 1M MTBI groups, HCs had significantly greater positive connectivity between the mPFC and regions of the left frontal and temporal poles, anterior cingulate gyrus, and right supramarginal gyrus, (Figure 18A) and between the PCC and regions of the precentral gyrus, bilateral inferior frontal gyrus, right frontal pole, and right supramarginal gyrus. (Figure 18B). HC showed significantly greater positive connectivity between the left LP seed region and right frontal pole (Figure 18C), as well as the right LP seed region and middle temporal gyrus (Figure 18D).

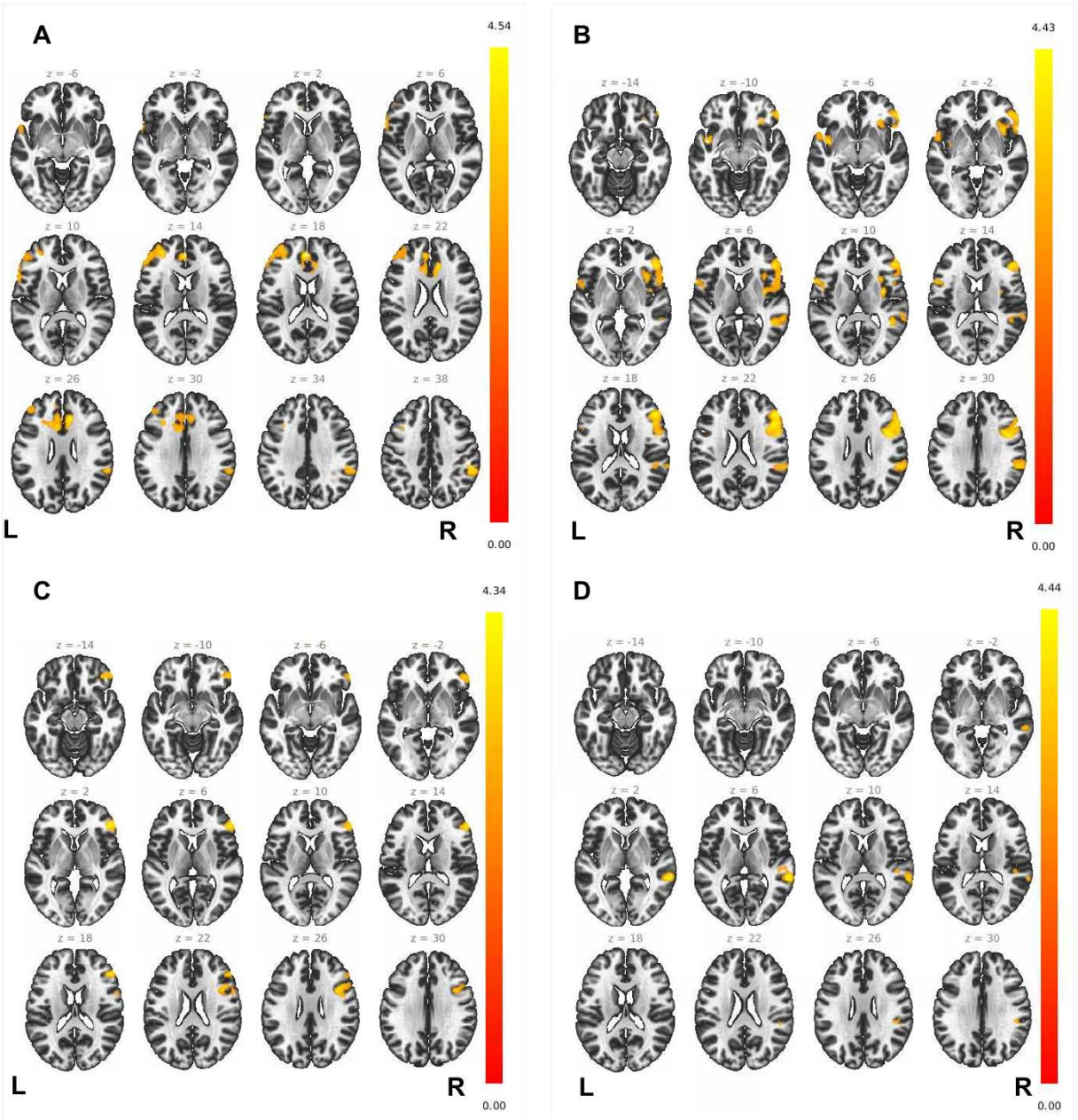


Figure 18. Greater functional connectivity in HC compared to 1M MTBI group. Seed-to-voxel connectivity with seed regions mPFC (panel A), PCC (panel B) and LP L (panel C) and LP R (panel D) for contrast HC > 2W TBI. Overlay shows significant clusters at thresholds of two-tailed, voxel-wise $p < .01$ and cluster-level $p < .05$, false discovery rate (FDR) corrected

3-Month Mild TBI (3M). HCs exhibited significantly greater seed-to-voxel connectivity from 5 of the 7 seed regions, when compared to the 3M MTBI group. Significantly stronger functional connectivity was found between the mPFC and regions of bilateral frontal poles, right inferior frontal gyrus, left occipital pole, and the frontal orbital cortex; between the PCC and bilateral occipital poles; between the ACC and right frontal pole; between the left LPFC and regions of the paracingulate gyrus (bilateral) and the anterior cingulate gyrus; and between the right PL seed region and right posterior superior temporal gyrus (see Table 23).

6-Month Mild TBI (6M). As shown in Table 23, functional connectivity differences between HCs and the 6M MTBI group were found in 4 of the 7 seed regions. HCs had significantly greater connectivity between the left LPFC and regions of the subcallosal/frontal medial cortex. In the HC groups, we found significantly stronger negative connectivity (anticorrelated) between the PCC and regions of the subcallosal cortex, frontal medial cortex, posterior cingulate gyrus, and precuneus, and significantly stronger positive connectivity between the PCC and the right inferior frontal gyrus and right middle frontal gyrus.

12-Month Mild TBI (12M). In HCs, compared to the 12M MTBI group, we found significantly stronger positive connectivity between the left LP and regions of the left precentral gyrus, left middle frontal gyrus, right posterior supramarginal gyrus, and right superior parietal lobule. PCC and lateral occipital cortex (bilateral), left occipital pole, left occipital fusiform gyrus, right temporal occipital fusiform cortex, bilateral precentral gyrus, right superior parietal lobule, right supramarginal gyrus, and right inferior frontal gyrus. When using the ACC seed region, HCs exhibited significantly greater connectivity to bilateral inferior lateral occipital cortices, compared to the 12M MTBI group (see Table 23).

Table 23. Functional connectivity differences between HCs and time since injury TBI groups.

	Peak MNI Coordinates			**Cluster size**	**p-FDR**
	X	**Y**	**Z**		
Healthy Control > 2-week mild TBI					
ACC seed					
Precentral gyrus R	46	-06	62	839	0.007
LPFC.L seed					
Subcallosal cortex	-12	28	-06	986	0.002
Posterior cingulate gyrus	-02	-50	12	553	0.03
LPFC.R seed					
Putamen L	-28	-04	06	983	0.002
Putamen R	12	02	-06	579	0.02
Healthy Control > 1-month mild TBI					
mPFC seed					
Frontal pole L	-30	46	14	1072	0.008
Anterior cingulate gyrus	-04	44	18	1059	0.008
Posterior supramarginal gyrus R	54	-36	40	554	0.02
LP.L seed					
Frontal pole R	48	36	02	1241	0.0005
LP.R					
Middle temporal gyrus R	60	-38	04	584	0.04
PCC seed					
Precentral gyrus R	44	04	28	3271	< 0.0001
Posterior supramarginal gyrus R	46	-44	08	1113	0.0004
Inferior frontal gyrus L	-40	00	-06	594	0.01
Healthy Control > 3-month mild TBI					
mPFC seed					
Frontal pole R	20	44	-16	706	0.01
Occipital pole L	-26	-104	04	661	0.01
Frontal pole L	-44	46	18	511	0.03
Frontal orbital cortex R	46	18	-18	461	0.04
LP.R seed					
Posterior superior temporal gyrus R	42	-28	04	571	0.04
PCC seed					
Occipital pole R	50	-84	02	679	0.02
Occipital pole L	-26	-104	02	552	0.03
ACC seed					
Frontal pole R	28	42	38	965	0.004
LPFC.L seed					
Paracingulate gyrus L	-10	50	-02	553	0.03
Anterior cingulate gyrus	12	52	18	552	0.03
Healthy Control > 6-month mild TBI					
mPFC seed					
Precuneus cortex	08	-50	44	641	0.02
PCC seed					
Subcallosal cortex	04	14	-16	723	0.01
Inferior frontal gyrus R	50	36	22	703	0.01
Posterior cingulate gyrus	-04	-48	16	546	0.02
ACC seed					
Anterior cingulate cortex	-06	50	12	573	0.04
LPFC.L seed					
Subcallosal cortex	-06	28	-10	652	0.03
Healthy Control > 12-month mild TBI					
mPFC seed					
Precuneus	20	-48	16	862	0.005
LP.L seed					
Precentral gyrus L	-34	06	36	607	0.04
Posterior supramarginal gyrus	44	-44	42	522	0.05
PCC seed					
Inferior lateral occipital cortex L	-14	-88	04	2858	<0.0001
Inferior lateral occipital cortex R	34	-52	-14	2135	<0.0001
Precentral gyrus L	-26	00	46	856	0.001
Superior parietal lobule R	30	-24	44	599	0.01
Precentral gyrus R	44	04	34	442	0.03
ACC seed					
Lateral occipital cortex L	-26	-72	-02	889	0.005
Lateral occipital cortex R	34	-72	08	558	0.03

Conclusion. *Based on the preceding analyses, the hypothesis was supported. Functional connectivity was weaker in MTBI groups compared to HCs and these differences were more widespread across DMN and TPN regions in later recovery stages. In the acute stage of recovery (i.e., 2W), only 3 seed regions connecting 5 clusters showed weaker connectivity compared to HCs. However, by the chronic recovery stage (i.e., 12M), 4 seed regions connecting 10 clusters showed weaker connectivity. Large-scale disruptions in functional connectivity appear to differ based on time since injury, and may have implications for functional outcome measures following mild TBI.*

Hypothesis 12: Functional connectivity within the DMN and TPN will predict neuropsychological performance.

It was predicted that functional connectivity would predict performance on neurocognitive outcome measures. Therefore, we assessed the associations between each of the 11 significant functional connections and the 13 neurocognitive factor scores. In section 3.C.II, we described the initial preprocessing steps for functional connectivity using the CONN program. The outcomes for this hypothesis are based on the same sample of participants from the UA described earlier (HC: n = 35 total [15 male, 20 female], age M = 24.40, SD = 5.95; mTBI: n = 121 total [43 male; 78 female], age M = 24.76, SD = 7.48).

To predict neuropsychological performance from brain connectivity, we conducted a series of stepwise linear regression analyses with the 11 functional brain connections (extracted as Fisher's z-transformed correlations between regions) as predictors and each of the 13 neurocognitive factor scores separately. Each neurocognitive factor will be presented below for the full sample (HC + all mTBI participants), followed by a breakdown of separate analyses by injury group (i.e., HC, 2W, 1M, 3M, 6M, 12M).

F1—Verbal Memory

Total Sample: There were no significant predictors of verbal memory performance when the sample as a whole was considered.

HC: For the HC group only, there were no significant predictors of verbal memory performance.

2W: For the 2W group only, one predictor emerged as highly significant (R = .932, R^2 = .869, F = 53.12, p = .00009) and was retained in the model. Overall, greater positive connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* was strongly associated with greater verbal memory in the 2W group (β = .932, t = 7.29, p = .00009).

1M: For the 1M group only, one predictor emerged as significant (R = .419, R^2 = .176, F = 4.47, p = .047) and was retained in the model. Overall, greater positive connectivity between the *PCC (seed)* and *Right Lateral Occipital Cortex* was associated with greater verbal memory in the 1M group (β = .419, t = 2.12, p = .047).

3M: For the 3M group only, there were no significant predictors of verbal memory performance.

6M: For the 6M group only, there were no significant predictors of verbal memory performance.

12M: For the 12M group only, there were no significant predictors of verbal memory performance.

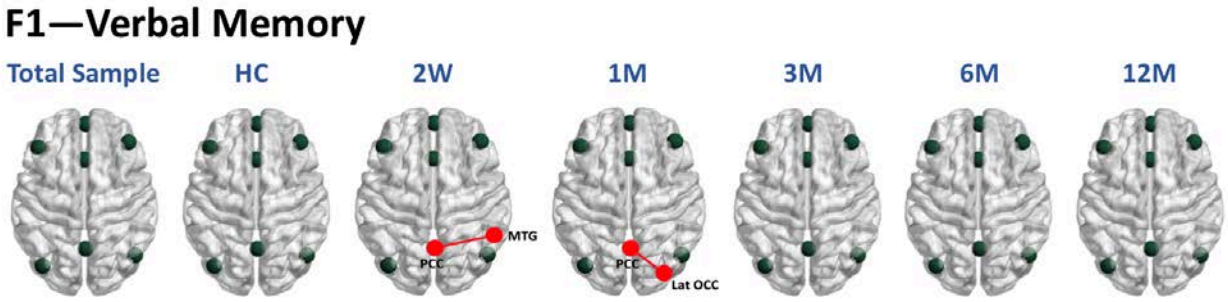


Figure 19. Functional connectivity correlated with Verbal Memory. Red indicates positive connectivity and blue indicates negative (anticorrelated) connectivity.

F2—Attention/Executive Function

Total Sample: For the Total Sample, one predictor emerged as significant (R = .18, R^2 = .033, F = 5.18, p = .024) and was retained in the model. Overall, negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Precuneus (inferior)* was associated with greater attention and executive control in the Total Sample (β = -.18, t = -2.28, p = .024).

HC: For the HC group only, there were no significant predictors of Attention/Executive Function performance.

2W: For the 2W group only, there were no significant predictors of Attention/Executive Function performance.

1M: For the 1M group only, one predictor emerged as significant (R = .457, R^2 = .209, F = 5.56, p = .028) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Lateral Occipital Cortex* was associated with greater attention and executive control in the 1M group (β = -.457, t = -2.36, p = .028).

3M: For the 3M group only, there were no significant predictors of Attention/Executive Function performance.

6M: For the 6M group only, two predictors emerged as significant (R = .70, R^2 = .490, F = 9.12, p = .002) and were retained in the model. Overall, a combination of greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.601, t = -3.66, p = .002) and greater negative (anticorrelated) connectivity between the *Left*

LPFC (seed) and *Left Paracingulate Cortex* (β = -.403, t = -2.54, p = .024) was associated with greater attention and executive control in the 6M group.

12M: For the 12M group only, two predictors emerged as significant (R = .499, R^2 = .249, F = 5.80, p = .007) and were retained in the model. Overall, a combination of greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = -.467, t = -3.09, p = .004) and greater positive connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = .324, t = 2.15, p = .039) was associated with greater attention and executive control in the 6M group.

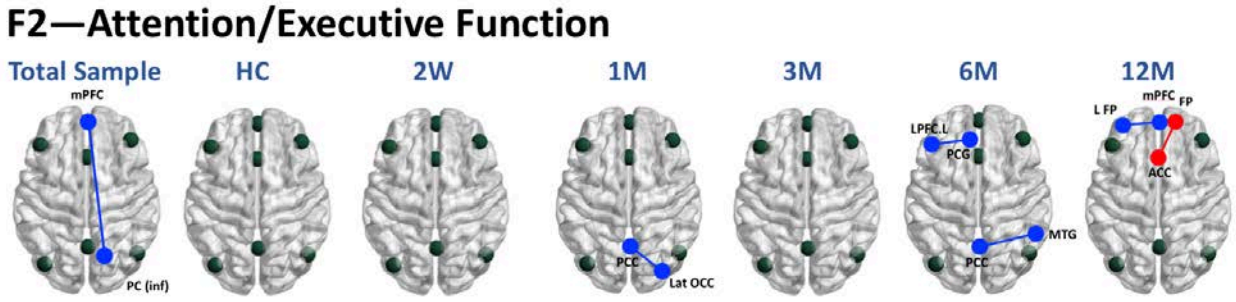


Figure 20. Functional connectivity correlated with Attention/Executive Function. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F3—Post-Concussion Syndrome (PCS)/Emotional Disturbance

Total Sample: For the Total Sample, one predictor emerged as significant (R = .193, R^2 = .037, F = 5.93, p = .016) and was retained in the model. Overall, negative (anticorrelated) connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* was associated with worse PCS/emotional symptom severity in the Total Sample (β = -.19, t = -2.44, p = .016).

HC: For the HC group, there were no significant predictors of PCS/emotional disturbance.

2W: For the 2W group, two predictors emerged as highly significant (R = .872, R^2 = .562, F = 11.15, p = .007) and were retained in the model. Overall, a linear combination of greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.525, t = -2.54, p = .039) and greater positive connectivity between *mPFC* and *Right Precuneus (superior)* (β = .50, t = 2.42, p = .046) was associated with worse PCS/emotional symptom severity at 2W.

1M: For the 1M group, there were no significant predictors of PCS/emotional disturbance.

3M: For the 3M group, there were no significant predictors of PCS/emotional disturbance.

6M: For the 6M group, there were no significant predictors of PCS/emotional disturbance.

12M: For the 12M group, two predictors emerged as significant (R = .49, R^2 = .24, F = 5.53, p = .008) and were retained in the model. Overall, a combination of greater positive connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = .451, t = 2.93, p = .006) and greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Frontal Pole* (β = -.361, t = -2.34, p = .025) was associated with worse PCS/emotional symptom severity at 12M.

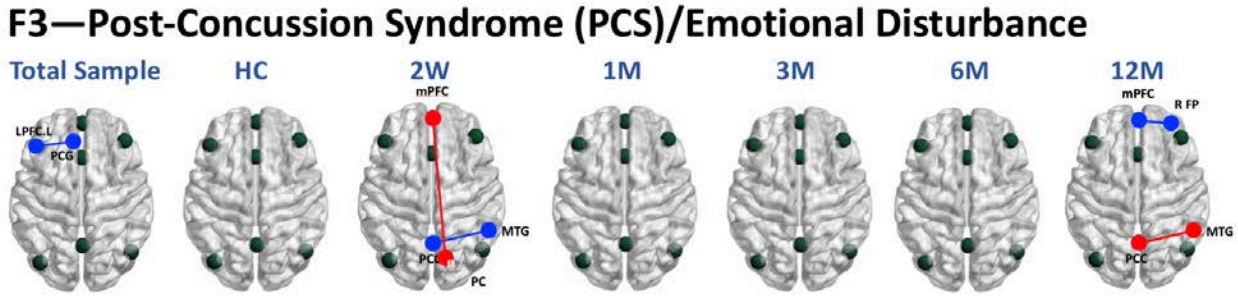


Figure 21. Functional connectivity correlated with Post-Concussion Syndrome (PCS) symptoms and emotional disturbance. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F4—Aggression

Total Sample: For the Total Sample, one predictor emerged as significant (R = .187, R^2 = .035, F = 5.55, p = .020) and was retained in the model. Overall, positive connectivity between the *PCC (seed)* and *Right Inferior Frontal Gyrus* was associated with increased aggression in the Total Sample (β = .187, t = 2.36, p = .020).

HC: For the HC group, there were no significant predictors of aggression.

2W: For the 2W group, one predictor emerged as significant (R = .719, R^2 = .518, F = 8.58, p = .019) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Left Lateral Occipital Cortex* (β = -.719, t = -2.93, p = .019) was associated with greater aggression at 2W.

1M: For the 1M group, there were no significant predictors of aggression.

3M: For the 3M group, there were no significant predictors of aggression.

6M: For the 6M group, one predictor emerged as significant (R = .675, R^2 = .455, F = 16.71, p = .001) and was retained in the model. Overall, greater positive connectivity between the *PCC (seed)* and *Right Lateral Occipital Cortex* (β = .675, t = 4.09, p = .001) was associated with greater aggression at 6M.

12M: For the 12M group, there were no significant predictors of aggression.

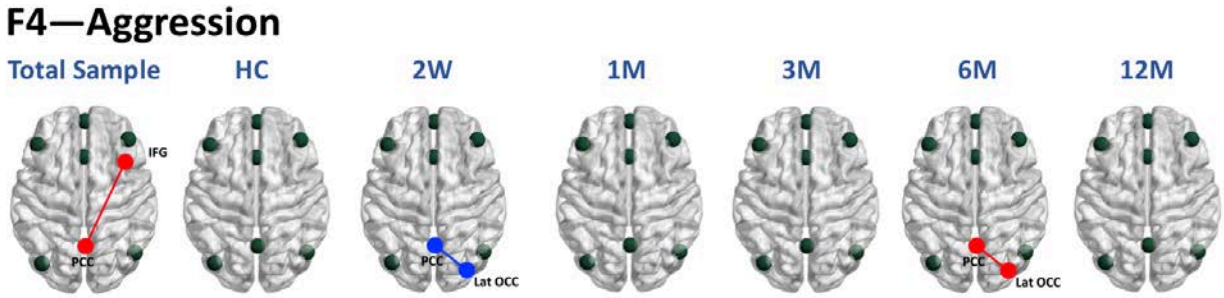


Figure 22. Functional connectivity correlated with higher aggression. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F5—Visual Memory

Total Sample: For the Total Sample, there were no significant predictors of visual memory.

HC: For the HC group, one predictor emerged as significant (R = .471, R^2 = .222, F = 9.42, p = .004) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Right Precuneus (superior)* (β = .471, t = 3.07, p = .004) was associated with greater visual memory.

2W: For the 2W group, there were no significant predictors of visual memory.

1M: For the 1M group, one predictor emerged as significant (R = .498, R^2 = .248, F = 6.94, p = .016) and was retained in the model. Overall, greater positive connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = .498, t = 2.63, p = .016) was associated with greater visual memory.

3M: For the 3M group, there were no significant predictors of visual memory.

6M: For the 6M group, one predictor emerged as significant (R = .504, R^2 = .254, F = 6.81, p = .017) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Right Precuneus (superior)* (β = .504, t = 2.61, p = .017) was associated with greater visual memory at 6M.

12M: For the 12M group, two predictors emerged as significant (R = .663, R^2 = .440, F = 13.73, p = .00004) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Precuneus (superior)* (β = -.679, t = -5.09, p = .00001) and greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.372, t = -2.79, p = .008) was associated with greater visual memory at 12M.

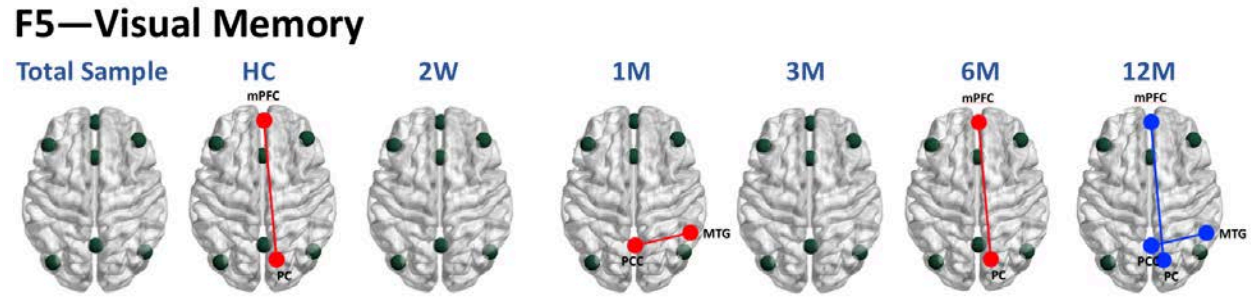


Figure 23. Functional connectivity correlated with higher visual memory. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F6—Sleep Quality (Disturbance)

Total Sample: For the Total Sample, one predictor emerged as significant (R = .179, R^2 = .032, F = 5.13, p = .025) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Inferior Frontal Gyrus* (β = -.179, t = -2.26, p = .025) was associated with greater sleep disturbance.

HC: For the HC group, there were no significant predictors of sleep disturbance.

2W: For the 2C group, there were no significant predictors of sleep disturbance.

1M: For the 1M group, there were no significant predictors of sleep disturbance.

3M: For the 3M group, there were no significant predictors of sleep disturbance.

6M: For the 6M group, there were no significant predictors of sleep disturbance.

12M: For the 12M group, there were no significant predictors of sleep disturbance.

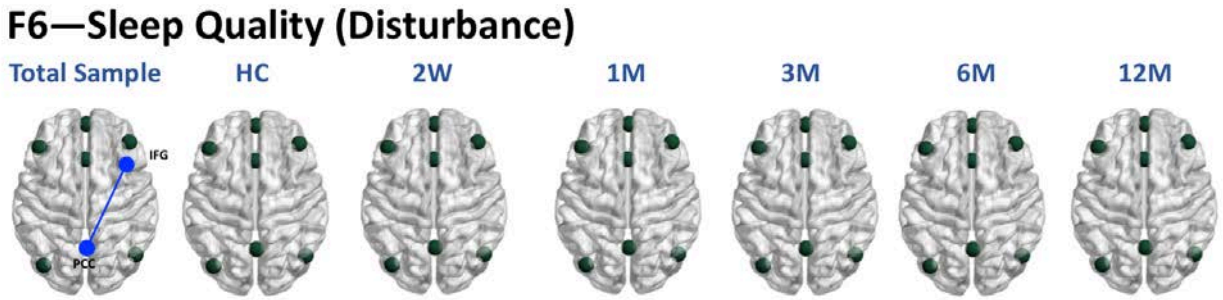


Figure 24. Functional connectivity correlated with sleep disturbance. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F7—Motor Speed

Total Sample: For the Total Sample, one predictor emerged as significant (R = .190, R^2 = .036, F = 5.77, p = .017) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = -.19, t = -2.40, p = .017) was associated with greater motor speed.

HC: For the HC group, there were no significant predictors of motor speed.

2W: For the 2W group, there were no significant predictors of motor speed.

1M: For the 1M group, one predictor emerged as significant (R = .50, R^2 = .25, F = 6.98, p = .015) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = -.50, t = -2.64, p = .015) was associated with greater motor speed.

3M: For the 3M group, there were no significant predictors of motor speed.

6M: For the 6M group, one predictor emerged as significant (R = .450, R^2 = .202, F = 5.07, p = .036) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.45, t = -2.25, p = .036) was associated with greater motor speed.

12M: For the 12M group, one predictor emerged as significant (R = .323, R^2 = .104, F = 4.19, p = .048) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = -.323, t = -2.05, p = .048) was associated with greater motor speed at 12M.

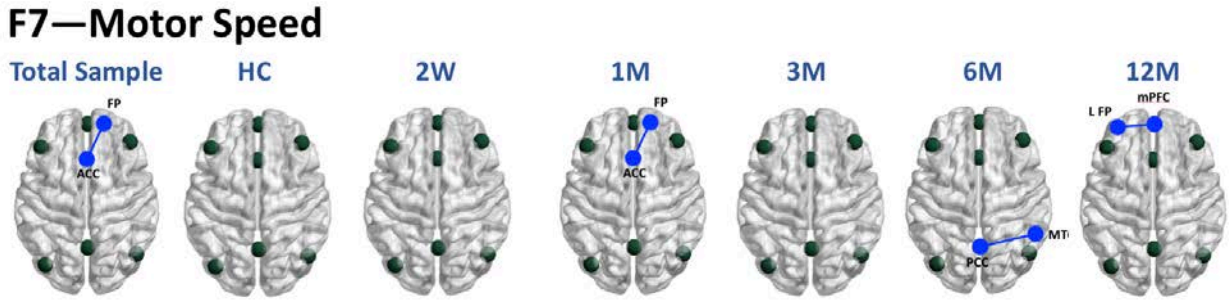


Figure 25. Functional connectivity correlated with faster motor speed. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F8—Vigilance

Total Sample: For the Total Sample, two predictors emerged as significant (R = .306, R^2 = .093, F = 7.88, p = .001) and were retained in the model. Overall, a linear combination of greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Precuneus*

(superior) (β = -.27, t = -3.30, p = .001) and greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.26, t = -3.19, p = .002) was associated with greater vigilance performance.

HC: For the HC group, there were no significant predictors of vigilance performance.

2W: For the 2W group, two predictors emerged as significant (R = .900, R^2 = .809, F = 14.87, p = .003) and were retained in the model. Overall, a linear combination of greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Precuneus (superior)* (β = -1.027, t = -5.44, p = .001) and greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Frontal Pole* (β = -.573, t = -3.03, p = .019) was associated with greater motor speed.

1M: For the 1M group, there were no significant predictors of vigilance performance.

3M: For the 3M group, there were no significant predictors of vigilance performance.

6M: For the 6M group, there were no significant predictors of vigilance performance.

12M: For the 12M group, one predictor emerged as significant (R = .478, R^2 = .229, F = 10.67, p = .002) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* (β = -.478, t = -3.27, p = .002) was associated with greater vigilance performance at 12M.

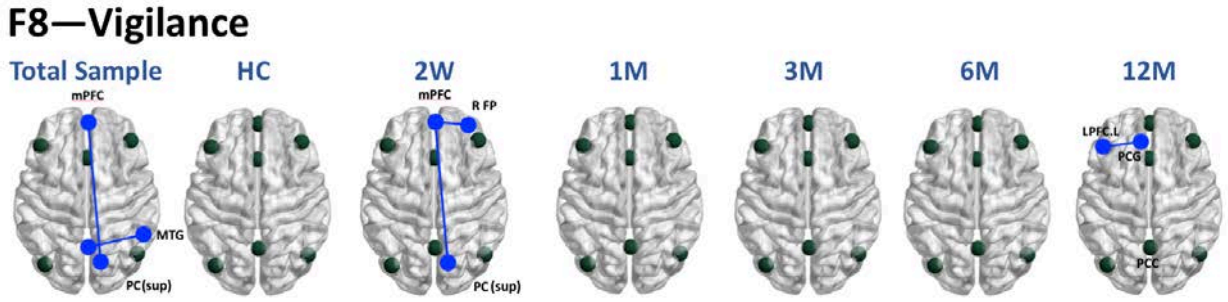


Figure 26. Functional connectivity correlated with greater psychomotor vigilance. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F9—Cognitive Errors

Total Sample: For the Total Sample, one predictor emerged as significant (R = .174, R^2 = .030, F = 4.83, p = .029) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = .174, t = 2.20, p = .029) was associated with more cognitive errors.

HC: For the HC group, there were no significant predictors of cognitive errors.

2W: For the 2W group, two predictors emerged as significant (R = .799, R^2 = .638, F = 20.95, p = .006) and were retained in the model. Overall, a linear combination of greater positive connectivity between the *PCC (seed)* and *Right Inferior Frontal Gyrus* (β = .853, t = 5.92, p = .001) and greater negative (anticorrelated) connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* (β = -.470, t = -3.27, p = .014) was associated with more cognitive errors at 2W.

1M: For the 1M group, one predictor emerged as significant (R = .571, R^2 = .326, F = 10.18, p = .004) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = .571, t = 3.19, p = .004) was associated with more cognitive errors at 1M.

3M: For the 3M group, one predictor emerged as significant (R = .45, R^2 = .202, F = 6.60, p = .016) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.450, t = -2.57, p = .016) was associated with more cognitive errors at 3M.

6M: For the 6M group, one predictor emerged as significant (R = .551, R^2 = .303, F = 8.71, p = .008) and was retained in the model. Overall, greater positive connectivity between the *Right Lateral Prefrontal Cortex (seed)* and *Frontal Medial Cortex* (β = .551, t = 2.95, p = .008) was associated with more cognitive errors at 6M.

12M: For the 12M group, there were no significant predictors of cognitive errors.

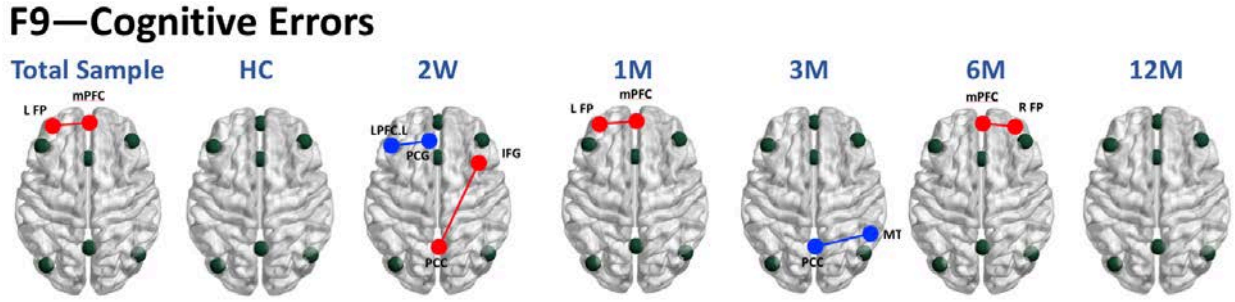


Figure 27. Functional connectivity correlated with more cognitive errors. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F10—Daily Functioning

Total Sample: For the Total Sample, one predictor emerged as significant (R = .193, R^2 = .037, F = 5.96, p = .016) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = .193, t = 2.44, p = .016) was associated with better daily functioning.

HC: For the HC group, there were no significant predictors of daily functioning.

2W: For the 2W group, one predictor emerged as significant (R = .679, R^2 = .461, F = 6.84, p = .031) and was retained in the model. Overall, greater positive connectivity between the *PCC (seed)* and *Right Lateral Occipital Cortex* (β = .679, t = 2.62, p = .031) was associated with better daily functioning at 2W.

1M: For the 1M group, one predictor emerged as significant (R = .452, R^2 = .205, F = 5.41, p = .030) and was retained in the model. Overall, greater positive connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* (β = .452, t = 2.33, p = .030) was associated with better daily functioning at 1M.

3M: For the 3M group, there were no significant predictors of daily functioning.

6M: For the 6M group, there were no significant predictors of daily functioning.

12M: For the 12M group, one predictor emerged as significant (R = .351, R^2 = .123, F = 5.04, p = .031) and was retained in the model. Overall, greater positive connectivity between the *mPFC (seed)* and *Left Frontal Pole* (β = .351, t = 2.25, p = .031) was associated with better daily functioning at 12M.

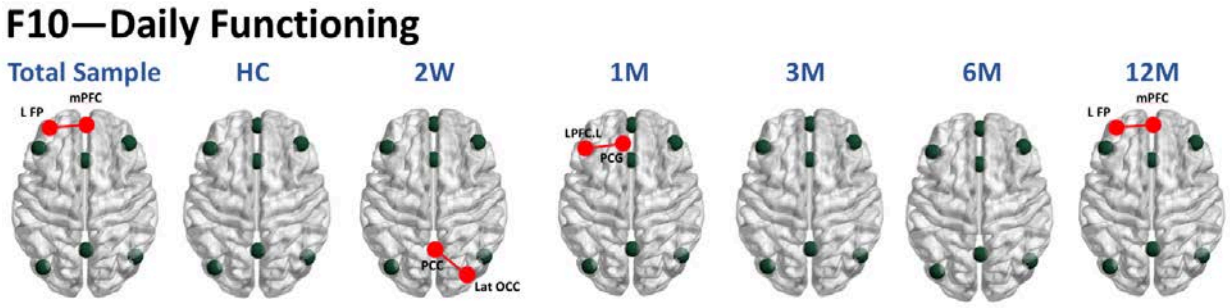


Figure 28. Functional connectivity correlated with better daily functioning. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F11—Concept Formation

Total Sample: For the Total Sample, two predictors emerged as significant (R = .257, R^2 = .066, F = 5.40, p = .005) and were retained in the model. Overall, a linear combination of greater positive connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* (β = .256, t = 3.06, p = .003) and greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.189, t = -2.25, p = .026) was associated with greater concept formation.

HC: For the HC group, there were no significant predictors of concept formation.

2W: For the 2W group, there were no significant predictors of concept formation.

1M: For the 1M group, two predictors emerged as significant (R = .643, R^2 = .414, F = 7.07, p = .005) and were retained in the model. Overall, a linear combination of greater positive connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Left Paracingulate Cortex* (β = .533, t = 3.09, p = .006) and greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Right Middle Temporal Gyrus* (β = -.429, t = -2.49, p = .022) was associated with greater concept formation.

3M: For the 3M group, there were no significant predictors of concept formation.

6M: For the 6M group, there were no significant predictors of concept formation.

12M: For the 12M group, there were no significant predictors of concept formation.

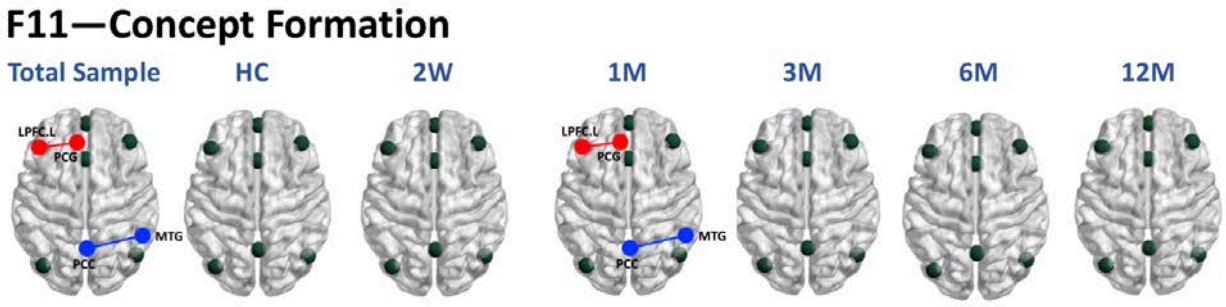


Figure 29. Functional connectivity correlated with greater concept formation ability. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F12—Impulsivity

Total Sample: For the Total Sample, one predictor emerged as significant (R = .158, R^2 = .025, F = 3.92, p = .049) and was retained in the model. Overall, greater positive connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = .158, t = 1.98, p = .049) was associated with greater impulsivity.

HC: For the HC group, two predictors emerged as significant (R = .53, R^2 = .28, F = 6.24, p = .005) and were retained in the model. Overall, a linear combination of greater negative (anticorrelated) connectivity between the *PCC (seed)* and *Left Lateral Occipital Cortex* (β = -.342, t = -2.21, p = .034) and greater positive connectivity between the *Right Lateral Prefrontal Cortex (seed)* and *Frontal Medial Cortex* (β = .327, t = 2.11, p = .043) was associated with greater impulsivity.

2W: For the 2W group, one predictor emerged as significant (R = .632, R^2 = .399, F = 5.32, p = .050) and was retained in the model. Overall, greater positive connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = .632, t = 2.31, p = .050) was associated with higher impulsivity at 2W.

1M: For the 1M group, there were no significant predictors of impulsivity.

3M: For the 3M group, there were no significant predictors of impulsivity.

6M: For the 6M group, there were no significant predictors of impulsivity.

12M: For the 12M group, two predictors emerged as significant (R = .497, R^2 = .247, F = 5.73, p = .007) and were retained in the model. Overall, a linear combination of greater negative (anticorrelated) connectivity between the *mPFC (seed)* and *Right Frontal Pole* (β = -.576, t = -3.53, p = .002) and greater positive connectivity between the *Left Lateral Prefrontal Cortex (seed)* and *Paracingulate Cortex* (β = .368, t = 2.14, p = .039) was associated with greater impulsivity at 12M.

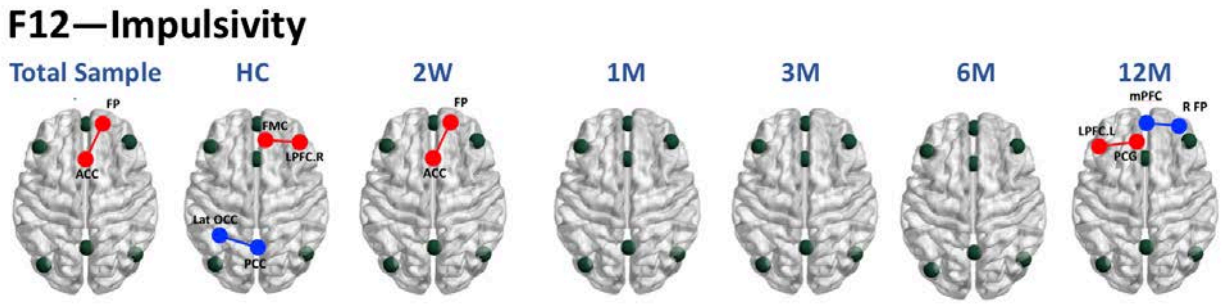


Figure 30. Functional connectivity correlated with higher impulsivity. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

F13—Processing Speed

Total Sample: When the Total Sample was considered together, there were no significant predictors of processing speed.

HC: For the HC group, there were not significant predictors of processing speed.

2W: For the 2W group, one predictor emerged as significant (R = .634, R^2 = .402, F = 5.37, p = .049) and was retained in the model. Overall, greater negative (anticorrelated) connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = -.634, t = -2.32, p = .049) was associated with faster processing speed at 2W.

1M: For the 1M group, there were no significant predictors of processing speed.

3M: For the 3M group, there were no significant predictors of processing speed.

6M: For the 6M group, there were no significant predictors of processing speed.

12M: For the 12M group, one predictor emerged as significant (R = .366, R^2 = .134, F = 5.57, p = .024) and was retained in the model. Overall, greater positive connectivity between the *ACC (seed)* and *Right Frontal Pole* (β = .366, t = 2.36, p = .024) was associated with faster processing speed at 12M.

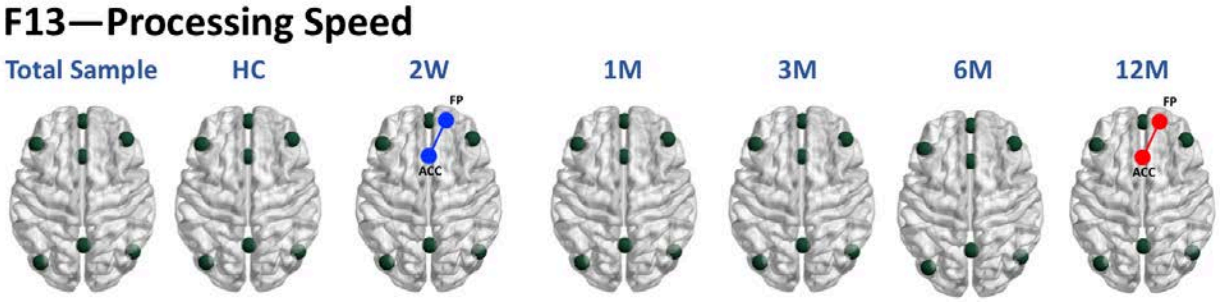


Figure 31. Functional connectivity correlated with faster processing speed. Red indicates positive connectivity and blue indicates negative (anticorrelated) regional connectivity.

Conclusion: *Based on the preceding analyses, the hypothesis is supported. We conclude that functional connectivity between the DMN and specific task positive regions was predictive of neuropsychological performance, particularly for individuals with mTBI. Moreover, our data suggest that the associations between connectivity and various neurocognitive abilities is different across TSI groups.*

Hypothesis 13: Functional connectivity within the DMN and TPN will predict group membership.

It was predicted that resting state functional connectivity (FC) would result in accurate classification of individuals into TSI groups. Section 3.C.II, described the initial preprocessing steps for functional connectivity using the CONN program. The outcomes for this hypothesis are based on the same sample of participants from the UA described earlier (HC: n = 35 total [15 male, 20 female], age M = 24.40, SD = 5.95; mTBI: n = 121 total [43 male; 78 female], age M = 24.76, SD = 7.48).

To predict group membership, FC brain connections (extracted as Fisher's z-transformed correlations between regions) were used as predictors, with the TSI group membership as the dependent variable. Of note, all analyses revealed that one functional connection variable, "*mPFC to R Precuneus (inferior)*" was found to produce excessively large odds ratios, suggesting that it may be a spurious variable with unusually large influence. Therefore, this variable was removed from all logistic regression analyses and the final analyses included 10 functional connectivity predictor variables.

Two sets of logistic regression analyses were conducted, 1) binary logistic regression to discriminate between HC and mTBI groups, and 2) multinomial logistic regression to permit fine-grained discrimination among the HC group as well as the 5 TSI groups (2W, 1M, 3M, 6M, 12M).

Prediction of HC vs mTBI (Binary Logistic Regression)

Simultaneous Variable Entry: The first analysis involved simultaneous entry of all 10 predictor variables. At the initial baseline step (step 0), all participants (35 HC, 121 mTBI) were classified as mTBI (i.e., 77.6% accurate). Entry of all 10 variables (step 1) resulted in a significant model (χ^2 (10) = 44.78, p = .000002), suggesting that the combined predictors were effective at predicting group membership (Nagelkerke R^2 = .381). The overall prediction of group membership improved to 82.1% with the inclusion of the FC variables. Table 24 shows the classification table at each step.

Table 24. Classification tables before and after simultaneous entry of 10 resting state functional connections (FC) for predicting healthy control (HC) from any mild traumatic brain injury (mTBI). Overall, there was a significant increase in prediction with the addition of the FC variables.

Step 0: Baseline Block

Classification Table[a,b]

			Predicted		
			is_mTBI		Percentage Correct
	Observed		0	1	
Step 0	is_mTBI	0	0	35	.0
		1	0	121	100.0
	Overall Percentage				77.6

a. Constant is included in the model.

b. The cut value is .500

Step 1: Final Block

Classification Table[a]

			Predicted		
			is_mTBI		Percentage Correct
	Observed		0	1	
Step 1	is_mTBI	0	15	20	42.9
		1	8	113	93.4
	Overall Percentage				82.1

a. The cut value is .500

The individual predictive value of each functional connection is listed in Table 25. The table shows that four connections were statistically significant in predicting HC versus mTBI group

Table 25. Results from the binary logistic regression for simultaneous entry of all 10 resting state functional connections.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Step 1[a]	mPFC to R Fontalpole	1.159	2.130	0.296	1	0.586	3.188	0.049	207.119
	mPFC to R precuneus sup	0.697	2.699	0.067	1	0.796	2.009	0.010	398.426
	PCC to L Lat Occip	**4.265**	**1.343**	**10.087**	**1**	**0.001**	**71.167**	**5.119**	**989.385**
	PCC to R IFG	4.138	2.773	2.227	1	0.136	62.678	0.274	14362.509
	PCC to R MTG	**-4.801**	**2.299**	**4.362**	**1**	**0.037**	**0.008**	**0.000**	**0.744**
	PCC to R Lat Occip	-1.983	2.488	0.635	1	0.425	0.138	0.001	18.049
	ACC to R Frontalpole salience	-2.061	1.693	1.481	1	0.224	0.127	0.005	3.519
	L LPFC to L paracingulate	**-2.646**	**1.297**	**4.161**	**1**	**0.041**	**0.071**	**0.006**	**0.902**
	R LPFC to Frontalmedial cortex	-0.656	2.270	0.084	1	0.773	0.519	0.006	44.373
	mPFC to L Frontalpole	**-4.211**	**2.404**	**3.070**	**1**	**0.080**	**0.015**	**0.000**	**1.648**
	Constant	1.066	0.843	1.598	1	0.206	2.903		

a. Variable(s) entered on step 1: mPFC to R Fontalpole, mPFC to R precuneus sup, PCC to L Lat Occip, PCC to R IFG, PCC to R MTG, PCC to R Lat Occip, ACC to R Frontalpole salience, L LPFC to L paracingulate, R LPFC to Frontalmedial cortex, mPFC to L Frontalpole.

membership. Thus, FC was able to discriminate between HC and mTBI groups when all 10 connections were entered into the regression equation simultaneously.

Stepwise Variable Entry: The preceding analysis showed that there were only a few resting state connections that provided unique prediction of group membership once accounting for other connections. Therefore, to increase parsimony in the conclusions, we ran a second model of the same predictors using a forward stepwise entry process. The stepwise entry process continued through three steps, resulting in a significant model at each step. The final step (Step 3) included three predictor variables (see Table 26) and was statistically optimal (χ^2 (3) = 35.28, p = .0000001), suggesting that the combined predictors were effective at predicting group membership (Nagelkerke R^2 = .309). The overall prediction of group membership improved to 83.3% with the inclusion of the three FC variables. Table 27 shows the classification table at each step.

Table 26. Results from the binary logistic regression for stepwise forward entry of all 10 resting state functional connections to predict binary group membership. The final equation included three predictor variables that significantly discriminated between HC and mTBI groups.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	**PCC to R Lat Occip**	**-6.393**	**1.501**	**18.144**	**1**	**0.000**	**0.002**	**0.000**	**0.032**
	Constant	2.691	0.433	38.671	1	0.000	14.750		
Step 2[b]	**PCC to L Lat Occip**	**3.038**	**1.104**	**7.569**	**1**	**0.006**	**20.862**	**2.396**	**181.675**
	PCC to R Lat Occip	**-5.834**	**1.586**	**13.534**	**1**	**0.000**	**0.003**	**0.000**	**0.065**
	Constant	1.371	0.621	4.868	1	0.027	3.938		
Step 3[c]	**PCC to L Lat Occip**	**2.865**	**1.142**	**6.299**	**1**	**0.012**	**17.548**	**1.873**	**164.393**
	PCC to R Lat Occip	**-4.449**	**1.732**	**6.598**	**1**	**0.010**	**0.012**	**0.000**	**0.348**
	L LPFC to L paracingulate	**-2.440**	**1.103**	**4.888**	**1**	**0.027**	**0.087**	**0.010**	**0.758**
	Constant	1.858	0.688	7.286	1	0.007	6.411		

a. Variable(s) entered on step 1: PCC to R Lat Occip.

b. Variable(s) entered on step 2: PCC to L Lat Occip.

c. Variable(s) entered on step 3: L LPFC to L paracingulate.

Classification Table[a,b]

			Predicted is_mTBI 0	Predicted is_mTBI 1	Percentage Correct
Step 0	Observed is_mTBI	0	0	35	.0
		1	0	121	100.0
	Overall Percentage				77.6

a. Constant is included in the model.

b. The cut value is .500

Classification Table[a]

			Predicted is_mTBI 0	Predicted is_mTBI 1	Percentage Correct
Step 1	Observed is_mTBI	0	7	28	20.0
		1	5	116	95.9
	Overall Percentage				78.8
Step 2	is_mTBI	0	11	24	31.4
		1	4	117	96.7
	Overall Percentage				82.1
Step 3	is_mTBI	0	12	23	34.3
		1	3	118	97.5
	Overall Percentage				83.3

a. The cut value is .500

Table 27. Classification tables showing the improvement in classification with each model. The final model in Step 3 produced the best classification.

This pattern of findings resulted in a sensitivity = .975 and specificity = .343. Based on the data, we extracted the predicted values for each participant from the regression equation and conducted a receiver operating characteristic (ROC) analysis. As shown in Figure 32, the analysis was predictive above chance, with an area under the ROC curve of .807. This allowed us to determine optimal cutoffs to optimize sensitivity and specificity. As shown in Figure 32, an optimized cutoff would provide sensitivity of .78 and specificity of .77.

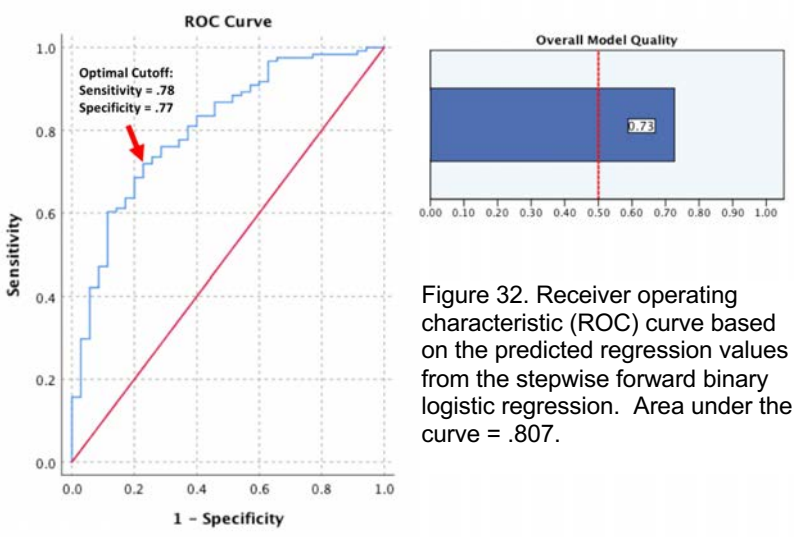


Figure 32. Receiver operating characteristic (ROC) curve based on the predicted regression values from the stepwise forward binary logistic regression. Area under the curve = .807.

Prediction of Time-Since-Injury (TSI) Group (Multinomial Logistic Regression)

The goal here was to determine whether the FC values could be useful to discriminate among the 6 groups and predict group membership reliably. The first analysis involved a multinomial logistic regression with simultaneous entry of all 10 FC variables as predictors and the six TSI groups (HC, 2W, 1M, 3M, 6M, 12M) as outcomes. With six groups, the chance expectation for any group membership would be 16.67%.

Simultaneous Variable Entry: Entry of all 10 variables resulted in a significant model ($\chi 2$ (50) = 109.04, p = .000003), suggesting that the combined predictors were effective at predicting group membership (Nagelkerke R^2 = .519). As shown in Table 28, the combined FC variables did an excellent job of classifying all categories of injury well, with an overall

Table 28. Classification table following simultaneous entry of 10 resting state functional connections (FC) for predicting membership in one of the six groups. Chance levels would be at 16.67%. Overall, the 10 FC variables were significantly predictive of group membership, with an average accuracy of 49.4%, which was well above the level expected by chance.

Classification

	Predicted						
Observed	HC	2W	1M	3M	6M	12M	Percent Correct
HC	23	1	1	3	0	7	65.7%
2W	3	2	1	1	1	2	20.0%
1M	3	0	9	2	3	6	39.1%
3M	4	0	2	12	1	9	42.9%
6M	2	2	3	2	10	3	45.5%
12M	5	0	5	2	5	21	55.3%
Overall Percentage	25.6%	3.2%	13.5%	14.1%	12.8%	30.8%	49.4%

classification accuracy of 49.4% (recall that accuracy by random chance would be 16.67%). The accuracy of classification ranged from a low of 20% (2W), to 65.7% (HC).

Table 29. Results from the multinomial logistic regression for simultaneous entry of all 10 resting state functional connections to predict membership in one of six time-since-injury groups (HC, 2W, 1M, 3M, 6M, 12M).

Parameter Estimates									
								95% Confidence Interval for Exp(B)	
TSI_group[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	Lower Bound	Upper Bound
1	Intercept	-1.526	1.589	0.923	1	0.337			
	mPFC to R Fontalpole	1.437	3.802	0.143	1	0.705	4.209	0.002	7254.625
	mPFC to R precuneus sup	2.657	4.480	0.352	1	0.553	14.258	0.002	92810.843
	PCC to L Lat Occip	4.296	2.495	2.964	1	0.085	73.391	0.552	9763.193
	PCC to R IFG	0.245	4.826	0.003	1	0.959	1.278	9.980E-05	16372.748
	PCC to R MTG	-6.999	4.881	2.056	1	0.152	0.001	6.390E-08	13.038
	PCC to R Lat Occip	2.004	4.481	0.200	1	0.655	7.421	0.001	48375.481
	ACC to R Frontalpole	3.783	3.446	1.205	1	0.272	43.938	0.051	37709.129
	L LPFC to L paracingulate	**-4.900**	**2.320**	**4.460**	**1**	**0.035**	**0.007**	**7.886E-05**	**0.703**
	R LPFC to Frontalmedial cortex	-4.829	4.217	1.311	1	0.252	0.008	2.057E-06	31.088
	mPFC to L Frontalpole	-5.640	4.249	1.762	1	0.184	0.004	8.591E-07	14.687
2	Intercept	-1.450	1.261	1.321	1	0.250			
	mPFC to R Fontalpole	-1.815	2.894	0.393	1	0.531	0.163	0.001	47.303
	mPFC to R precuneus sup	1.312	3.620	0.131	1	0.717	3.714	0.003	4476.579
	PCC to L Lat Occip	**4.131**	**1.805**	**5.241**	**1**	**0.022**	**62.253**	**1.812**	**2138.919**
	PCC to R IFG	6.892	3.875	3.164	1	0.075	984.495	0.495	1956450.682
	PCC to R MTG	**-11.860**	**3.583**	**10.959**	**1**	**0.001**	**7.066E-06**	**6.304E-09**	**0.008**
	PCC to R Lat Occip	-1.423	3.438	0.171	1	0.679	0.241	0.000	203.521
	ACC to R Frontalpole	-0.911	2.471	0.136	1	0.712	0.402	0.003	51.013
	L LPFC to L paracingulate	-1.849	1.801	1.054	1	0.305	0.157	0.005	5.372
	R LPFC to Frontalmedial cortex	-0.214	3.079	0.005	1	0.945	0.807	0.002	337.472
	mPFC to L Frontalpole	-2.904	3.228	0.809	1	0.368	0.055	9.802E-05	30.656
3	Intercept	0.238	1.064	0.050	1	0.823			
	mPFC to R Fontalpole	3.448	2.893	1.420	1	0.233	31.446	0.108	9127.388
	mPFC to R precuneus sup	-2.896	3.433	0.711	1	0.399	0.055	6.606E-05	46.212
	PCC to L Lat Occip	**4.848**	**1.721**	**7.931**	**1**	**0.005**	**127.461**	**4.366**	**3720.747**
	PCC to R IFG	5.838	3.577	2.665	1	0.103	343.195	0.310	380189.018
	PCC to R MTG	2.591	3.385	0.586	1	0.444	13.343	0.018	10161.354
	PCC to R Lat Occip	-5.433	3.195	2.891	1	0.089	0.004	8.328E-06	2.293
	ACC to R Frontalpole	-3.311	2.156	2.357	1	0.125	0.036	0.001	2.498
	L LPFC to L paracingulate	**-4.139**	**1.729**	**5.733**	**1**	**0.017**	**0.016**	**0.001**	**0.472**
	R LPFC to Frontalmedial cortex	-1.441	2.939	0.240	1	0.624	0.237	0.001	75.204
	mPFC to L Frontalpole	-4.753	3.087	2.371	1	0.124	0.009	2.032E-05	3.659
4	Intercept	-2.048	1.255	2.664	1	0.103			
	mPFC to R Fontalpole	4.042	3.050	1.756	1	0.185	56.937	0.144	22483.250
	mPFC to R precuneus sup	1.394	3.735	0.139	1	0.709	4.032	0.003	6094.641
	PCC to L Lat Occip	**6.902**	**1.908**	**13.091**	**1**	**0.000**	**994.405**	**23.648**	**41814.691**
	PCC to R IFG	6.658	3.810	3.053	1	0.081	779.242	0.445	1364766.799
	PCC to R MTG	**-10.179**	**3.701**	**7.564**	**1**	**0.006**	**3.797E-05**	**2.687E-08**	**0.054**
	PCC to R Lat Occip	1.242	3.348	0.138	1	0.711	3.464	0.005	2449.872
	ACC to R Frontalpole	-2.063	2.373	0.756	1	0.385	0.127	0.001	13.298
	L LPFC to L paracingulate	**-3.785**	**1.825**	**4.301**	**1**	**0.038**	**0.023**	**0.001**	**0.812**
	R LPFC to Frontalmedial cortex	-6.154	3.397	3.281	1	0.070	0.002	2.726E-06	1.657
	mPFC to L Frontalpole	-4.363	3.283	1.766	1	0.184	0.013	2.046E-05	7.940
5	Intercept	0.011	0.998	0.000	1	0.991			
	mPFC to R Fontalpole	0.309	2.455	0.016	1	0.900	1.363	0.011	167.480
	mPFC to R precuneus sup	1.559	3.136	0.247	1	0.619	4.753	0.010	2218.791
	PCC to L Lat Occip	**3.257**	**1.531**	**4.523**	**1**	**0.033**	**25.973**	**1.291**	**522.512**
	PCC to R IFG	0.607	3.377	0.032	1	0.857	1.835	0.002	1373.459
	PCC to R MTG	-2.857	2.822	1.024	1	0.311	0.057	0.000	14.515
	PCC to R Lat Occip	-1.904	2.835	0.451	1	0.502	0.149	0.001	38.599
	ACC to R Frontalpole	-2.603	1.969	1.748	1	0.186	0.074	0.002	3.512
	L LPFC to L paracingulate	-2.129	1.517	1.970	1	0.160	0.119	0.006	2.326
	R LPFC to Frontalmedial cortex	2.017	2.683	0.565	1	0.452	7.514	0.039	1445.618
	mPFC to L Frontalpole	-3.776	2.775	1.851	1	0.174	0.023	9.959E-05	5.277

a. The reference category is: 0.

The full parameter estimates for each classification are presented in Table 29. As evident in the table, most of the prediction was limited to only a few resting state connections that yielded highly significant odds ratios. Therefore, to enhance the parsimony of the predictive model, we ran the same analysis again using a forward stepwise entry procedure to limit the predictive variables to only those contributing significantly to the model. That analysis is presented in the next section below.

Stepwise Variable Entry: To improve the parsimony of prediction, we conducted a multinomial logistic regression with forward stepwise entry of the 10 FC variables to predict membership in the six groups (HC, 2W, 1M, 3M, 6M, 12M). As shown in Table 30, the analysis proceeded through 4 steps before reaching tolerance levels. The best fitting and most parsimonious model occurred by Step 4, resulting in a significant model (χ^2 (5) = 12.04, p = .034), suggesting that the combined predictors were effective at predicting group membership (Nagelkerke R^2 = .393).

Table 30. Model summary of the stepwise forward entry of the resting state functional connectivity (FC) variables for predicting membership among the six time-since-injury groups.

Step Summary

Model		Action	Effect(s)	Model Fitting Criteria -2 Log Likelihood	Effect Selection Tests Chi-Square[a,b]	df	Sig.
Step 0	0	Entered	Intercept	537.330	.		
Step 1	1	Entered	PCC to R MTG	504.663	32.667	5	.000
Step 2	2	Entered	ACC to R Frontalpole	489.257	15.406	5	.009
Step 3	3	Entered	R LPFC to Frontalmedial cortex	474.594	14.663	5	.012
Step 4	4	Entered	PCC to L Lat Occip	462.557	12.036	5	.034

Stepwise Method: Forward Stepwise

a. The chi-square for entry is based on the likelihood ratio test.

b. The chi-square for removal is based on the likelihood ratio test.

As shown in Table 31, the reduced 4 connection solution did a good job of classifying all categories of injury, with an overall classification accuracy of 37.8% (recall that accuracy by random chance would be 16.67%). The accuracy of classification ranged from a low of 10%

Table 31. Classification table following stepwise entry of four resting state functional connections (FC) for predicting membership in one of the six groups. Chance levels would be at 16.67%. Overall, the four FC variables were significantly predictive of group membership, with an average accuracy of 37.8%, which was well above the level expected by chance, but not as good as the full 10 variable model shown earlier.

Classification

	Predicted						
Observed	HC	2W	1M	3M	6M	12M	Percent Correct
HC	20	0	3	4	0	8	57.1%
2W	3	1	1	2	2	1	10.0%
1M	5	0	8	0	3	7	34.8%
3M	3	1	2	5	4	13	17.9%
6M	3	0	4	2	8	5	36.4%
12M	9	0	3	6	3	17	44.7%
Overall Percentage	27.6%	1.3%	13.5%	12.2%	12.8%	32.7%	37.8%

(2W), to 57.1% (HC). However, it should be noted that the classification accuracy was inferior to the full model described above when all FC variables were entered into the model.

Based on the four-connection model, the full parameter estimates for each TSI group classification are presented in Table 32.

Table 32. Results from the multinomial logistic regression for stepwise forward entry resulting in four retained resting state functional connections to predict membership in one of six time-since-injury groups (HC, 2W, 1M, 3M, 6M, 12M).

Parameter Estimates									
TSI_group[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
1	Intercept	-1.472	1.105	1.776	1	0.183			
	PCC to L Lat Occip	3.277	2.106	2.420	1	0.120	26.490	0.427	1644.747
	PCC to R MTG	-5.951	3.391	3.080	1	0.079	0.003	3.382E-06	2.003
	ACC to R Frontalpole	3.048	2.221	1.883	1	0.170	21.064	0.271	1636.804
	R LPFC to Frontalmedial cortex	**-6.854**	**2.689**	**6.496**	**1**	**0.011**	**0.001**	**5.423E-06**	**0.205**
2	Intercept	-0.786	0.844	0.867	1	0.352			
	PCC to L Lat Occip	2.836	1.558	3.312	1	0.069	17.048	0.804	361.572
	PCC to R MTG	**-11.040**	**2.764**	**15.957**	**1**	**0.000**	**1.605E-05**	**7.132E-08**	**0.004**
	ACC to R Frontalpole	1.068	1.749	0.373	1	0.542	2.909	0.094	89.636
	R LPFC to Frontalmedial cortex	-2.779	2.075	1.793	1	0.181	0.062	0.001	3.626
3	Intercept	-0.509	0.756	0.454	1	0.501			
	PCC to L Lat Occip	**3.496**	**1.461**	**5.727**	**1**	**0.017**	**32.995**	**1.883**	**578.199**
	PCC to R MTG	-0.631	2.283	0.076	1	0.782	0.532	0.006	46.704
	ACC to R Frontalpole	-2.626	1.495	3.085	1	0.079	0.072	0.004	1.356
	R LPFC to Frontalmedial cortex	**-4.167**	**1.962**	**4.512**	**1**	**0.034**	**0.015**	**0.000**	**0.725**
4	Intercept	-1.513	0.907	2.783	1	0.095			
	PCC to L Lat Occip	**5.124**	**1.677**	**9.338**	**1**	**0.002**	**168.023**	**6.282**	**4494.386**
	PCC to R MTG	**-7.320**	**2.745**	**7.108**	**1**	**0.008**	**0.001**	**3.050E-06**	**0.144**
	ACC to R Frontalpole	0.606	1.748	0.120	1	0.729	1.833	0.060	56.379
	R LPFC to Frontalmedial cortex	**-4.972**	**2.190**	**5.155**	**1**	**0.023**	**0.007**	**9.474E-05**	**0.507**
5	Intercept	-0.329	0.702	0.220	1	0.639			
	PCC to L Lat Occip	**2.732**	**1.295**	**4.454**	**1**	**0.035**	**15.369**	**1.215**	**194.395**
	PCC to R MTG	-3.680	2.117	3.020	1	0.082	0.025	0.000	1.601
	ACC to R Frontalpole	**-2.781**	**1.399**	**3.953**	**1**	**0.047**	**0.062**	**0.004**	**0.961**
	R LPFC to Frontalmedial cortex	-0.469	1.745	0.072	1	0.788	0.625	0.020	19.134

a. The reference category is: 0.

Conclusion: *Based on the preceding analyses, we conclude that the hypothesis is supported. Overall, we found that functional connectivity between the DMN and specific task positive regions was predictive of group membership. This was supported for simple discrimination between HC and mTBI, and also for the more difficult capacity to accurately classify individuals within one of the six TSI groups (i.e., HC, 2W, 1M, 3M, 6M, 12M).*

Hypothesis 14: There will be a strong correlation between functional connectivity and DTI metrics of both DMN and TPN.

As described in section 3.C.II, neuroimaging data were preprocessed and imported into CONN to calculate functional connectivity (FC) and into DSI Studio to calculate normalized quantitative anisotropy (NQA). Areas of the brain where FC differed between the groups were used as seed

regions for tractography. This unique multimodal approach allows for a direct comparison between functional and structural connectivity in the brain.

As mentioned previously, the present sample participants with neuroimaging data collected at the UA. The sample was divided into groups based on time since injury and included one HC group, and 5 MTBI groups (**HC**: *n* = 32 total [15 male, 17 female], age *M* = 24.56, *SD* = 6.15; **2W**: *n* = 11 total [5 male; 6 female], age *M* = 25.64, *SD* = 8.19; **1M**: *n* = 21 total [6 male; 15 female], age *M* = 25.38, *SD* = 8.86; **3M**: *n* = 26 total [10 male; 16 female], age *M* = 26.62, *SD* = 8.11; **6M**: *n* = 21 total [5 male; 16 female], age *M* = 23.38, *SD* = 6.04; **12M**: *n* = 34 total [15 male; 19 female], age *M* = 24.03, *SD* = 7.26).

Deterministic tractography: Standard tracking parameters in DSI studio were used to complete deterministic fiber tracking. Tractography was conducted using the same 7 seed regions used in the functional connectivity analysis (mPFC, LPFC L, LPFC R, ACC, PCC, LP L, and LP R). Voxel clusters that differed between HC and MTBI groups, from the seed-to-voxel connectivity analyses, were used as end regions in the present tractography analyses.

As shown in Figure 33, deterministic tractography between the MPFC and right inferior precuneus resulted in 233 tracts (length = 138.11 mm, span = 103.79 mm, diameter = 3.49). Normalized quantitative anisotropy (NQA) was calculated for the resulting white matter tract and used in the subsequent analysis.

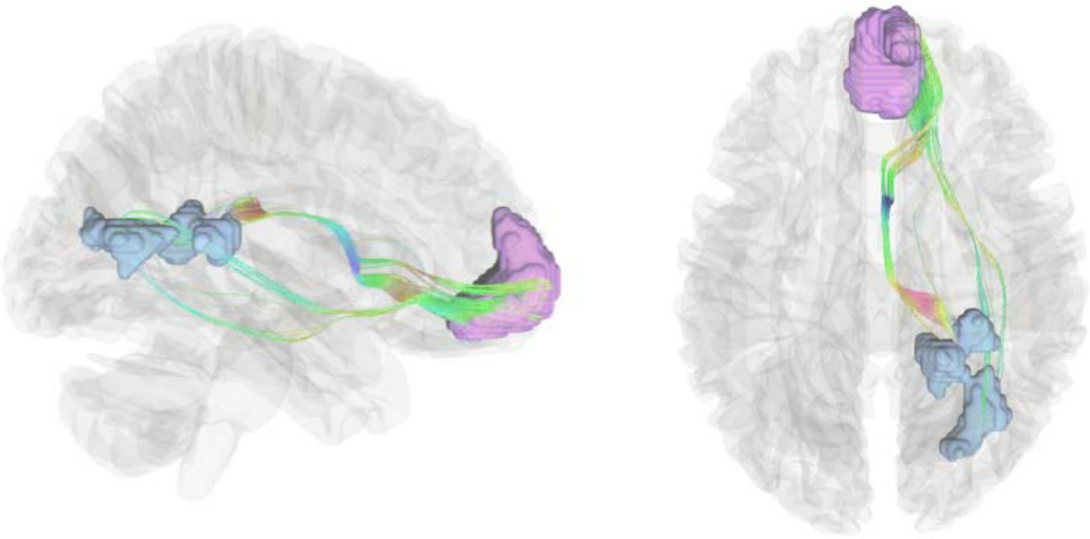


Figure 33. Deterministic tractography between the seed region in medial prefrontal cortex (mPFC; purple) and the end region in the right inferior precuneus (blue).

Deterministic fiber tracking was also successful between the ACC seed region and voxel cluster of the right frontal pole, resulting in 377 tracts (mean length = 46.53 mm, span = 21.51 mm, diameter = 4.00 mm) (see Figure 34). NQA was calculated for the resulting white matter and used in the analysis below. Fiber tracking was attempted between the remaining seed regions (LPFC L, LPFC R, PCC, LP L, and LP R) and associated voxel clusters (i.e., significant seed-to-voxel results from functional connectivity). However, these connections did not result in fiber

tracts and may be indicative of a lack of *direct* structural connectivity between regions as assessed using the present parameters.

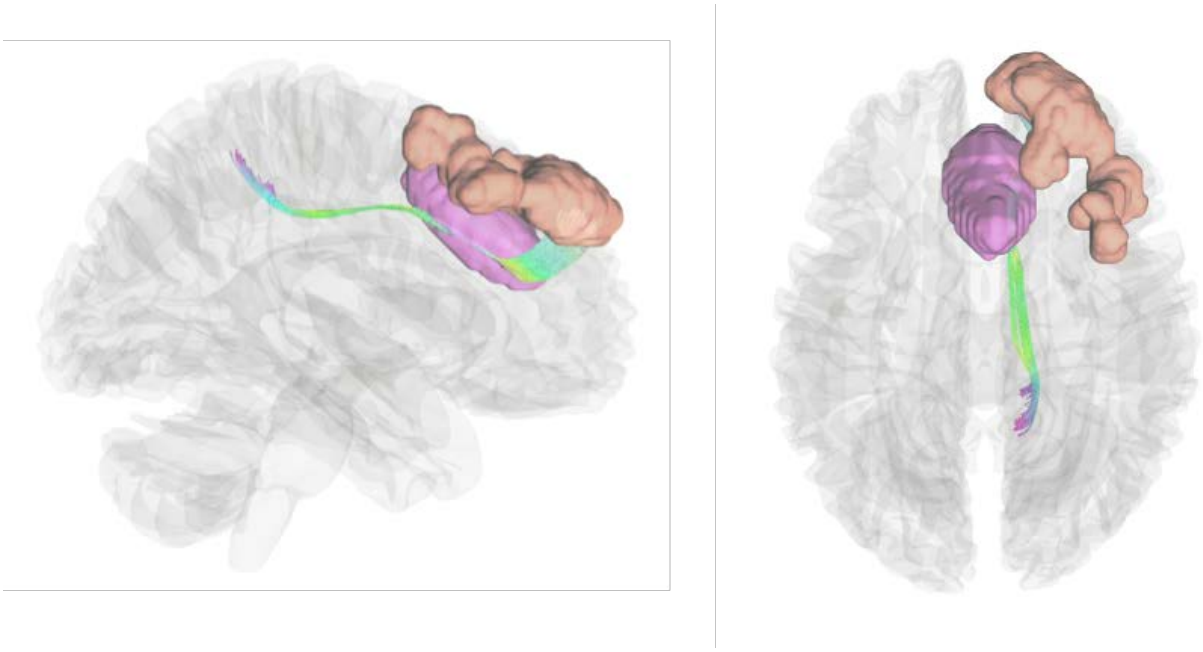


Figure 34. Deterministic tractography between the seed region in anterior cingulate cortex (ACC; purple) and the end region in the right frontal pole (tan).

Associations between FC and NQA:

Partial correlations, controlling for participant age and sex, were calculated between FC and the diffusion NQA for TSI groups separately. In the **3M** MTBI group, we found a statistically significant correlation between FC and NQA in the frontal regions (see Figure 35). In particular, higher functional connectivity between the ACC and right frontal pole was significantly correlated with higher NQA in structural connectivity between the same regions ($r = .56$, $p = .004$).

There we no other statistically significant associations between FC and NQA for the remaining groups (HC, 2W, 1M, 6M, and

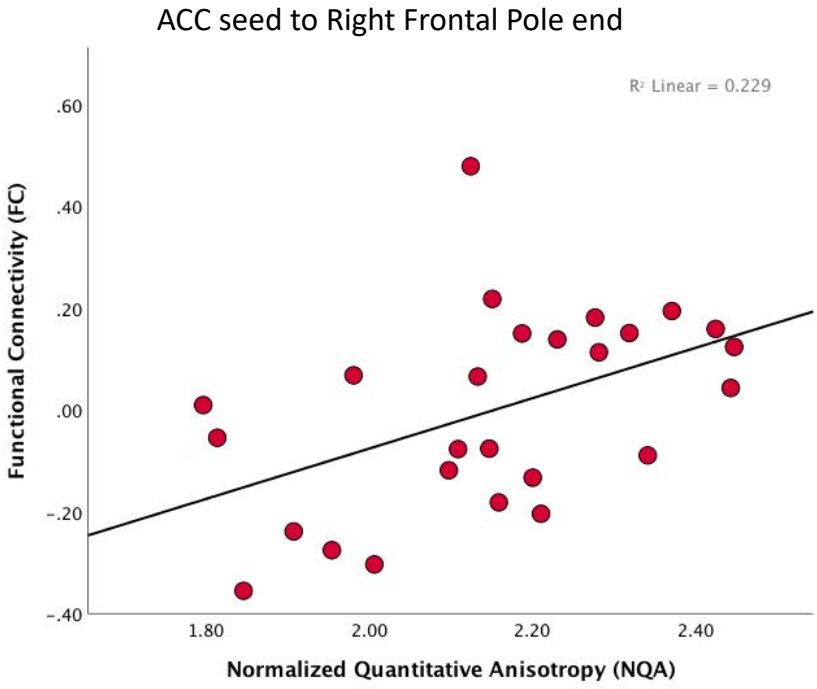


Figure 35. Positive correlation between functional connectivity (FC) and diffusion metric normalized quantitative anisotropy (NQA) in 3M group.

12M) either between the mPFC seed region and right inferior precuneus, or between the ACC seed region and right frontal pole.

Conclusion. *Results from the aforementioned analyses support the hypothesis. There was a strong significant correlation between functional connectivity and diffusion, as measured by normalized quantitative anisotropy (NQA), in regions of the brain associated with the DMN and TPN.*

3.F. Supplementary Analyses

Due to the large scope and nature of the project, we were able to collect extensive amounts of behavioral and neuroimaging data. Therefore, in addition to the primary hypotheses of the proposal, we have had the opportunity to conduct extensive supplementary analyses. These supplemental analyses will be presented in several sections, including an extensive analysis of voxel-based morphometry (VBM) data (section 3.F.I), and 2) a general chronological summary of preliminary findings that emerged over the multiple years of the study, many of which were presented at conferences or in preliminary publications (section 3.F.II).

3.F.I Gray Matter Volume (Voxel-Based Morphometry—VBM)

Although gray matter volume was not listed as a primary outcome variable in the original grant application, we have collected T1-weighted anatomical images on all of our participants, so it was possible to also compare groups on gray matter volume (GMV) using a technique known as Voxel Based Morphometry (VBM). We present these data as supplementary analyses that may help inform ongoing work on mTBI and clarify the current associations between brain structure and function.

Structural Neuroimaging Methods. 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. Data were analyzed using the general linear model (GLM) based on the standard contrasts available in SPM12, including simple and multiple regression, t-tests, and analysis of variance (ANOVA). All findings were thresholded at $p < .001$ for height and cluster corrected at $p < .05$ (FDR) for the whole brain (unless specific hypotheses focused on a specific structure—in such cases, a small volume correction was applied within the a priori defined regions of interest).

Total Sample GMV Comparisons

MTBI vs. HC. First, we compared the GMV of the HC group with the combined mTBI group (2W + 1M + 3M + 6M + 12M) between groups t-tests, controlling for total intracranial volume (TIV), sex, and age. Overall, as shown in Supplementary Figure S1, the analysis demonstrated that the mTBI group showed significantly reduced GMV within a small region within the right central sulcus, which was significant even after cluster-wise FDR correction (FDR $p < .05$). No other regions showed significant differences in GMV between the HC and mTBI groups. The central sulcus separates the primary motor cortex from the primary somatosensory cortex. Mapping of this region has suggested that it corresponds to the sensory perception and motor control of the lips and tongue (Petrides, Collins, Chakravarty, & Germann, 2020). *This finding raises the possibility that mTBI may affect the sensory-motor regions of the right central sulcus*.

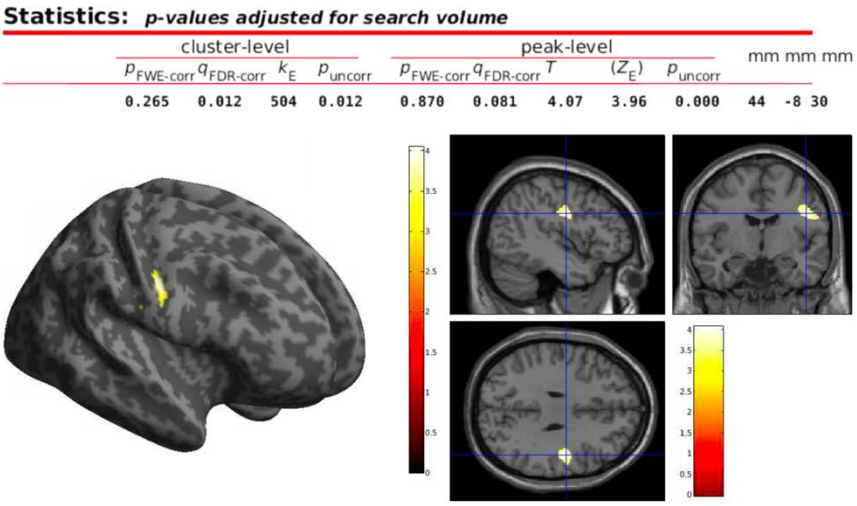


Figure S1. Voxel based morphometry (VBM) output for the comparison between HC and mTBI groups. Overall, the HC group showed significantly greater gray matter volume (GMV) than the combined mTBI groups within a region localized to the right central sulcus.

Although no other differences in GMV were statistically significant between HC and mTBI groups, we provide a surface rendering colormap in Figure S2 below showing the general trends between groups. Warmer colors represent areas where the mTBI group showed a trend toward greater GMV than HCs, while cooler colors reflect areas showing reduced GMV among mTBI individuals compared the HC group.

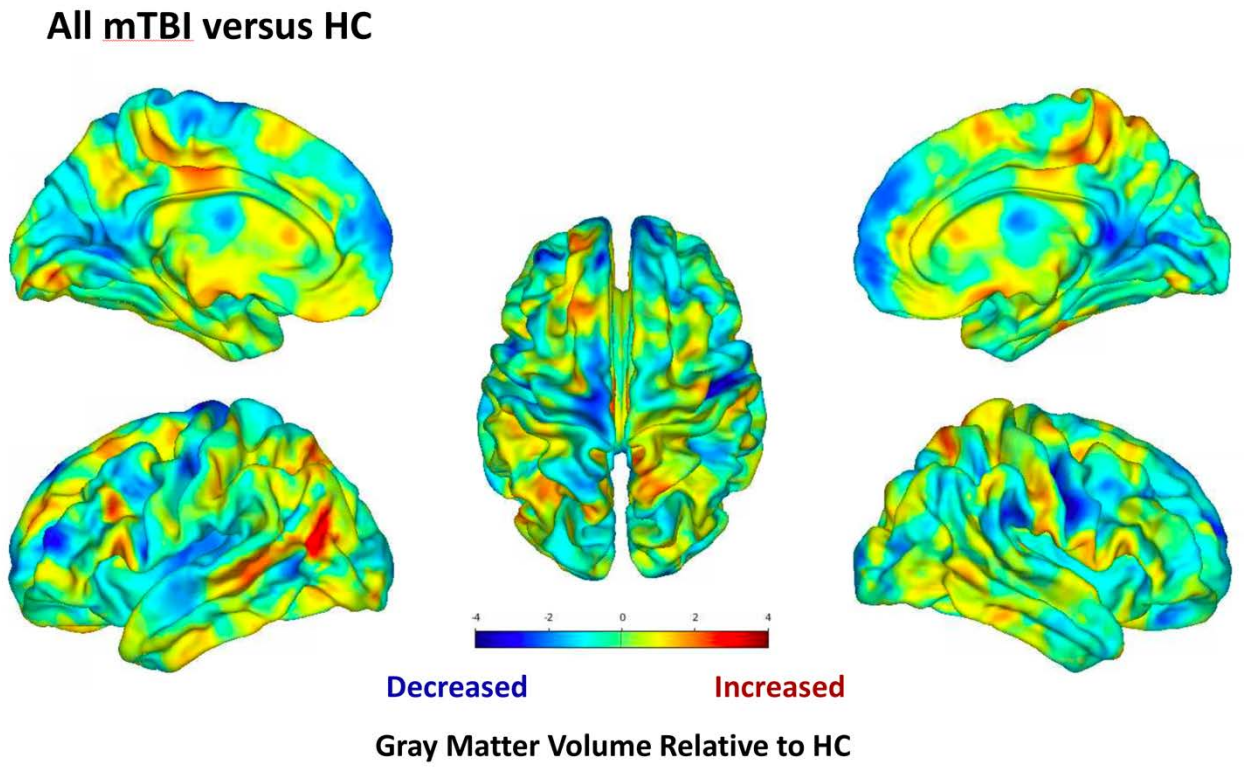


Figure S2. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of difference between the HC and mTBI groups. Warm colors reflect areas where the mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

All Group Omnibus Analysis of Variance. First, we compared the whole brain voxel-wise GMV across the six groups (HC, 2W, 1M, 3M, 6M, 12M) using a one-way ANOVA, controlling for total intracranial volume (TIV), sex, and age. The model design is shown in Figure S3. Figure S3 also provides a graphical representation of the F-values overlaid on a standard brain template. Warmer colors indicate greater F-values, while blue represents zero. As evident in the figure, there were regions showing some evidence of group differences at an uncorrected threshold, but once the FDR correction for multiple comparisons was applied, no regions showed

significant differences in GMV. *This suggests that cortical GMV does not differ significantly across the injury groups as a whole.*

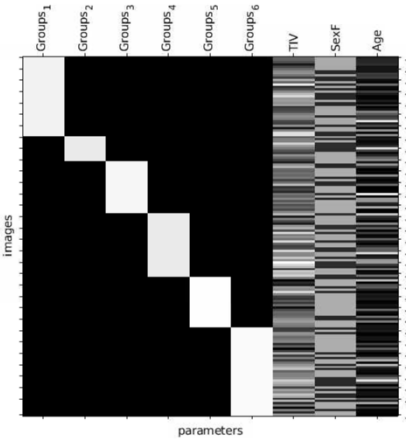
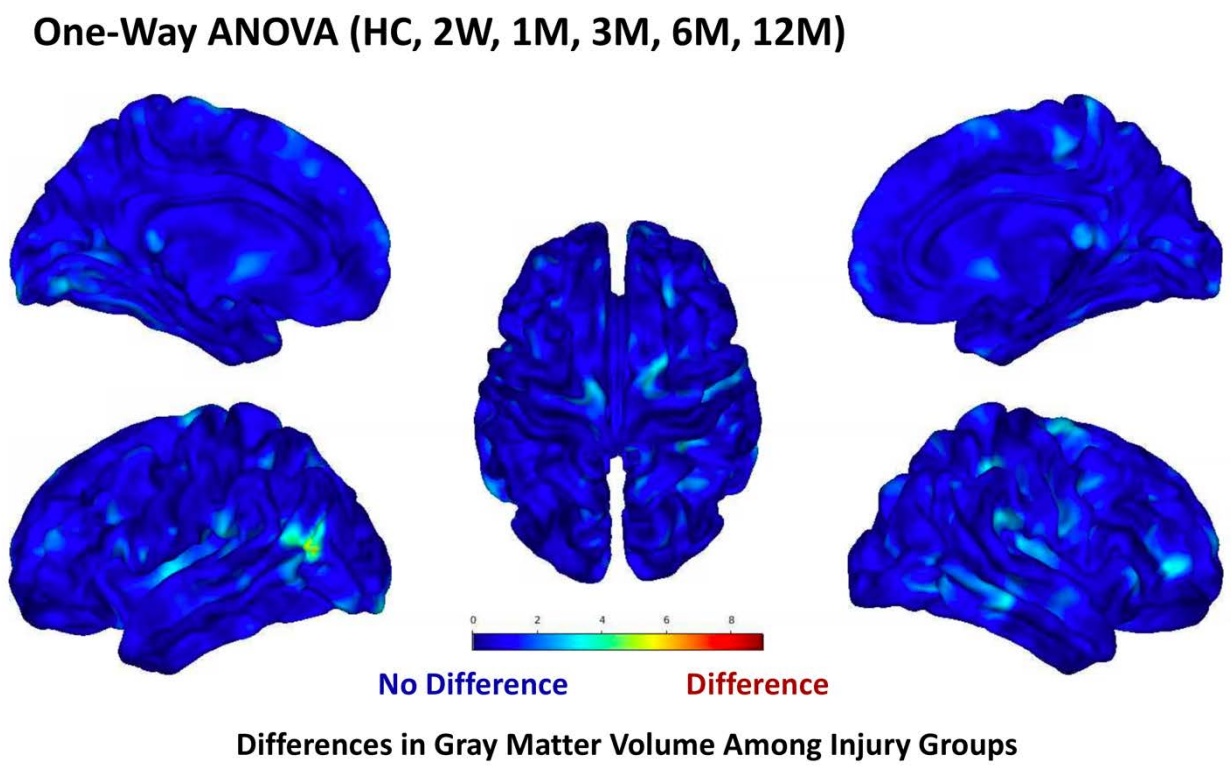


Figure S3. ANOVA results across all groups. LEFT: The statistical design for the ANOVA comparing HC (group 1) and each of the five mTBI groups (groups 2-6). The model was corrected for total intracranial volume (TIV), sex, and age. RIGHT: Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of differences across all six groups in terms of F-values. Warm colors reflect areas where the where the groups differed in GMV, while cool colors reflect regions where the groups did not differ. The colorbar shows the range of F-values, but does not reflect statistical significance.



All Participant TSI Correlation. To further explore the linear effect of time-since-injury on whole brain GMV, we conducted a simple linear regression analysis with the number of verified days post-injury as the predictor variable and GMV as the dependent variable. For this analysis, we excluded the HC group from the regression, since there was no time-since-injury for those individuals. Once multiple comparison correction (FDR) was applied to the data, no regions of GMV were significantly correlated with TSI, suggesting that, during the first 12 months post-injury, *the volume of gray matter does not appear to correlate linearly with the time since the injury occurred*. Nonetheless, in Figure S4, we provide the color maps showing the magnitude of the correlation with TSI. Warmer colors reflect regions showing nonsignificant positive

correlations between GMV TSI, and cooler colors reflect regions that show negative correlations between volume and TSI.

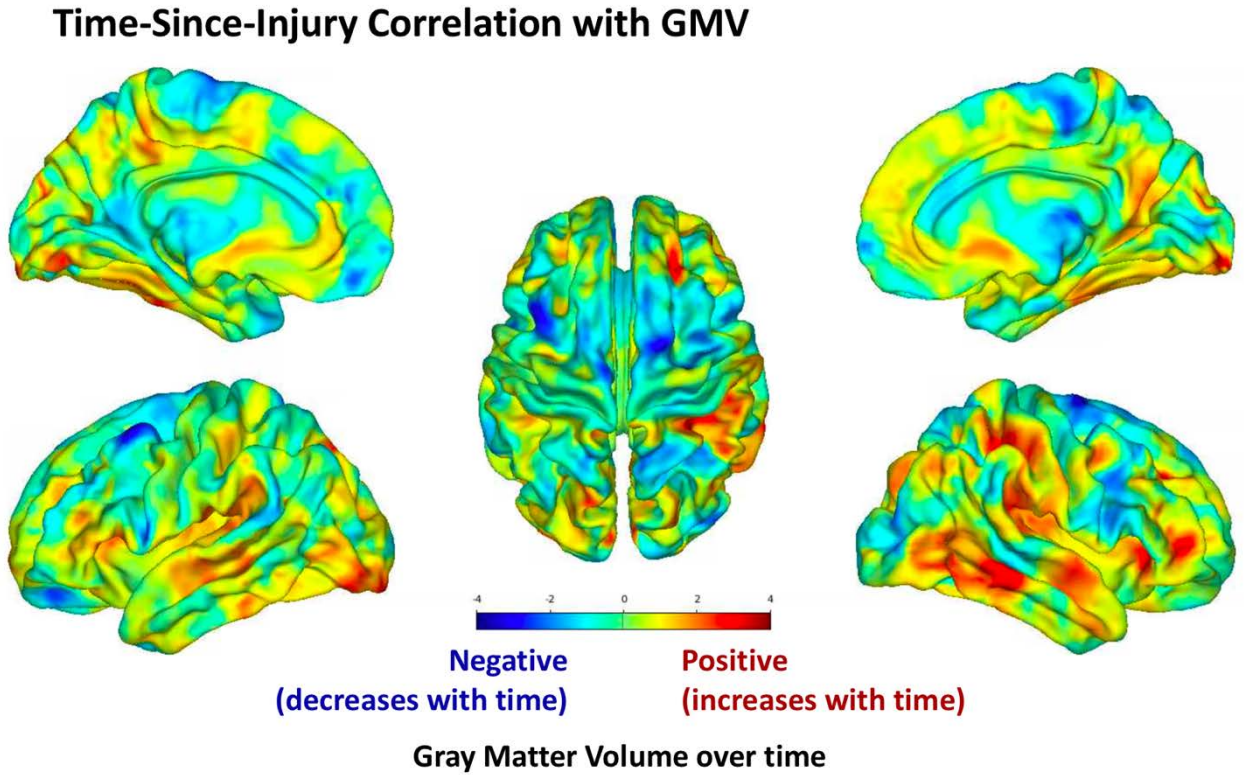


Figure S4. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with time-since-injury (TSI). Warm colors reflect areas where GMV was greater with longer TSI, while cooler colors reflect the negative correlations where GMV was reduced with longer TSI. The colorbar shows the range of T-values, but does not reflect statistical significance.

Pairwise Comparisons:

Next, for completeness in reporting and to allow the development of further hypotheses, we conducted pairwise comparisons of the GMV of each mTBI injury group relative to the HC group. These comparisons are outlined below:

2-Week vs. HC. Pairwise comparison between the 2W and HC group revealed only one region that showed greater GMV among those in the 2W group relative to the HC, which was significant using a cluster-wise FDR correction for multiple comparisons ($p = .011$). As shown below, this region was located within the left transverse occipital sulcus, as shown in Figure S5. The 2W group showed significantly greater GMV within this region of the left occipitoparietal cortex compared to healthy controls (and other injury groups as well).

Overall, this suggests that during the acute to sub-acute stage of an mTBI, within 2 weeks of the injury, there may be an increase in volume within the gray matter of the temporal-occipital junction, which is not evident by 4-weeks post-injury.

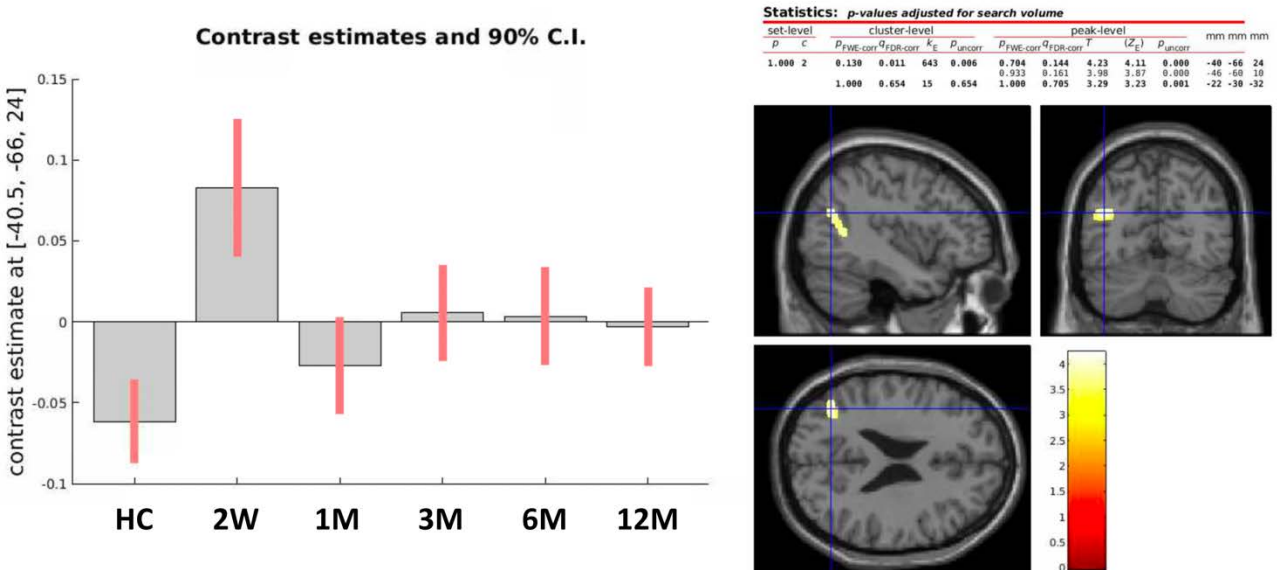


Figure S5. The contrast between the 2W and HC group showed greater GMV within a small region of the left temporoparietal regions among the 2W group. LEFT: mean contrast estimates for each of the six groups, showing that the 2W group showed significantly greater GMV relative to the HC (and other) groups. RIGHT: The region of larger GMV is displayed on a standardized template T1 image.

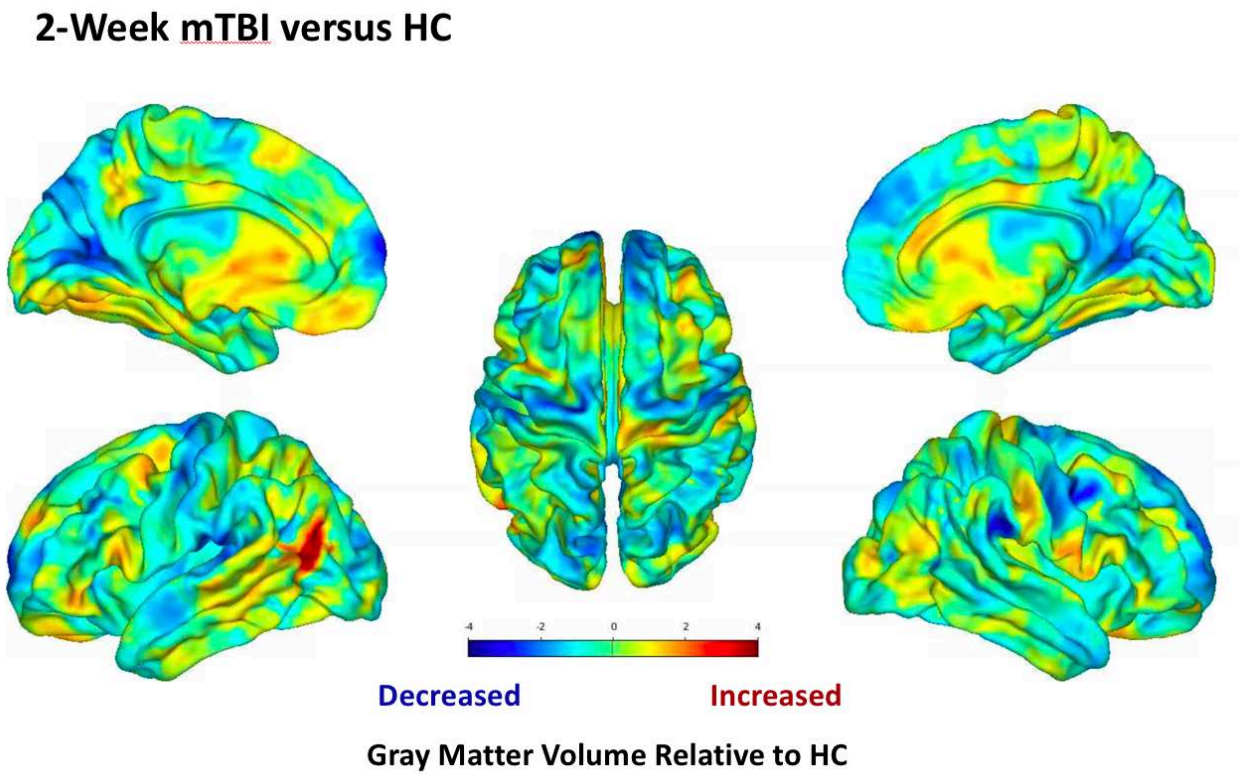


Figure S6. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of pair-wise difference between the 2W mTBI and HC group. Warm colors reflect areas where the 2W mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the 2W mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

While this could reflect sub-acute inflammatory processes, it may also be specific to the current

sample, which was smaller than all of the other samples in this study. Therefore, further work will be necessary to determine the reliability of this finding.

Figure S6 shows the un-thresholded color maps of the differences between the 2W group and the HC group. The warmer colors indicate regions of greater GMV among the 2W group compared to HCs, while the cooler colors indicate regions of decreased GMV of the 2W participants relative to HCs. The uncorrected threshold for significance at $p < .001$ was $T = 3.15$. Consistent with the statistically significant finding shown above, the maps clearly show increased GMV in the posterior parietal occipital region for those in the 2W group, which survived cluster-wise correction at $p < .05$. Although not statistically significant there were areas showing trends toward decreased GMV (cooler colors) in the 2W group, particularly in medial prefrontal, calcarine, and motor cortex, and the temporoparietal junction, suggesting potential regions for further exploration in future studies of the acute stage of mTBI.

1-Month vs. HC. After adjusting for multiple comparisons, pairwise comparison between the 1M and HC group did not reveal any significant differences in GMV between groups. Although differences were not significant, for completeness, Figure S7 displays the 1M mTBI group difference compared to the HC group, with warmer colors indicating trends toward greater gray matter volume in the 1M mTBI group relative to HC, while cooler colors show trends toward reduced volume in the mTBI group. The uncorrected threshold for significance at $p < .001$ was

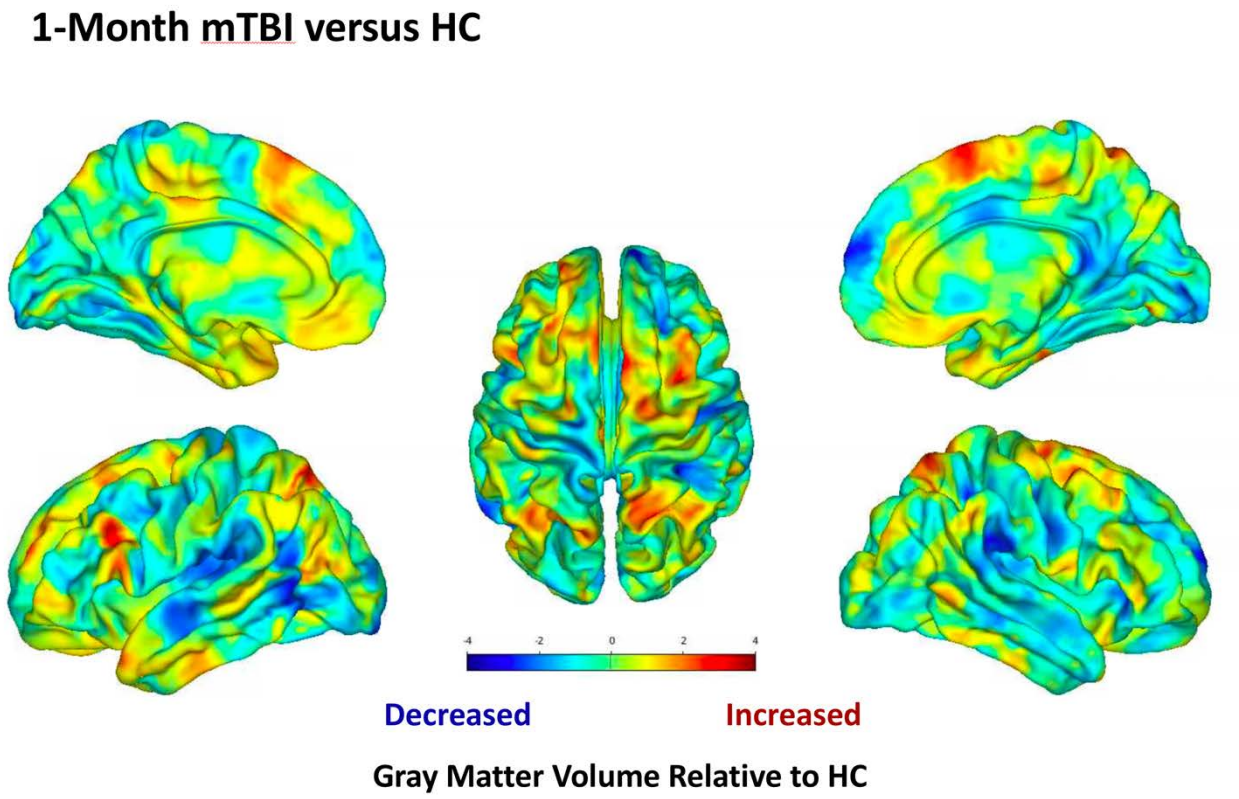


Figure S7. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of pair-wise difference between the 1M mTBI and HC group. Warm colors reflect areas where the 1M mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the 1M mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

T = 3.15. *These findings suggest that GMV does not differ significantly between 1M and HC groups.*

3-Month vs. HC. Upon adjusting for multiple comparisons, pairwise comparison between the 3M and HC group did not reveal any significant differences in GMV between groups. Although differences were not significant, for completeness, Figure S8 displays the 3M mTBI group difference compared to the HC group, with warmer colors indicating trends toward greater gray matter volume in the 3M mTBI group relative to HC, while cooler colors show trends toward reduced volume in the mTBI group. The uncorrected threshold for significance at $p < .001$ was T = 3.15.

These findings suggest that GMV does not differ significantly between 3M and HC groups.

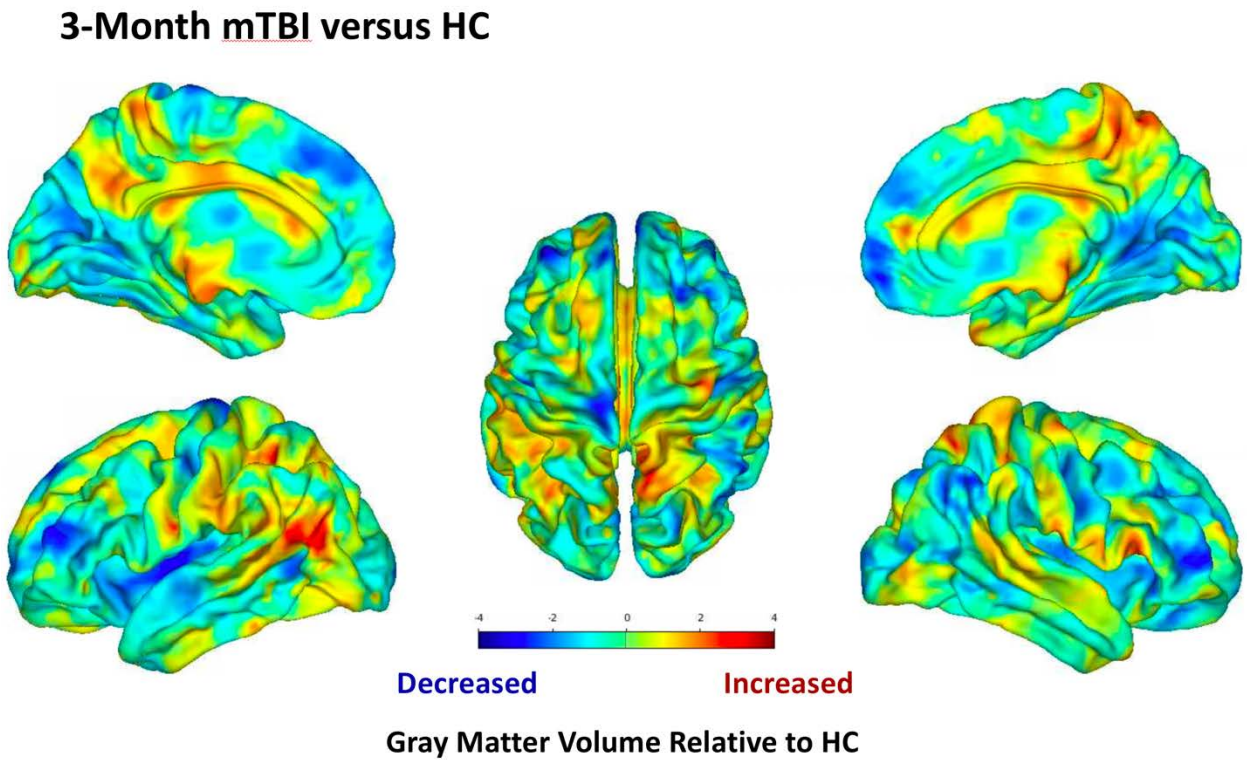


Figure S8. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of pair-wise difference between the 3M mTBI and HC group. Warm colors reflect areas where the 3M mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the 3M mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

6-Month vs. HC. After adjusting for multiple comparisons, pairwise comparison between the 6M and HC group did not reveal any significant differences in GMV between groups. Although differences were not significant, for completeness, Figure S9 displays the 6M mTBI group difference compared to the HC group, with warmer colors indicating trends toward greater gray matter volume in the 6M mTBI group relative to HC, while cooler colors show trends toward reduced volume in the mTBI group. The uncorrected threshold for significance at $p < .001$ was T = 3.15.

These findings suggest that GMV does not differ significantly between 6M and HC groups.

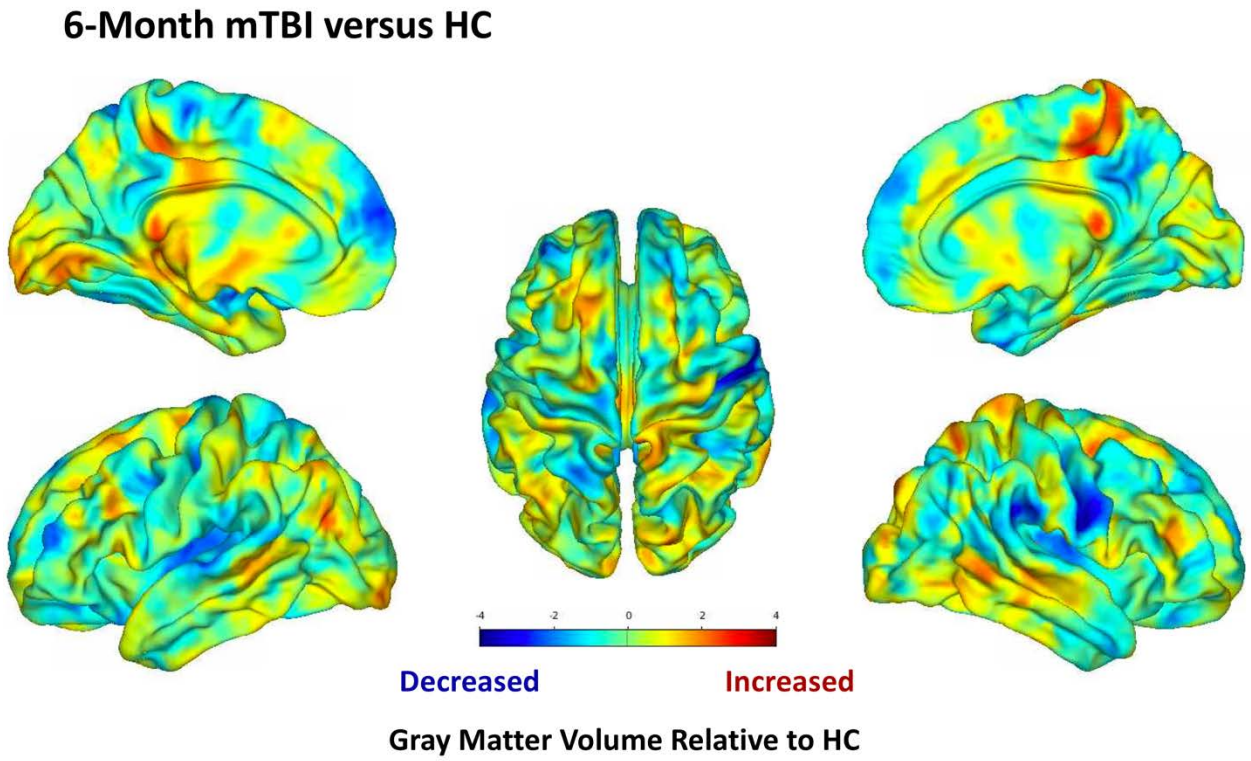


Figure S9. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of pair-wise difference between the 6M mTBI and HC group. Warm colors reflect areas where the 6M mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the 6M mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

12-Month vs. HC. The final group paired comparison was between the 12M mTBI group and the HC group. Again, we adjusted for multiple comparisons using a whole-brain FDR cluster-wise correction. However, after this correction, pairwise comparison between the 12M and HC group did not reveal any significant differences in GMV between groups. Again, despite the failure to reach significance in the paired comparison, we present the T-maps to show the general trends in GMV, regardless of statistical significance. Figure S10 displays the 12M mTBI group difference compared to the HC group, with warmer colors indicating trends toward greater gray matter volume in the 12M mTBI group relative to HC, while cooler colors show trends toward reduced volume in the mTBI group. The uncorrected threshold for significance at $p < .001$ was T = 3.15.

These findings suggest that GMV does not differ significantly between 12M and HC groups.

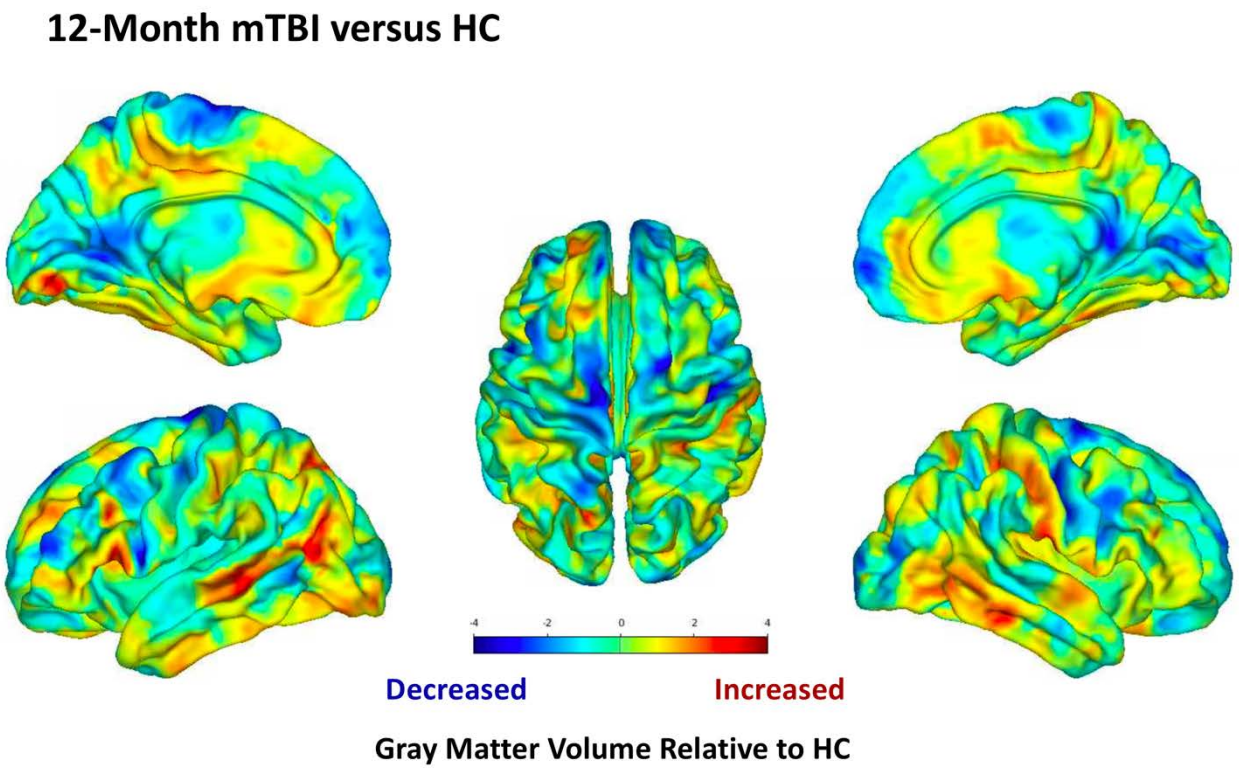


Figure S10. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of pair-wise difference between the 12M mTBI and HC group. Warm colors reflect areas where the 12M mTBI group showed greater GMV relative to the HC group. Cool colors reflect regions where the 12M mTBI group showed reduced GMV relative to the HC group. The colorbar shows the range of T-values, but does not reflect statistical significance.

Neurocognitive Component Correlations:

It was also of interest to determine the whole brain GMV correlations with the neurocognitive component scores derived from the PCA conducted on the summary metrics from the comprehensive assessment that was completed by each participant. As described in the main report, the PCA yielded 13 components from the 110 standardized test scores. These included: F1—Verbal Memory, F2—Attention/Executive Control, F3—Post-Concussion Syndrome/Emotional Disturbance, F4—Aggression, F5—Visuospatial Memory, F6—Sleep Quality (i.e., Sleep Disturbance), F7—Motor Speed, F8—Vigilance, F9—Cognitive Errors, F10—Daily Functioning, F11—Concept Formation, F12—Impulsivity, and F13—Processing Speed. These components accounted for 58.73% of the common variance in the test scores. These analyses were conducted with all participants (n = 158) from the University of Arizona sample included (if their T1 anatomical brain scan was of sufficient quality).

While GMV was not specifically hypothesized to correlate with these metrics in the primary study, we carried out a supplementary analysis in SPM12 using a multiple linear regression. All 13 components were entered into the analysis, along with the standard nuisance covariates of total intracranial volume, sex, and age. Data were analyzed at a height threshold of $p < .001$ uncorrected, with a cluster-wise FDR correction ($p < .05$) for multiple comparisons applied in each analysis. After correction for multiple comparisons, only two variables showed significant correlations with GMV.

The first was F6—Sleep Quality (i.e., Sleep Disturbance). As shown in Figure S11, increased sleep disturbance was associated with greater GMV within a large cluster of the right inferior

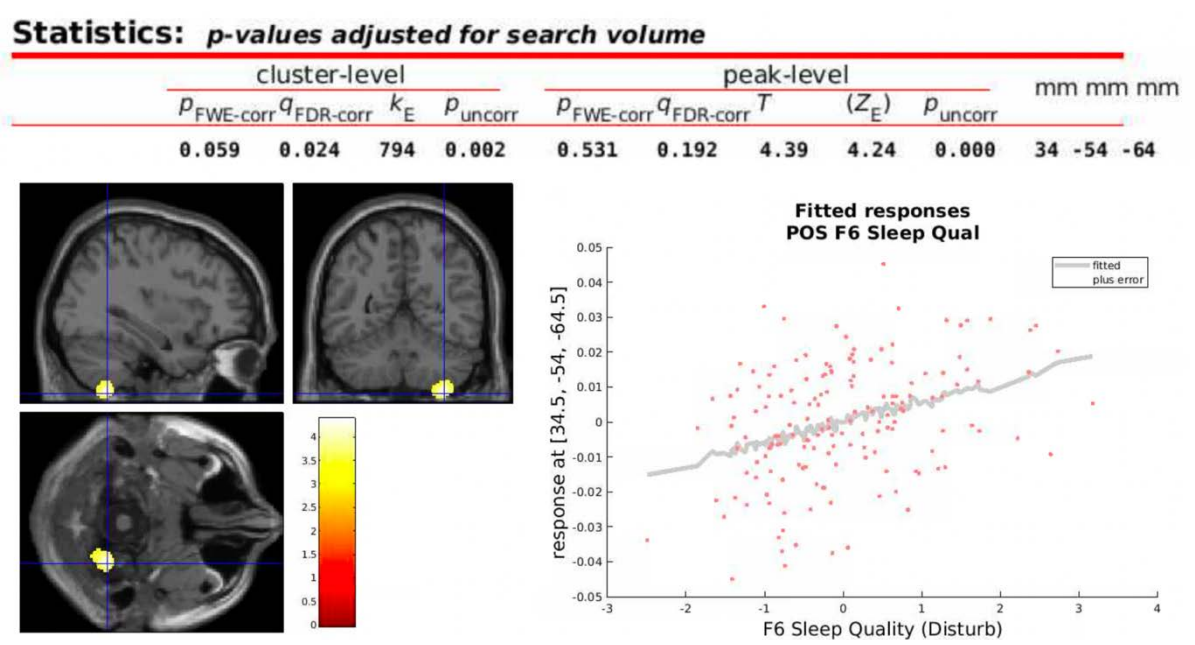


Figure S11. Gray matter volume (GMV) within the right inferior cerebellum was associated with greater sleep disturbance as measured by the component F6—Sleep Quality. The left figure shows the region where this association was identified, while the right figure shows the multiple regression scatterplot, with adjustment for all other components and covariates.

cerebellum, Area 8. Those individuals who tended to have larger volume within this region also tended to have the greatest difficulties with sleep.

The second component that showed a significant association with GMV was F7—Motor Speed. As shown below in Figure S12, individuals with greater volume within the motor cortex and left amygdala showed greater motor speed on a simple reaction time task.

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm	mm	mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.002	**2**	**0.018**	**0.004**	**1043**	**0.001**	**0.283**	**0.117**	**4.62**	**4.45**	**0.000**	**-27**	**6**	**-14**
						0.833	0.205	4.12	4.00	0.000	-44	14	-16
						0.940	0.205	3.98	3.87	0.000	-50	20	-22
		0.001	**0.001**	**1643**	**0.000**	**0.478**	**0.152**	**4.43**	**4.28**	**0.000**	**-46**	**-21**	**64**
						0.850	0.205	4.11	3.98	0.000	-28	-26	75
						0.997	0.348	3.72	3.63	0.000	-24	-38	74

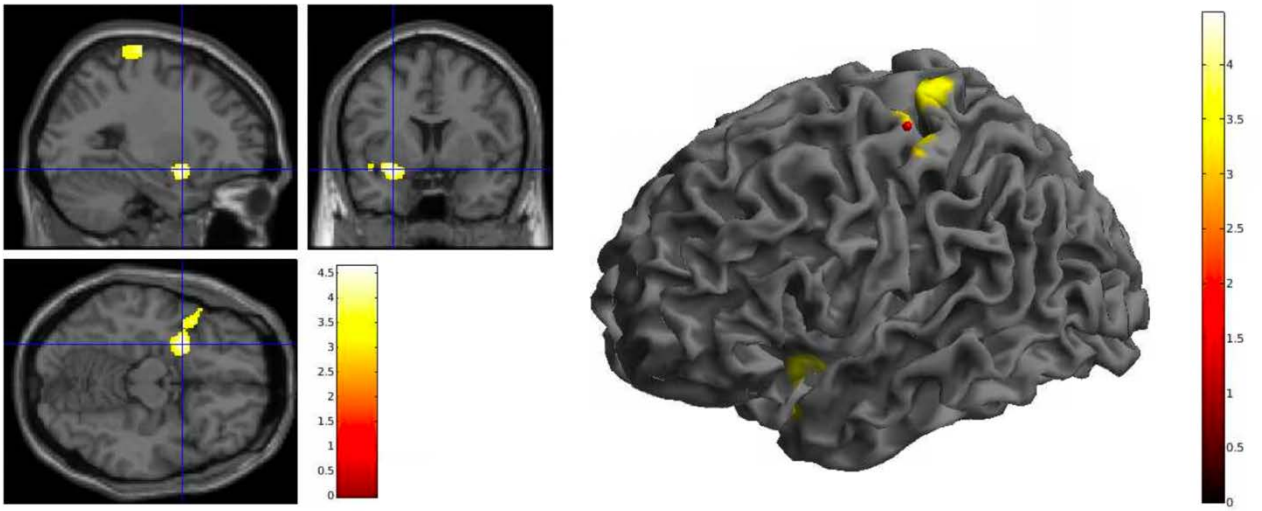


Figure S12. Gray matter volume (GMV) within the left motor cortex and left amygdala was correlated with faster motor speed/simple reaction time as measured by the component F7—Motor Speed. The left figure shows the region where this association was identified, while the right figure shows left hemisphere cortical regions where the correlation was present.

Although most GMV regional correlations did not survive stringent whole-brain corrections for multiple comparisons, it may still be useful for future work to have information regarding the cortical regions that showed non-significant correlation trends with each of the primary neurocognitive components that were identified. Therefore, in Figure S13, we present color maps reflecting the regional associations of GMV with each of the 13 neurocognitive component scores. As in previous sections, warmer colors reflect positive correlations such that greater GMV is associated with higher scores on the component, whereas cooler colors indicate negative correlations such that lower GMV within the region is associated with higher scores on the component.

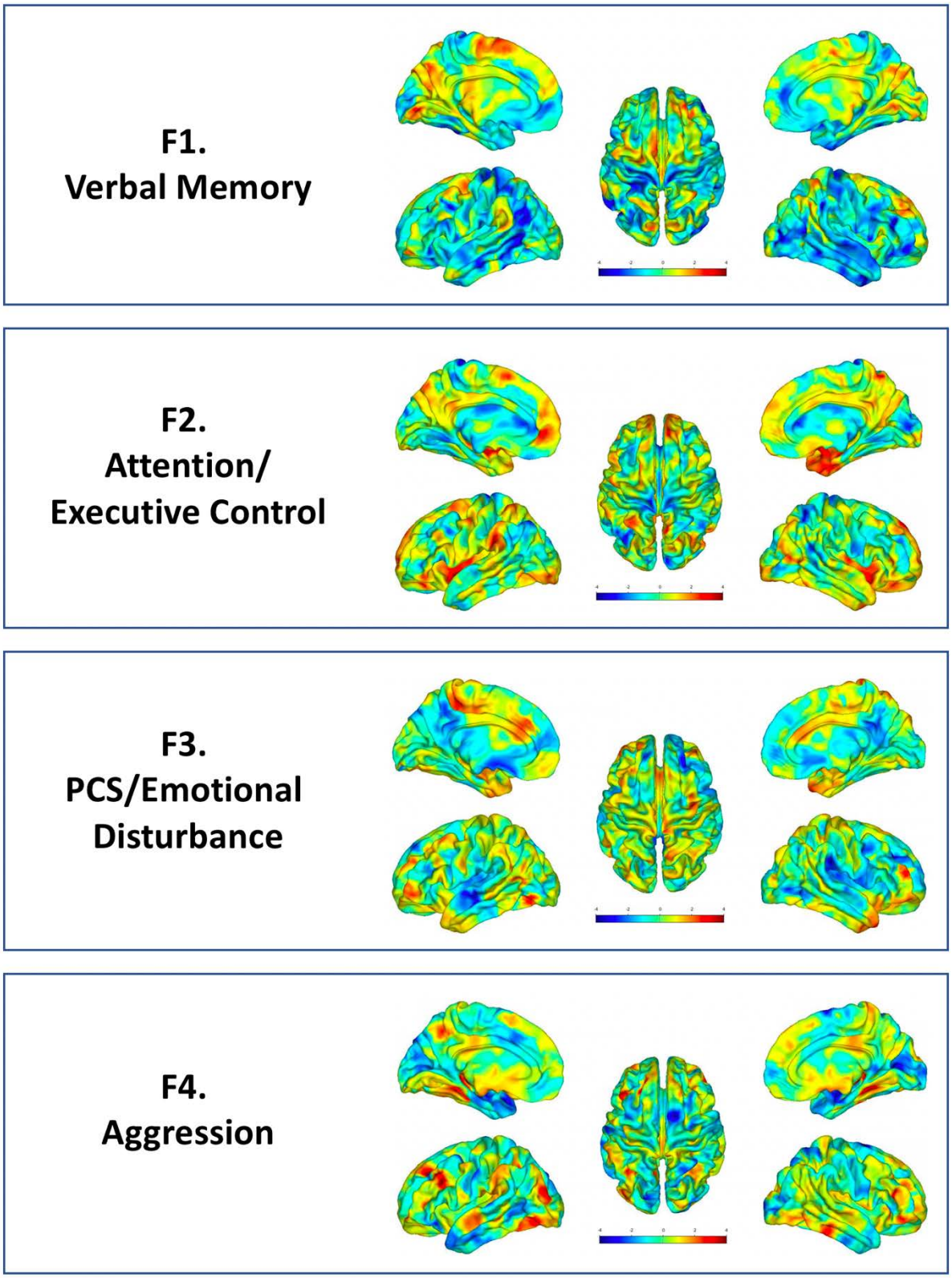
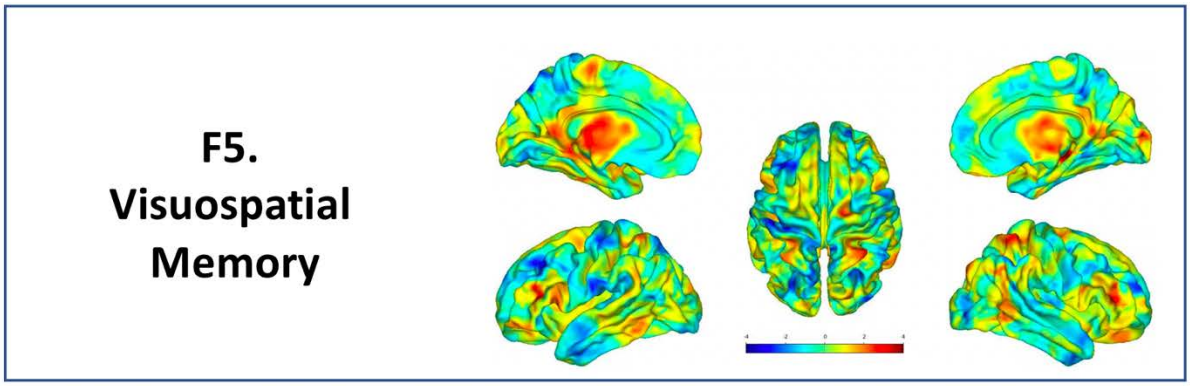
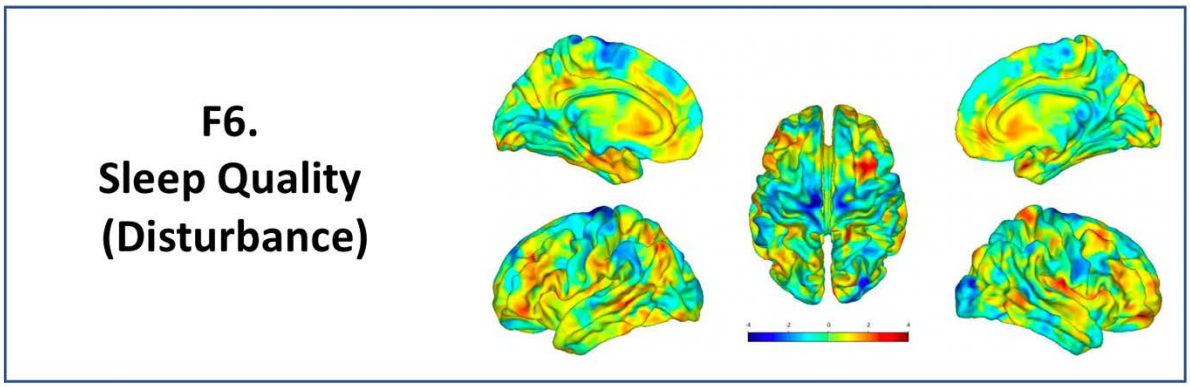
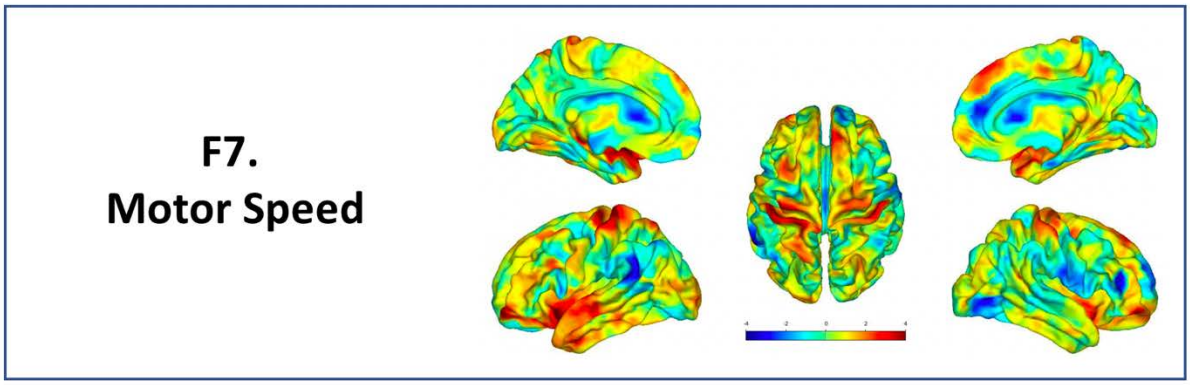


Figure S13. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with each of the 13 neurocognitive components. Warm colors reflect areas where GMV was greater with higher component scores, while cooler colors reflect the negative correlations where GMV was reduced among those with higher scores. The colorbar shows the range of T-values--not statistical significance.







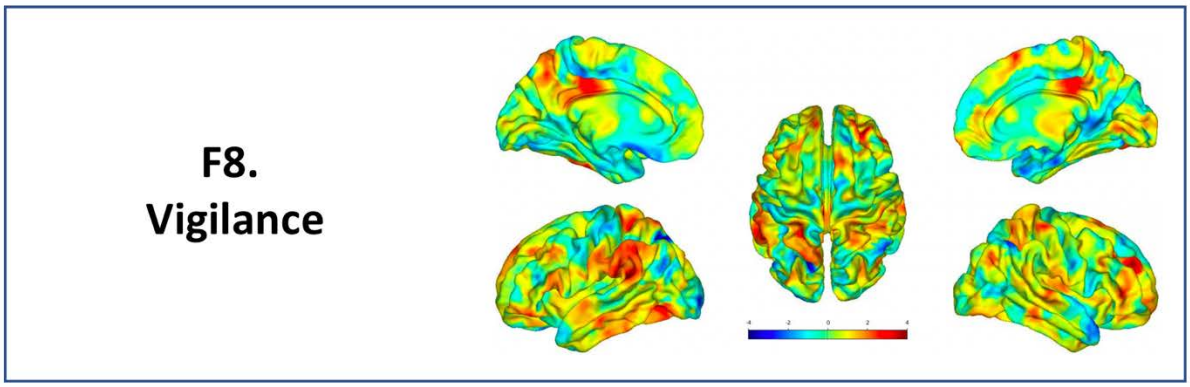


Figure S13. (continued)

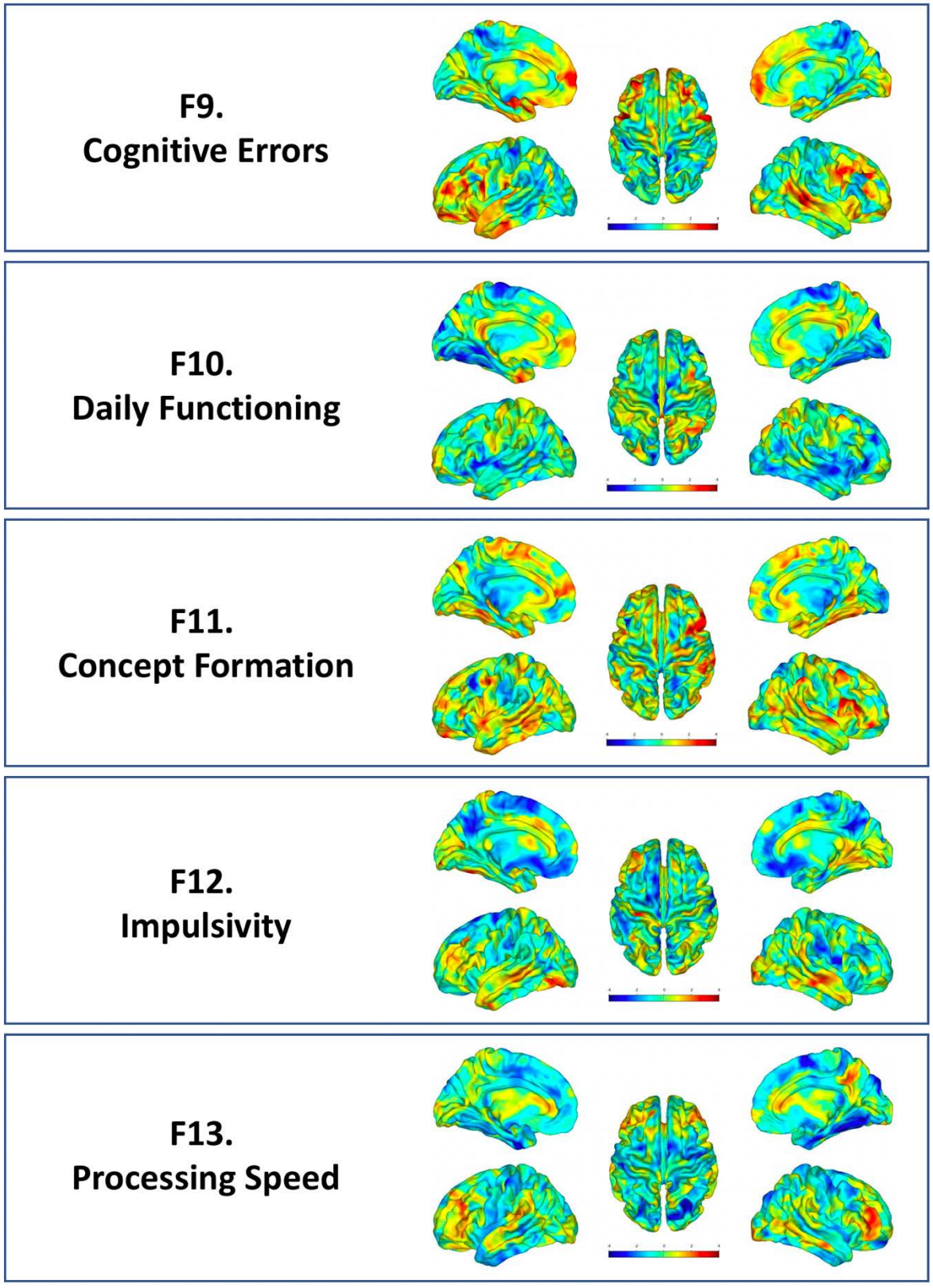


Figure S13. (continued)

Post-Concussion Symptom Correlations:

One of the major factors that affects the quality of life among individuals recovering from an mTBI is the persistence of post-concussion symptoms. These may or may not be associated with neurocognitive deficits. Here, we directly explored the association between post-concussive symptoms and GMV.

All MTBI Participants. First, we conducted a multiple regression analysis between GMV and scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). The questionnaire provides two primary outcomes, including an "early" symptom cluster defined by the first 3 items of the scale (RPQ-3) and a "late" symptom cluster defined by the last 13 items of the scale (RPQ-13), as well as separate scores for Cognitive, Somatic, and Emotional symptoms. We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): As shown in Figure S14, the RPQ-3 score was positively correlated with greater GMV within the inferior region of the right cerebellum. The areas of association were similar to those previously described for F6—Sleep Quality (Sleep Disturbance) in a previous section, further supporting the role of this area in symptom presentation among individuals with mTBI. This regional correlation was significant even after whole-brain cluster-wise FDR correction for multiple comparisons (FDR p = .004).

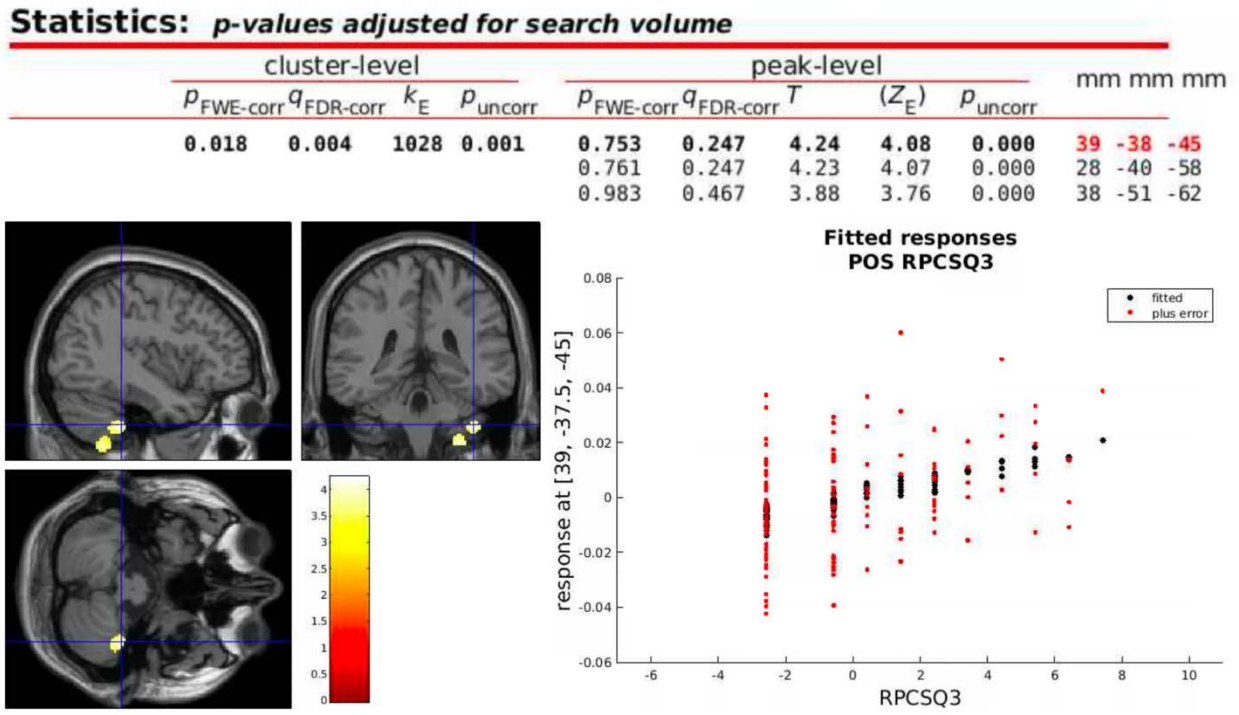


Figure S14. Gray matter volume (GMV) within the right inferior cerebellum was associated with higher scores on the RPQ-3 "early" symptom cluster of the RPCSQ. The left figure shows the region where this association was identified, while the right figure shows the multiple regression scatterplot, with adjustment for all other components and covariates.

The regression analysis also revealed a significant negative correlation between GMV and the RPQ-3 scores. As shown in Figure S15, this highly significant association was localized to the posterior thalamus, a region we have previously shown to be reduced in individuals with mTBI, and which increases with successful treatment. To further explore this association, we placed a regional mask over the bilateral thalami and found that, indeed, the posterior thalamus was smaller with greater "early" symptoms of concussion on the RPQ-3.

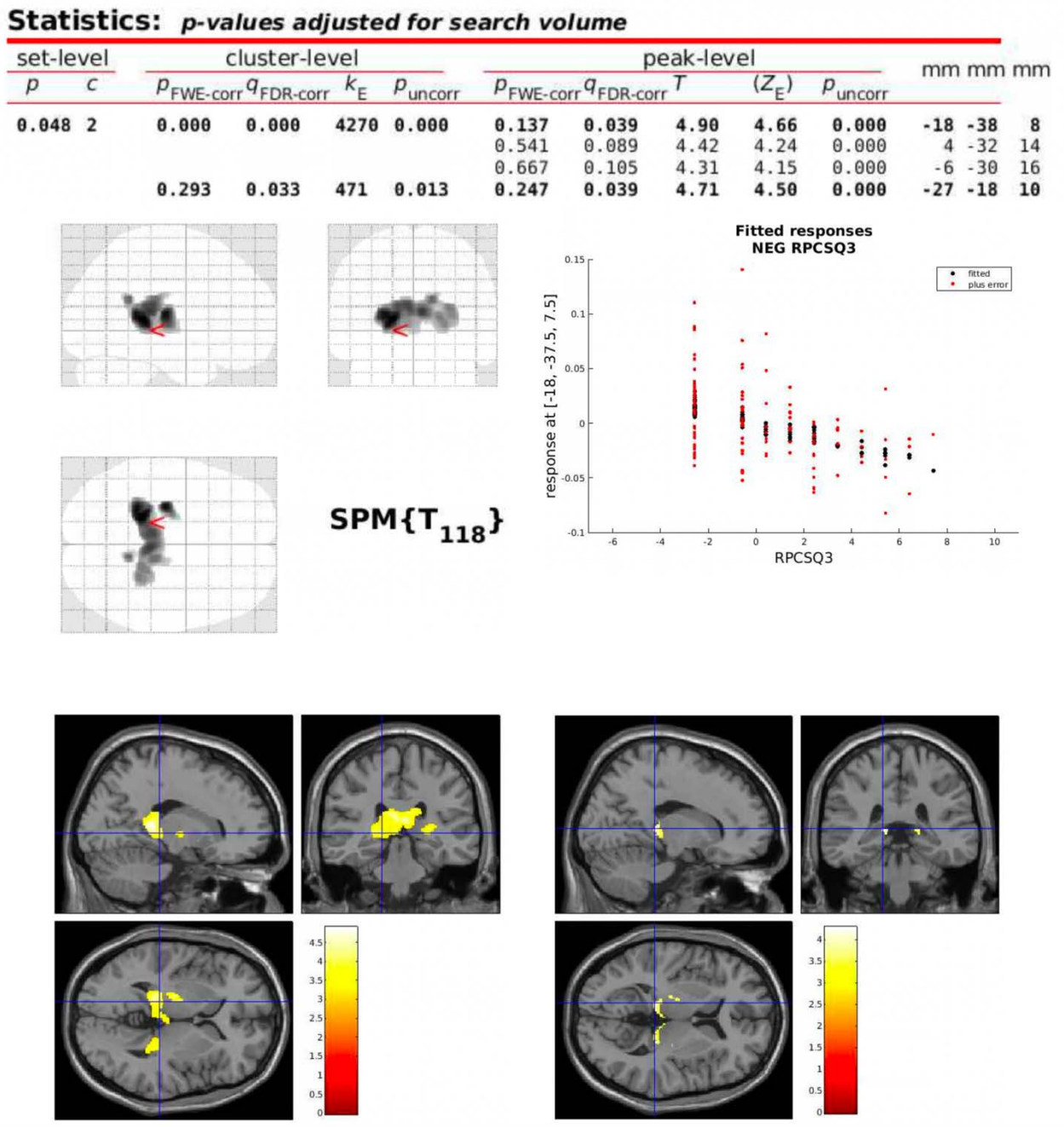


Figure S15. Gray matter volume (GMV) within the posterior thalamus was negatively correlated with concussion scores on the RPQ-3. Top Left: glass brain view. Top Right: scatterplot of peak voxel correlation. Bottom Left: Total active clusters. Bottom Right: Masked region including only the left and right thalamus.

Finally, for completeness of data, we also present the full correlation map of the gray matter surface areas with early symptom severity (see Figure S16). As the preceding analyses showed, there were no statistically significant regions of GMV correlations in the cortex. Therefore, these maps do not reflect statistical significance, but show the statistical T-maps of the correlations, which can inform future work. These maps show the regions that are positively correlated with greater symptom severity in warm colors, and the areas where reduced gray matter volume was associated with greater symptom severity in cool colors.

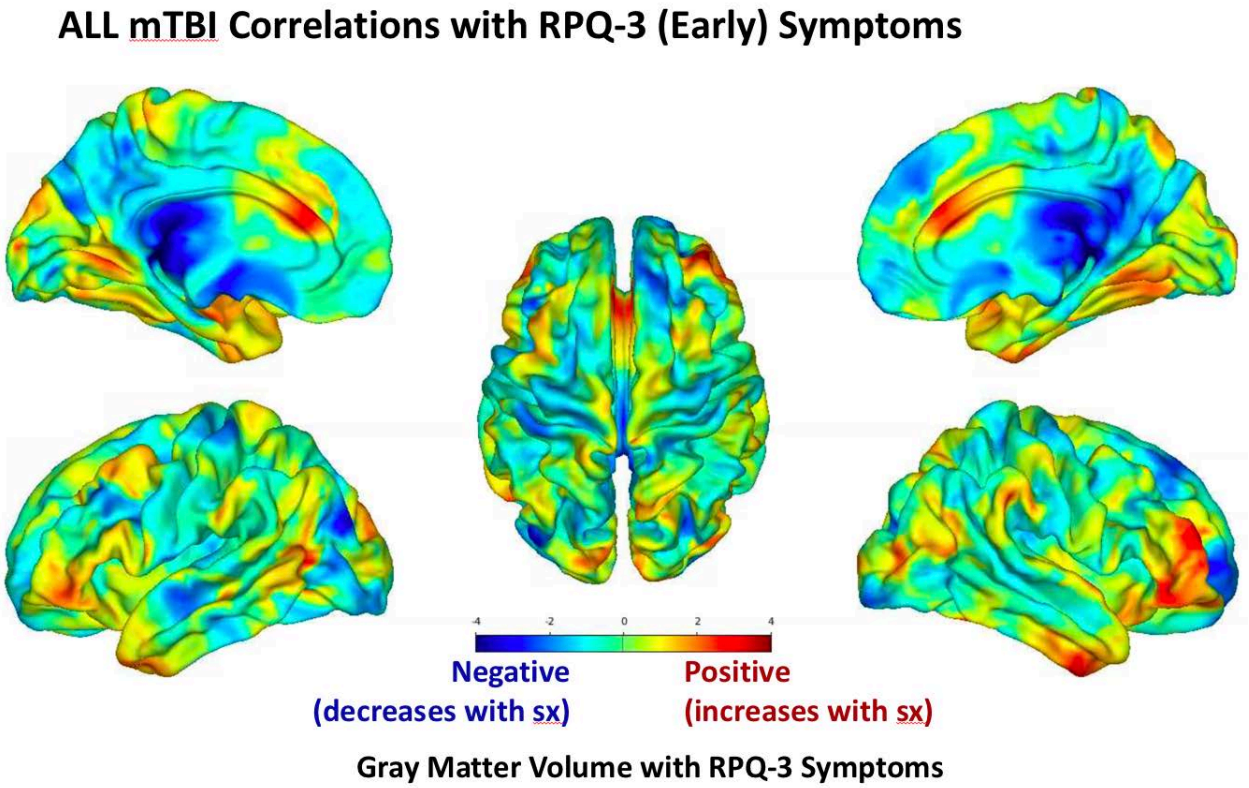


Figure 16. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with RPQ-3 Early Symptoms. Warm colors reflect areas where GMV was greater with higher PPQ-3, while cooler colors reflect the negative correlations where GMV was reduced with higher RPQ-3 symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Late Symptom Cluster (RPQ-13): Consistent with previous findings, the RPQ-13 score was positively correlated with greater GMV within the inferior region of the right cerebellum, further supporting the role of this area in symptom presentation among individuals with mTBI (see Figure S17 and S18). In this case, increased GMV within this region of the right cerebellum was associated with greater "late" symptoms of concussion as well. This regional correlation was significant even after whole-brain cluster-wise FDR correction for multiple comparisons (FDR p = .036). On the other hand, there were no significant negative correlations between GMV and RPQ-13.

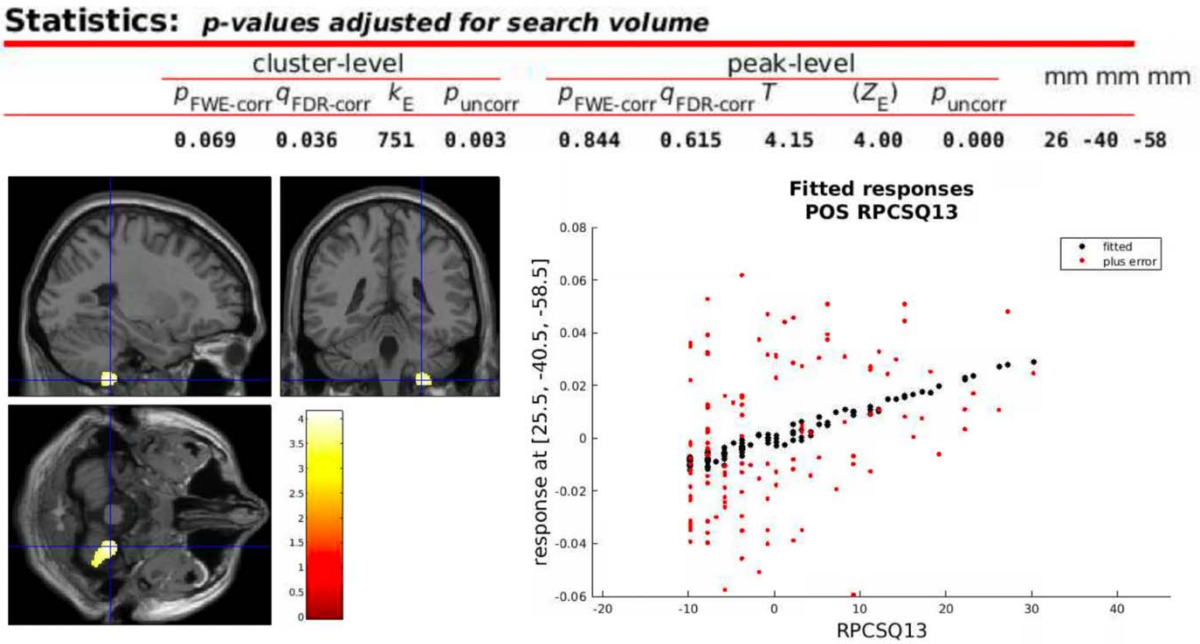


Figure S17. Gray matter volume (GMV) within the right inferior cerebellum was associated with higher scores on the RPQ-13 "late" symptom cluster of the RPCSQ. The left figure shows the region where this association was identified, while the right figure shows the multiple regression scatterplot, with adjustment for all other components and covariates.

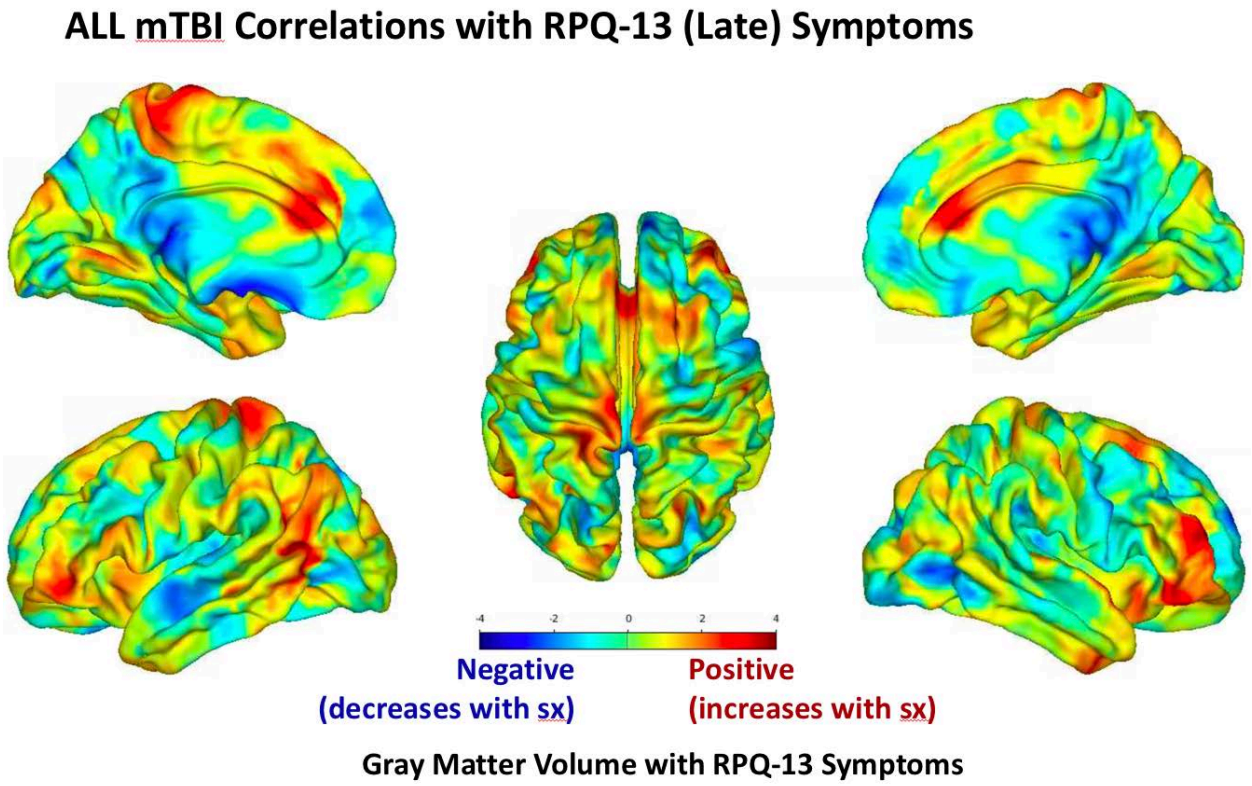


Figure S18. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with RPQ-3 Late Symptoms. Warm colors reflect areas where GMV was greater with higher RPQ-13, while cooler colors reflect the negative correlations where GMV was reduced with higher RPQ-13 symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Cognitive Symptom Cluster: We examined the correlations between GMV and the Cognitive Symptoms from the RPCSQ using the same methods described previously. However, there were no regions that were correlated with these symptoms, either positively or negatively. As with the prior analyses, we also include the correlation T-map for reference to show the general patter of correlations between GMV and cognitive symptoms on the RPCSQ (see Figure S19. These maps do not reflect statistical significance, but show the correlation trends, which may be useful in forming future hypotheses. Notably, this map is quite similar to the previous map for Late Symptoms.

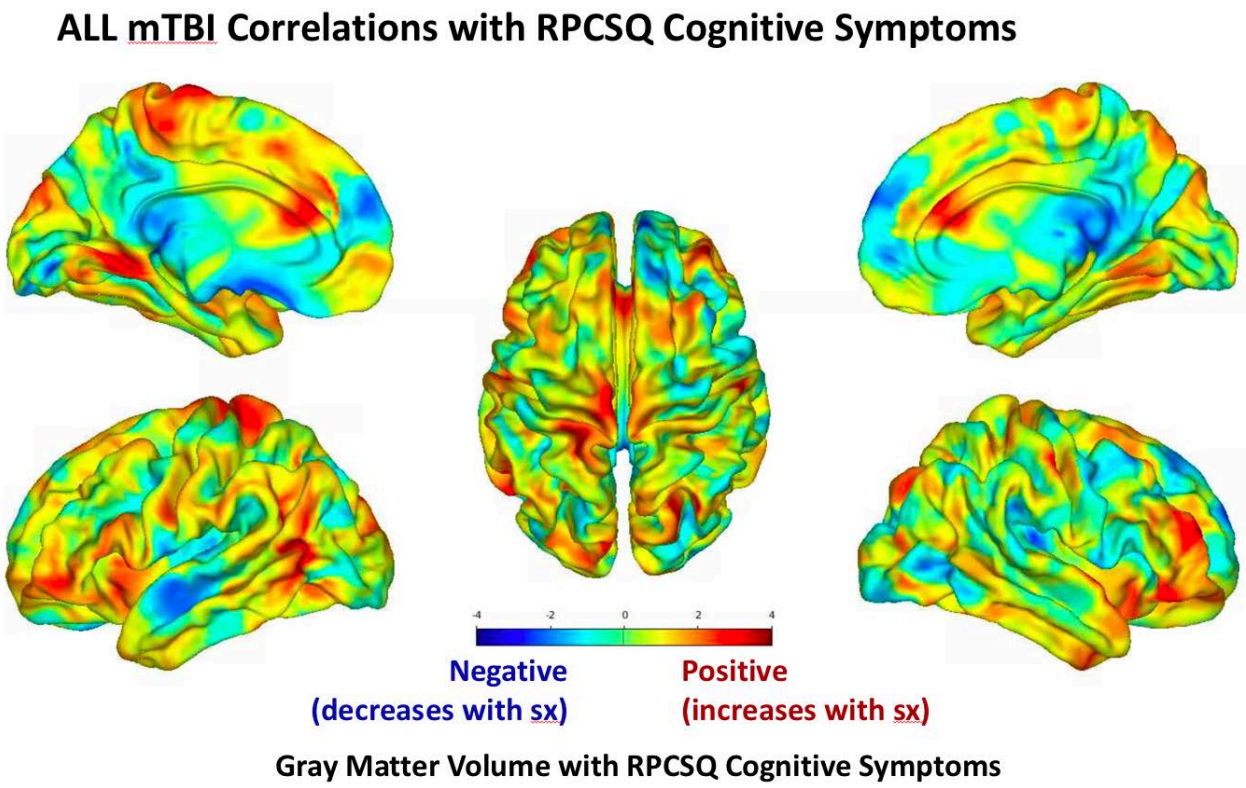


Figure S19. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with RPCSQ Cognitive Symptoms. Warm colors reflect areas where GMV was greater with higher Cognitive Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Cognitive symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Somatic Symptom Cluster: We examined the correlations between GMV and the Somatic Symptoms from the RPCSQ using the same methods described previously. This analysis yielded a significant region of association between GMV and somatic symptom complaints that was localized to the inferior right cerebellum (similar to findings discussed previously for sleep issues and the early symptom cluster of RPQ-3). As shown in Figure S20, greater somatic complaints were associated with larger gray matter within this region.

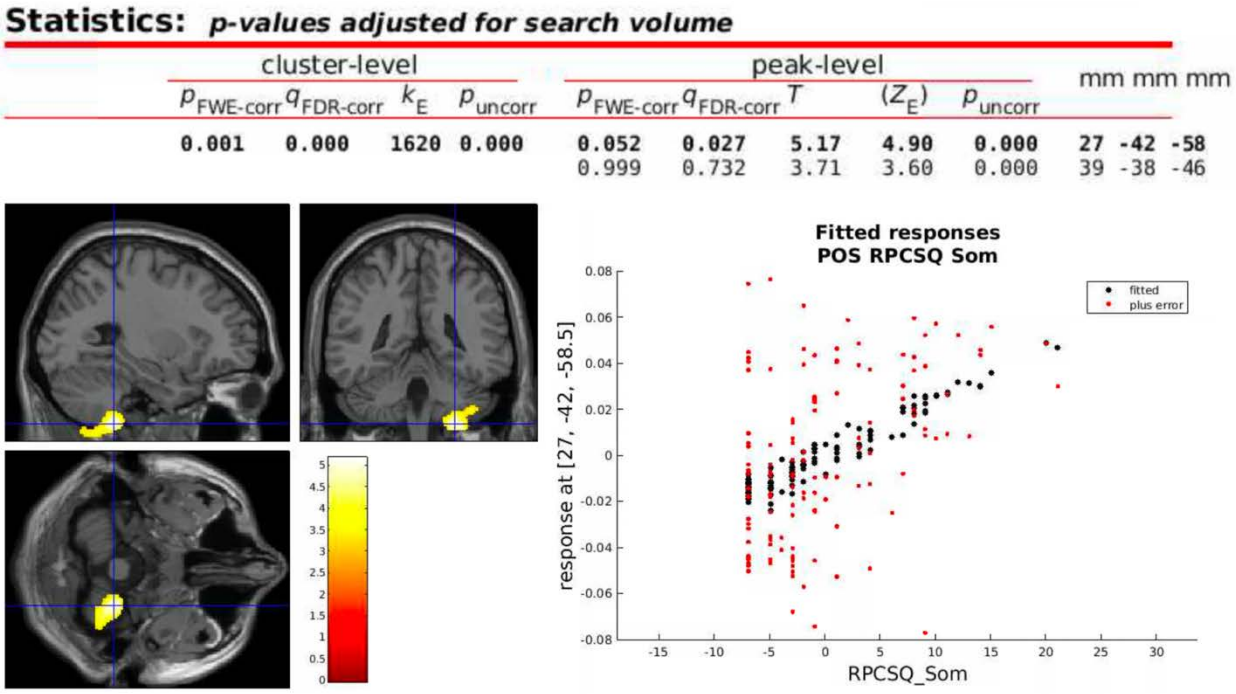


Figure S20. Gray matter volume (GMV) within the right inferior cerebellum was associated with higher scores on the Somatic symptom cluster of the RPCSQ. The left figure shows the region where this association was identified, while the right figure shows the multiple regression scatterplot, with adjustment for all other components and covariates.

The regression analysis also revealed a significant negative correlation between GMV and the Somatic Cluster scores within regions similar to that found for the RPQ-3 above. As shown in Figure S21, this highly significant association was localized to the posterior thalamus, a region we have previously shown to be reduced in individuals with mTBI, and which increases with successful treatment. It was of interest to isolate the areas of the thalamus from surrounding areas of activation, so we placed a regional mask over the bilateral thalami and found that, in fact, the posterior thalamus was smaller with greater scores on the Somatic Cluster of symptoms.

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm	mm	mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.092	**2**	**0.000**	**0.000**	**2333**	**0.000**	**0.232**	**0.121**	**4.73**	**4.52**	**0.000**	**-15**	**-34**	**16**
						0.724	0.212	4.26	4.10	0.000	-26	-40	12
						0.950	0.286	3.99	3.85	0.000	27	-39	15
		0.398	**0.049**	**410**	**0.019**	**0.750**	**0.212**	**4.24**	**4.08**	**0.000**	**-27**	**-18**	**10**

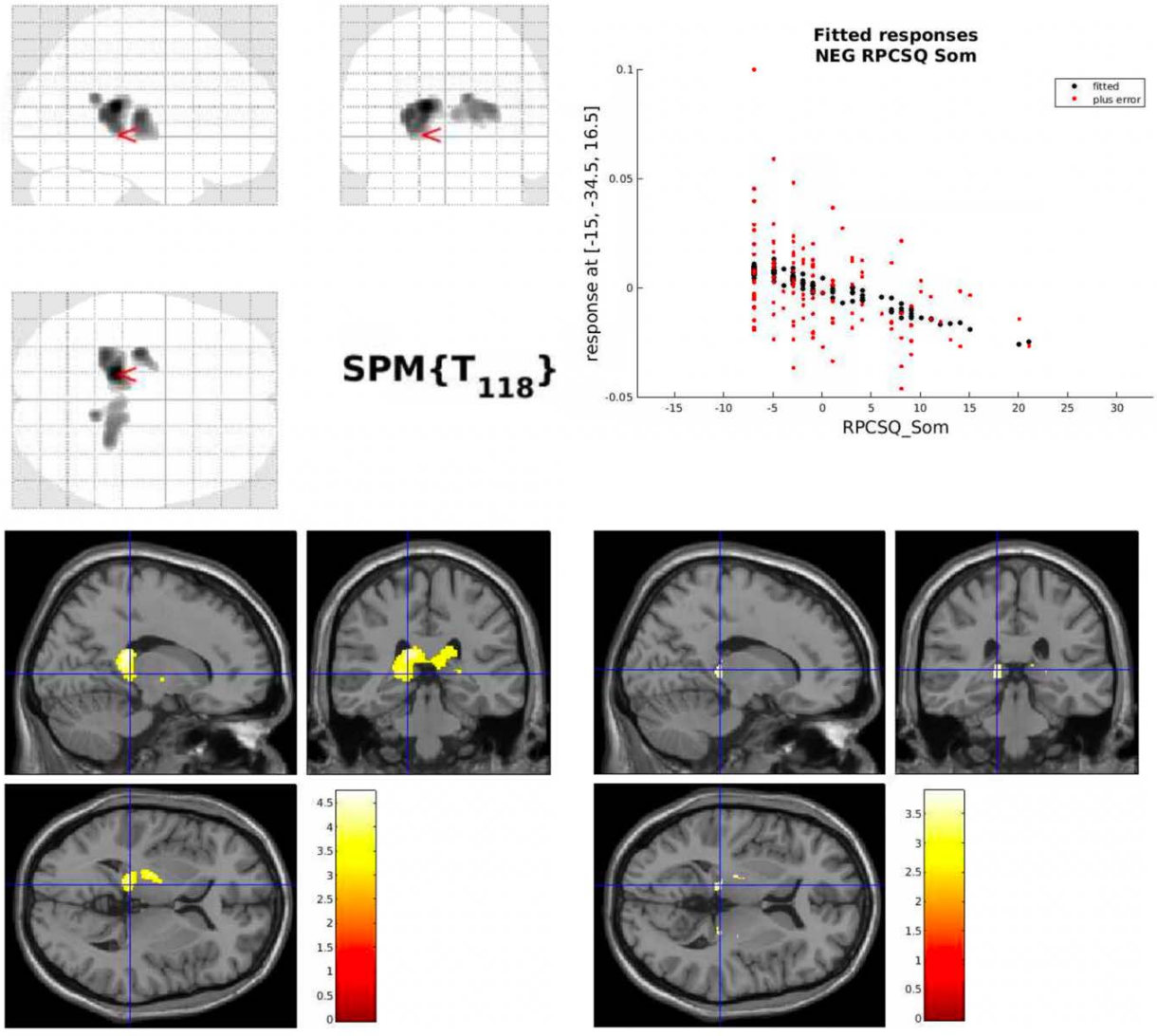


Figure S21. Gray matter volume (GMV) within the posterior thalamus was negatively correlated with scores on the Somatic symptom cluster of the RPCSQ. Top Left: glass brain view. Top Right: scatterplot of peak voxel correlation. Bottom Left: Total active clusters. Bottom Right: Masked region of the left and right thalamus.

Although no cortical regions were found to be associated with Somatic Symptoms on the RPCSQ, we again provide full cortical correlation maps for informational purposes and to generate additional hypotheses for future studies (see Figure S22). The maps to not reflect statistical significance, but show the pattern of regional correlations throughout the brain, with warmer colors reflecting nonsignificant positive correlations between GMV and greater Somatic symptoms, while cooler colors reflect negative correlations. These maps appear similar to those reported above for the RPQ-3 Early symptoms, with the greatest correlations being evident in the thalamus.

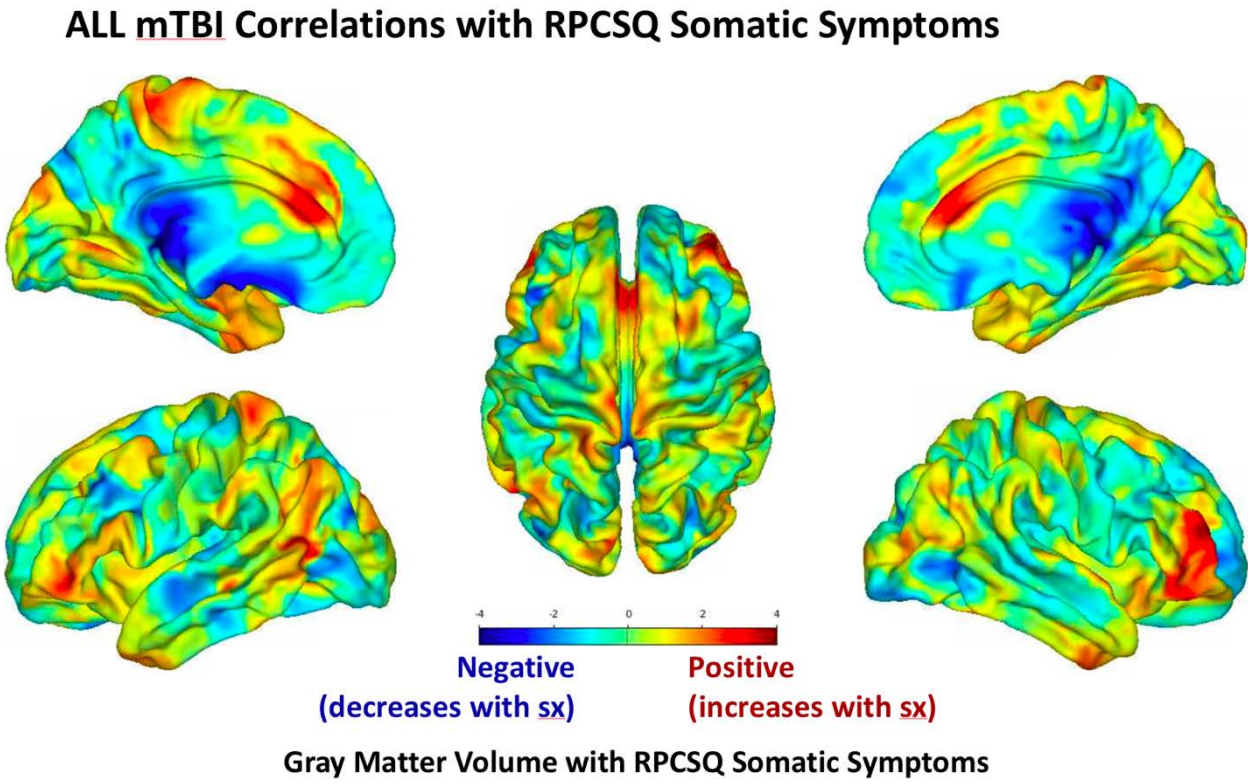


Figure S22. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with RPCSQ Somatic Symptoms. Warm colors reflect areas where GMV was greater with higher Somatic Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Somatic symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Emotional Symptom Cluster: We examined the correlations between GMV and the Emotional Symptom Cluster from the RPCSQ using the same methods described previously. Following correction for multiple comparisons using a whole-brain cluster-wise threshold, we found no significant associations between GMV and emotional symptoms from the RPCSQ. Full correlation maps are shown in Figure S23.

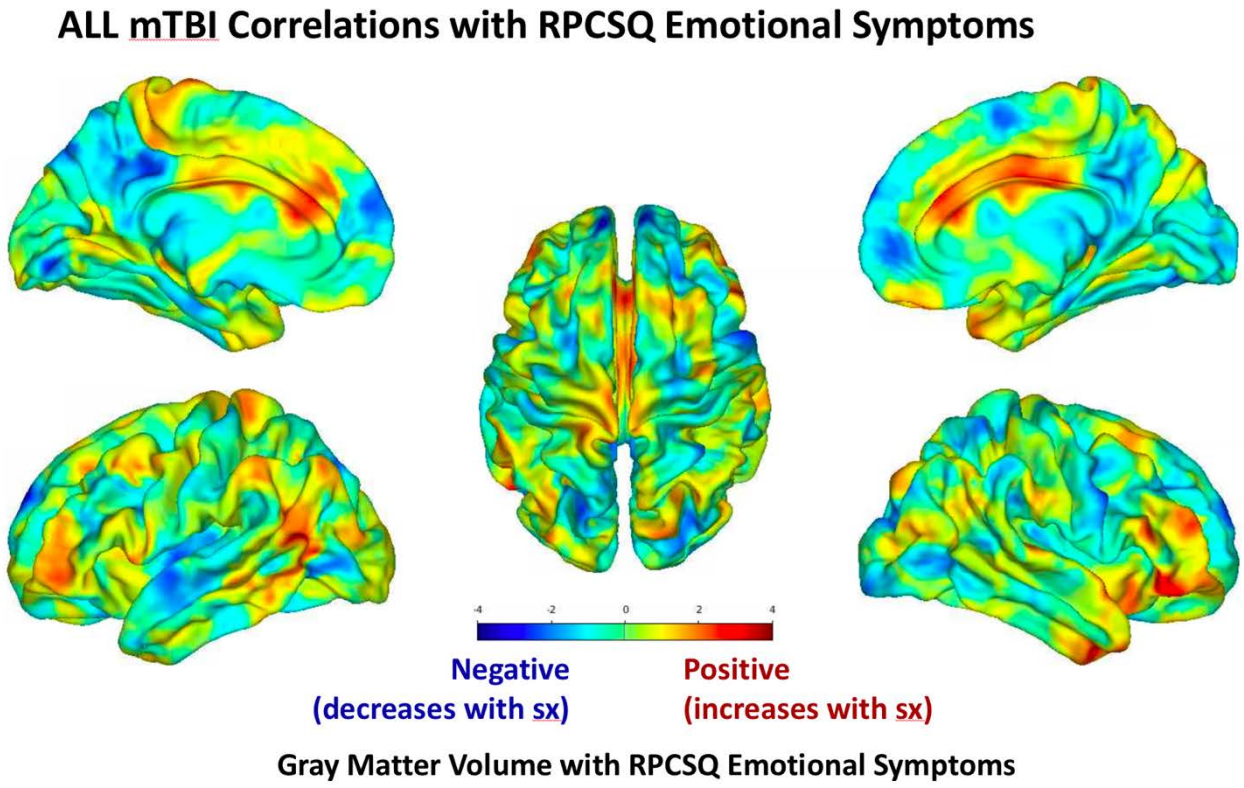


Figure S23. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the general pattern of correlations with RPCSQ Emotional Symptoms. Warm colors reflect areas where GMV was greater with higher Emotional Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Emotional symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Conclusions for All MTBI Patients: Overall, these findings suggest that post-concussion symptoms are associated with altered GMV when the entire sample of individuals with mTBI is considered (i.e., without regard to time since injury). Two major areas appear to be important in this regard. First, greater GMV in the inferior right cerebellum is positively associated with greater "early" symptoms of concussion and somatic symptoms. Conversely, decreased GMV within the posterior areas of the thalamus was associated with greater early symptoms and somatic symptoms of mTBI. These findings are consistent with other work suggesting that the thalamus may be particularly susceptible to injury during mTBI and when such injury leads to reduced volume of that region, somatic symptoms and sleep disruption may predominate. On the other hand, the "late" symptom cluster, and Cognitive and Emotional symptom clusters were not associated with differences in GMV in this sample.

Breakdown by Time-Since Injury Groups

2 Week Post-MTBI Participants. For the 2-week post-injury group, we conducted a multiple regression analysis between GMV and the various cluster scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): After FDR whole-brain correction for multiple comparisons, there were no significant positive or negative correlations between GMV and RPQ-3 scores. For completeness in reporting, we present the un-thresholded correlation maps for the 2-week sample alone (Figure S24). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

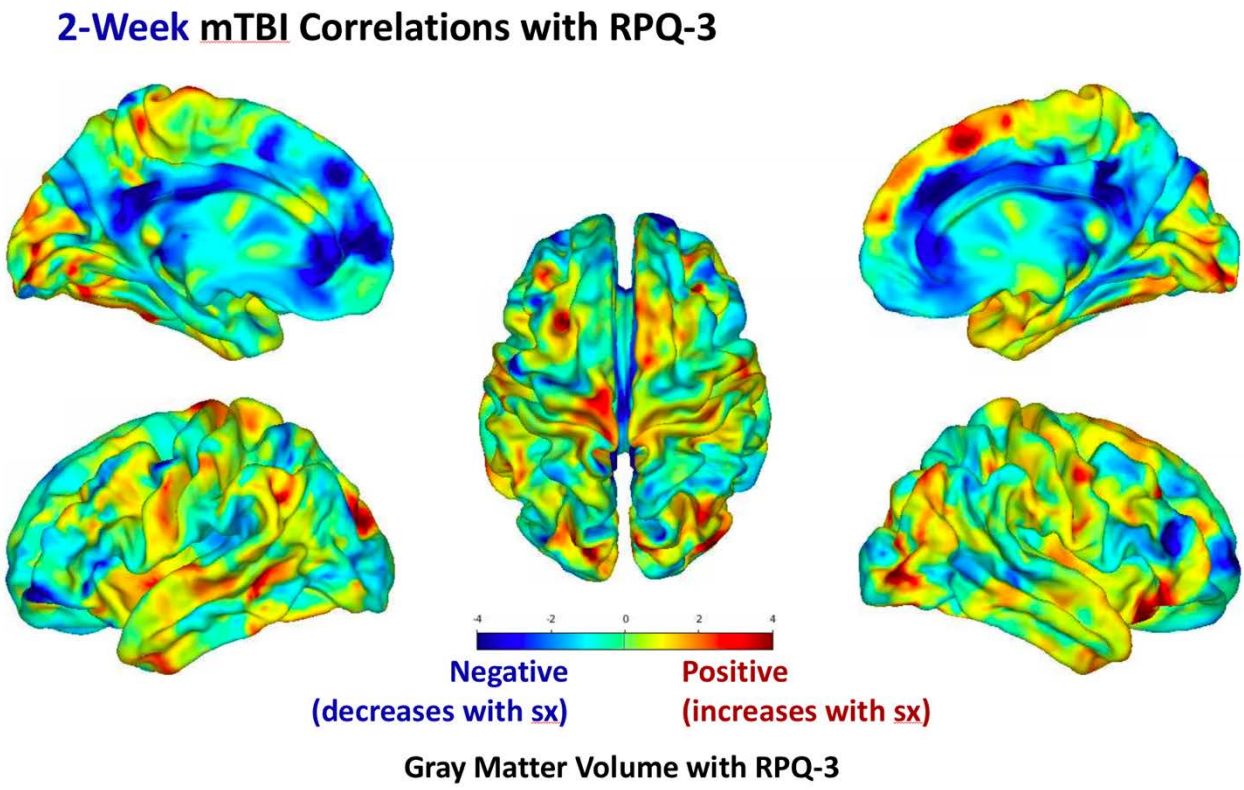


Figure S24. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **2-Week** pattern of correlations with RPQ-3 (Early) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Early symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Late Symptom Cluster (RPQ-13): After FDR whole-brain correction for multiple comparisons, there were no significant positive or negative correlations between GMV and RPQ-13 scores. For completeness in reporting, we present the un-thresholded correlation maps for the 2-week sample alone (Figure S25). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

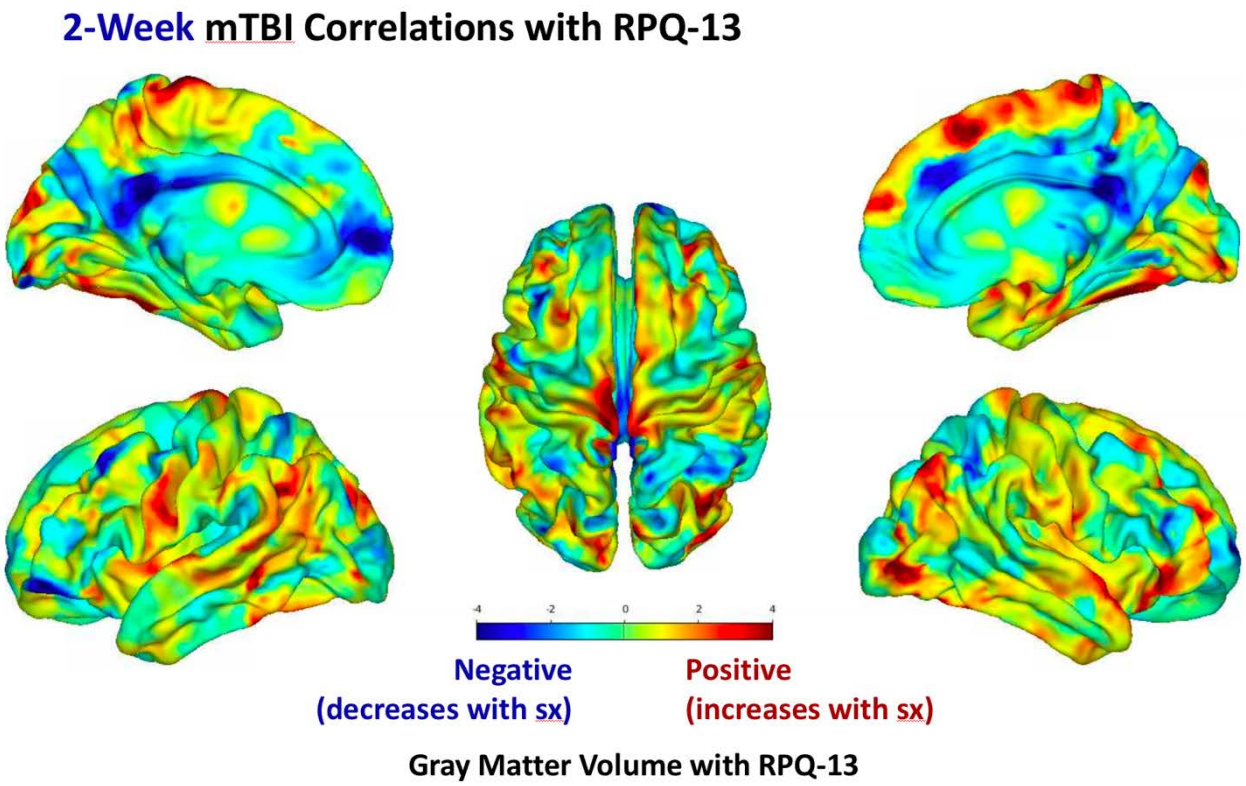


Figure S25. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **2-Week** pattern of correlations with RPQ-13 (Late) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Late symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

1 Month Post-MTBI Participants. For the 1-Month post-injury group, we conducted a multiple regression analysis between GMV and the various cluster scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): After FDR whole-brain correction for multiple comparisons, there were no regions showing either significant positive or negative correlation between GMV and RPQ-3.

Despite the lack of significant correlations, in order to ensure comprehensiveness in reporting, we present the un-thresholded correlation maps for the 1-Month sample alone for RPQ-3 (Figure S26). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

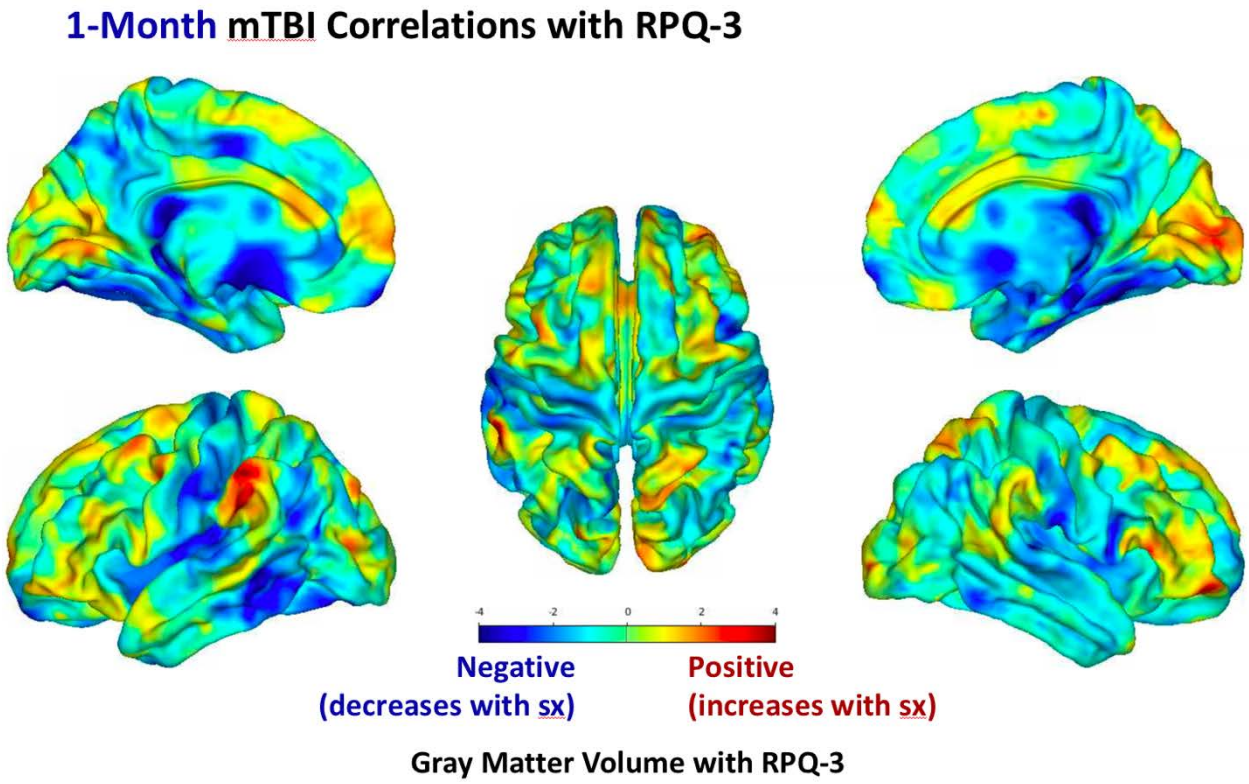


Figure 26. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **1-Month** pattern of correlations with RPQ-3 (Early) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Early symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Late Symptom Cluster (RPQ-13): After FDR whole-brain correction for multiple comparisons, there was a *significant positive correlation* between GMV and RPQ-13 (Late Symptom) scores within the right post-central gyrus. As shown in Figure S27., individuals with larger GMV in this region showed more late symptoms than those with less GMV at 1-month post-injury. There were no regions of negative correlation surviving correction for multiple comparisons.

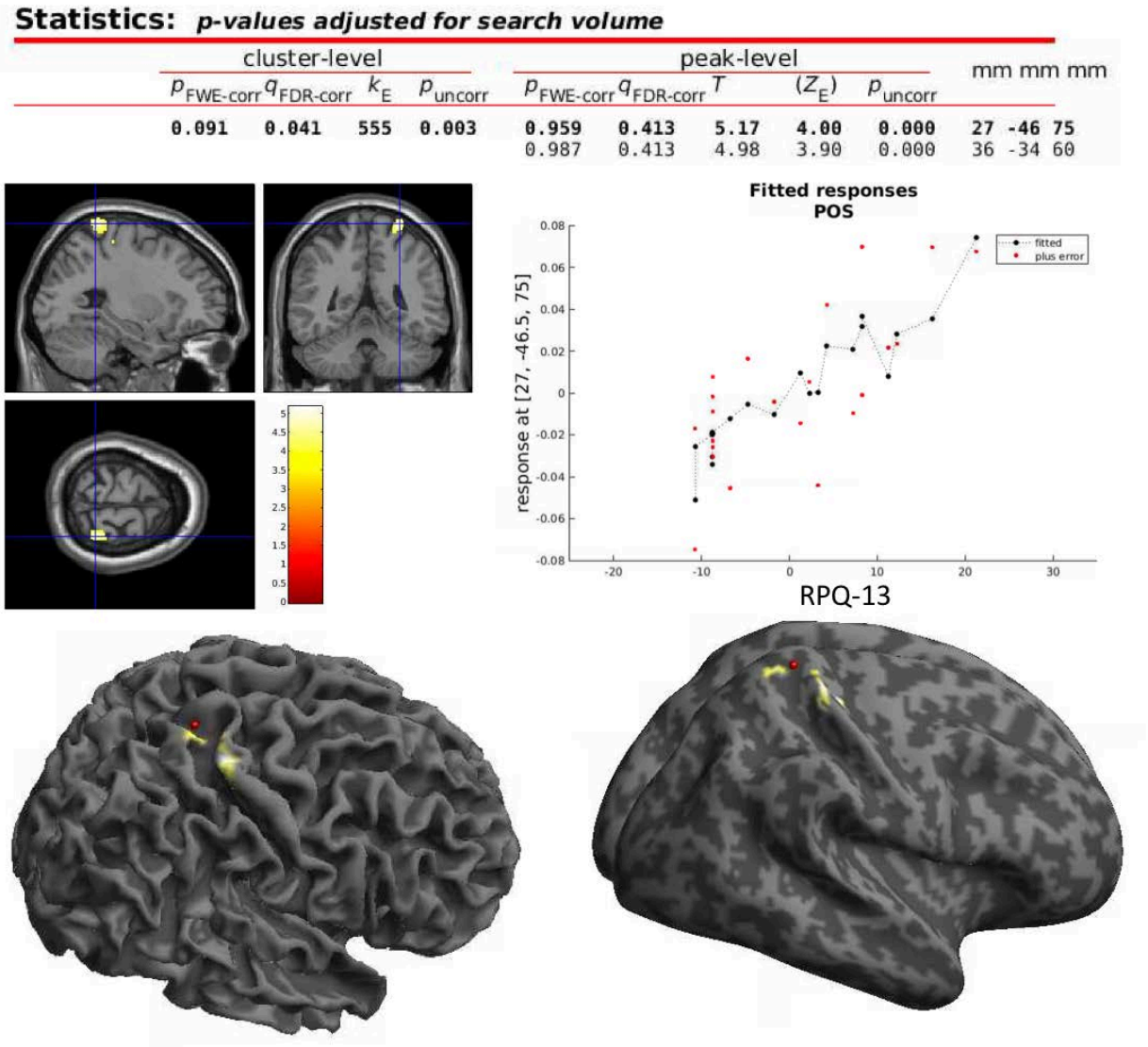


Figure S27. Gray matter volume (GMV) within the right post-central gyrus was correlated with scores on Early symptom scores on the RPQ-13 at 1-Month post injury. Top Left: x, y, z slices of the region of activation. Top Right: scatterplot of peak voxel correlation. Bottom Left: correlated regions on a cortical map of a standard brain. Bottom Right: regions of correlation overlaid on an inflated cortex map.

For completeness in reporting, we present the un-thresholded correlation maps for the 1-Month sample alone for RPQ-13 (Figure S28). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

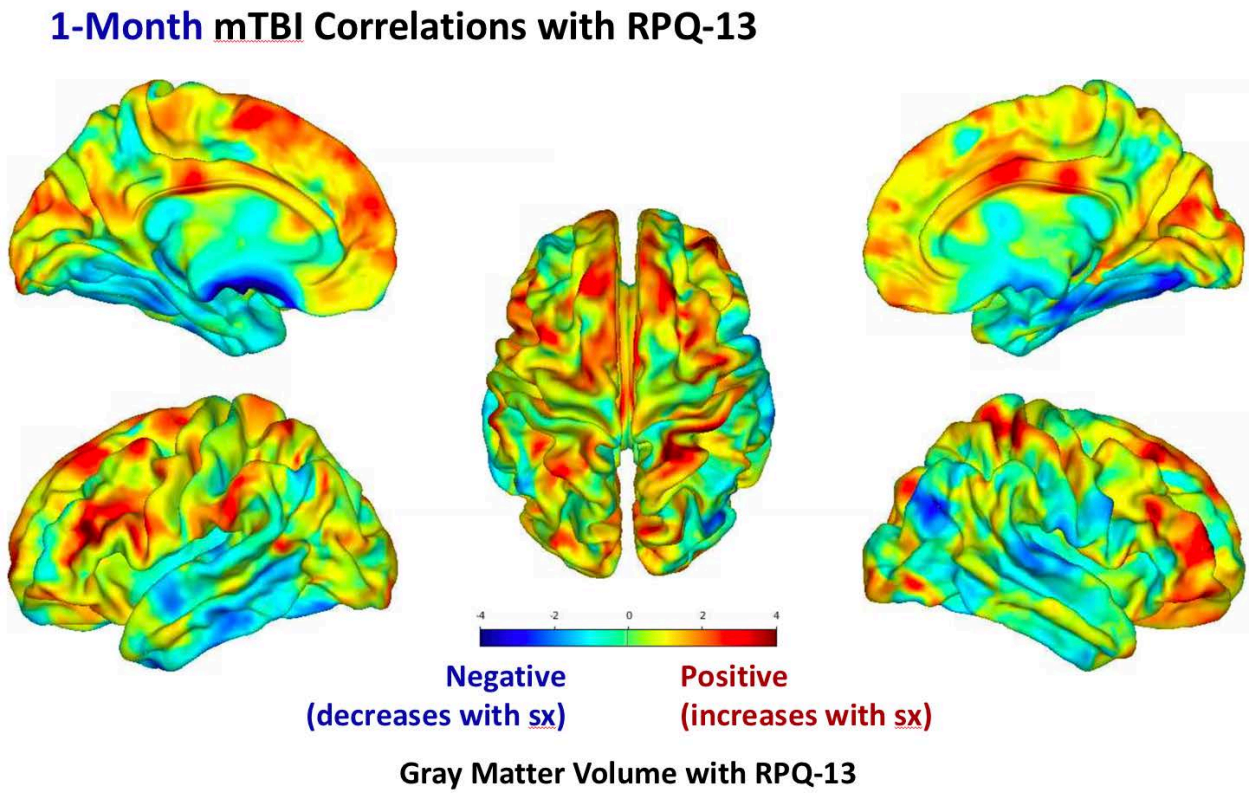


Figure S28. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **1-Month** pattern of correlations with RPQ-13 (Late) Symptoms. Warm colors reflect areas where GMV was greater with higher Late Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Late symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

3 Month Post-MTBI Participants. For the 3-Month post-injury group, we conducted a multiple regression analysis between GMV and the various cluster scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): After FDR whole-brain correction for multiple comparisons, there were *no regions* showing either significant positive or negative correlation between GMV and RPQ-3 scores. However, as shown in Figure S29, there was a marginally significant correlation in bilateral clusters corresponding to the inferior frontal operculi on the left and right hemisphere. Although these regions reached an FDR cluster-corrected significance level of $p = .062$, they did not survive correction for multiple comparisons, we present them here due to the important role of these regions in regulating brain activation on other areas of the cortex and the fact that they are clearly bilaterally represented, suggesting a potentially important finding for future work to explore.

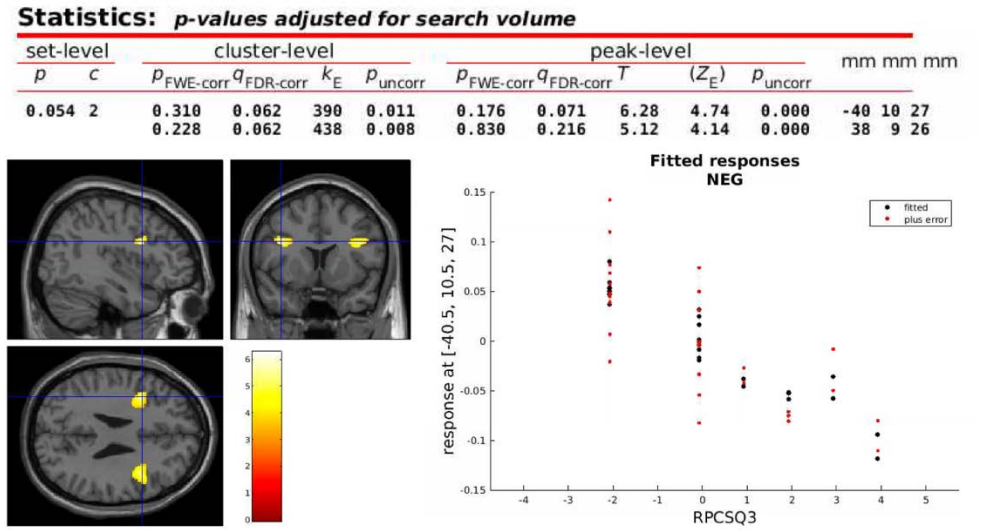


Figure S29. Gray matter volume (GMV) within bilateral regions corresponding to the inferior frontal opperculi was correlated with fewer RPQ-3 (Early) symptoms. These regions reached a trend level of significance (*p* = .062). The left figure shows the bilateral regions that were correlated with lower symptom scores. The right hand figure shows the scatterplot associated with the global maximum voxel.

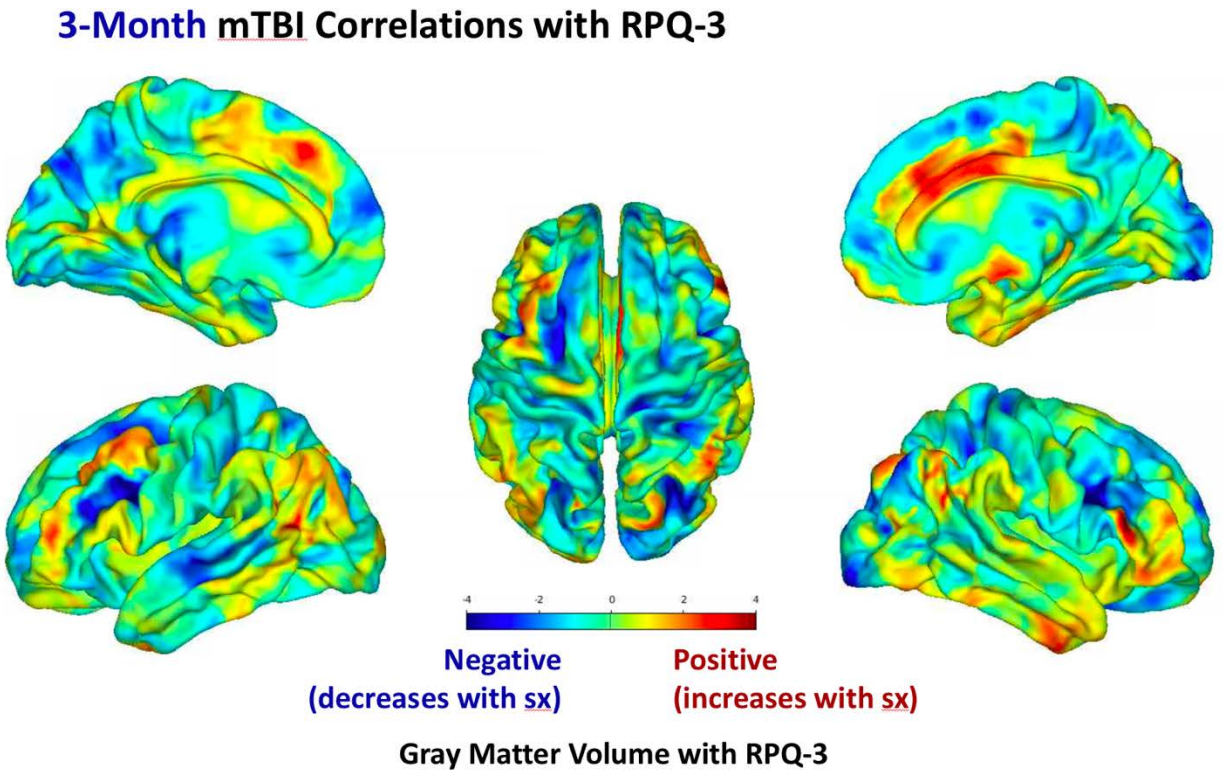


Figure S30. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **3-Month** pattern of correlations with RPQ-3 (Early) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Early symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Although statistically significant correlations were not found, we present the unthresholded correlation maps for the 3-Month sample alone for RPQ-3 (Figure S30). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons

Late Symptom Cluster (RPQ-13): After FDR whole-brain correction for multiple comparisons, there were *no regions* of either positive or negative correlation surviving FDR cluster-wise correction for multiple comparisons. Nonetheless, for completeness in reporting, we present the unthresholded correlation maps for the 3-Month sample alone for RPQ-13 Late symptoms (Figure S31). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

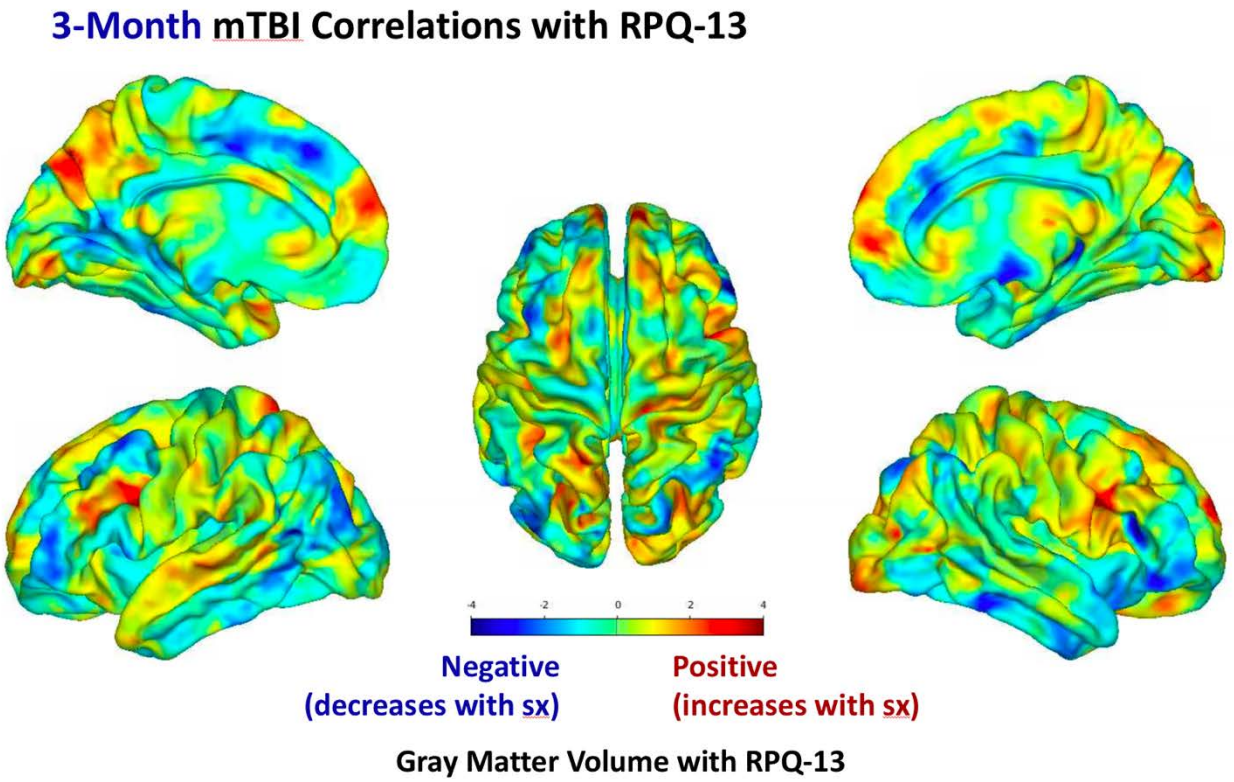


Figure S31. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **3-Month** pattern of correlations with RPQ-13 (Late) Symptoms. Warm colors reflect areas where GMV was greater with higher Late Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Late symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

6 Month Post-MTBI Participants. For the 6-Month post-injury group, we conducted a multiple regression analysis between GMV and the various cluster scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): After FDR whole-brain correction for multiple comparisons, there was a significant positive correlation between GMV and RPQ-3 (Early) scores (Figure S32). This cluster extended from the right precentral to the right postcentral gyrus, suggesting that it plays a role in sensory-motor functioning for the left side of the body. In contrast, *no regions showed significant negative correlations* at 6-months between GMV and RPQ-3 Early symptoms, after correction for multiple comparisons.

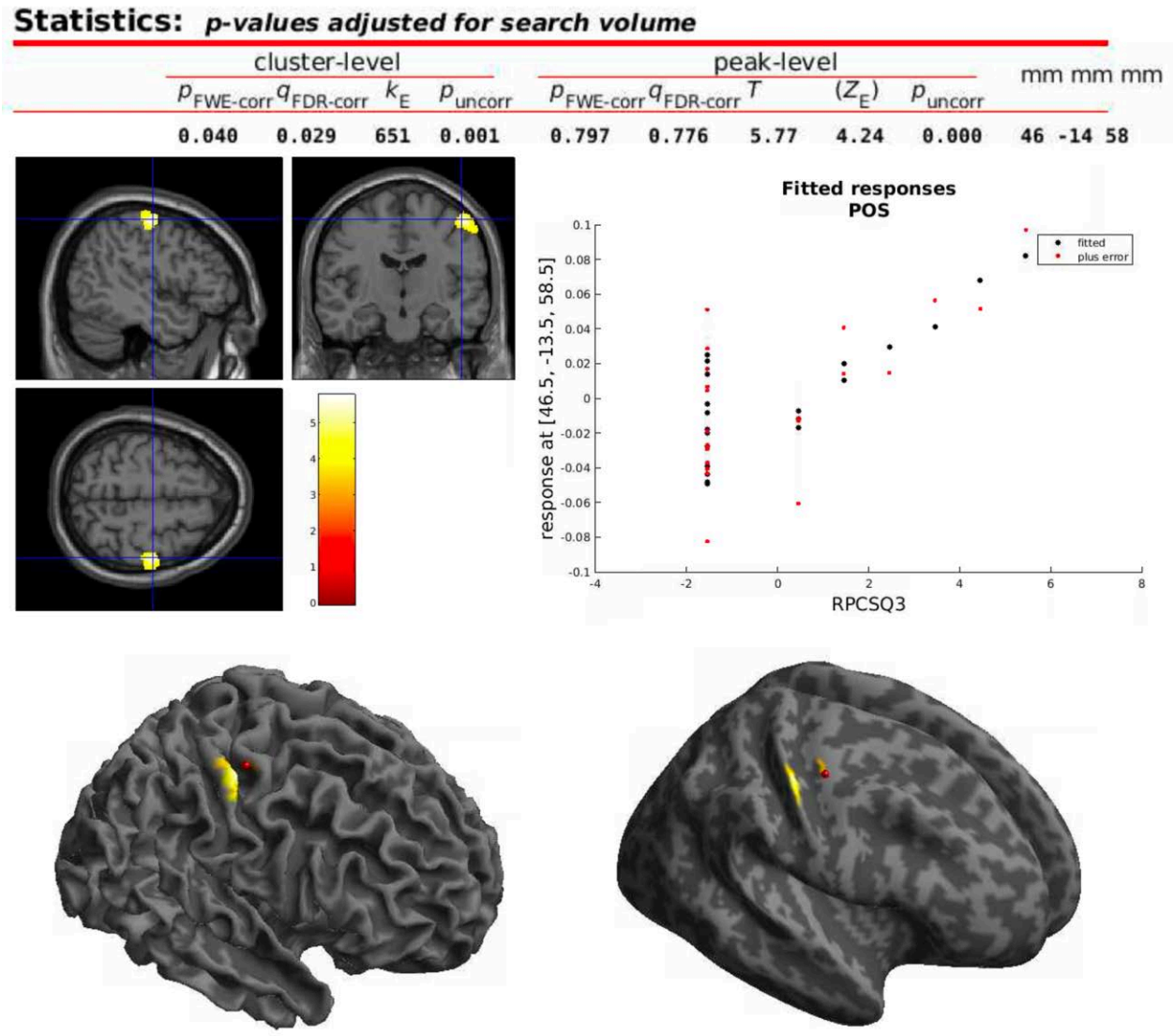


Figure S32. Gray matter volume (GMV) within a cluster of the right pre- to post-central gyrus was correlated with scores on Early symptom scores on the RPQ-13 at 6-Months post injury. Top Left: x, y, z slices of the region of activation. Top Right: scatterplot of peak voxel correlation. Bottom Left: correlated regions on a cortical map of a standard brain. Bottom Right: regions of correlation overlaid on an inflated cortex map.

For completeness, we present the un-thresholded correlation maps for the 6-Month sample alone for RPQ-3 (Figure S33). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparison.

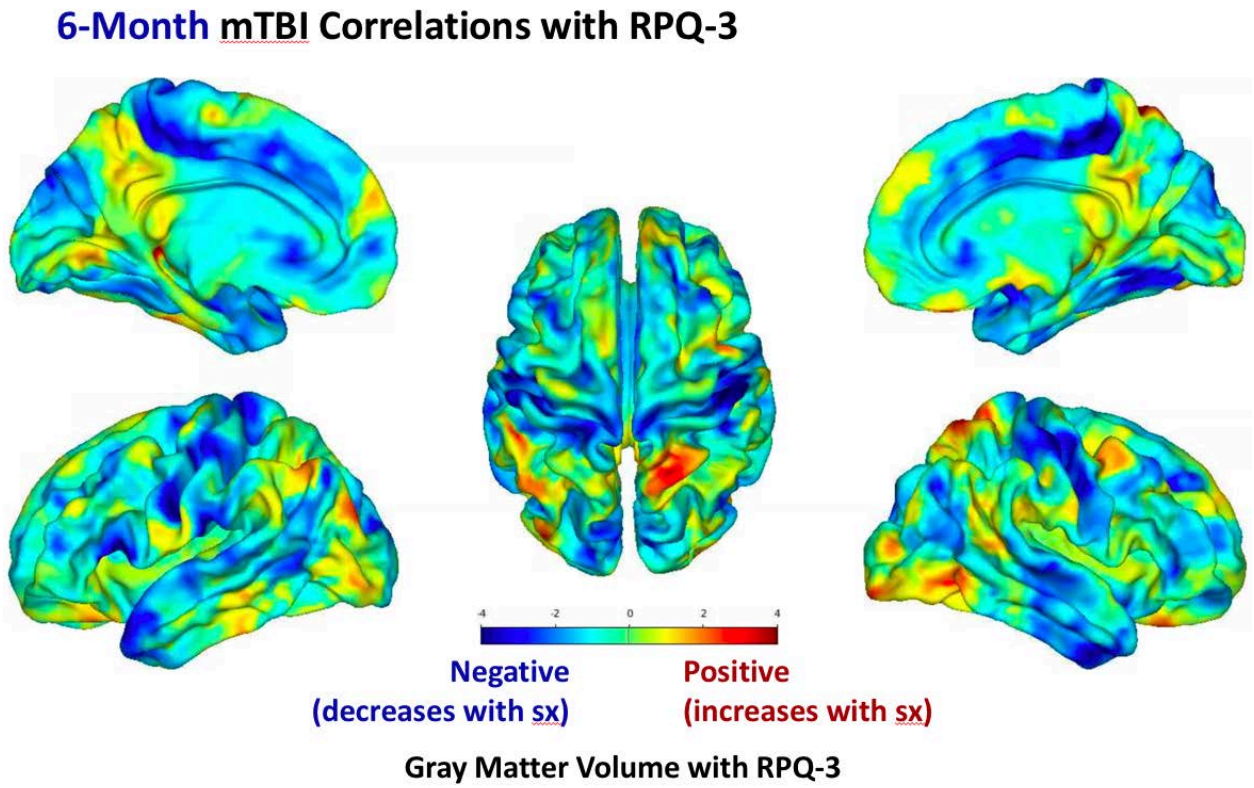


Figure S33. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **6-Month** pattern of correlations with RPQ-3 (Early) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Early symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Late Symptom Cluster (RPQ-13): After FDR whole-brain correction for multiple comparisons, there was a *significant positive correlation* between the Late symptom cluster (RPQ-13) and greater GMV within a region of the left postcentral gyrus/precuneus (Figure S34). In contrast, no negative correlations were found after correction for multiple comparisons.

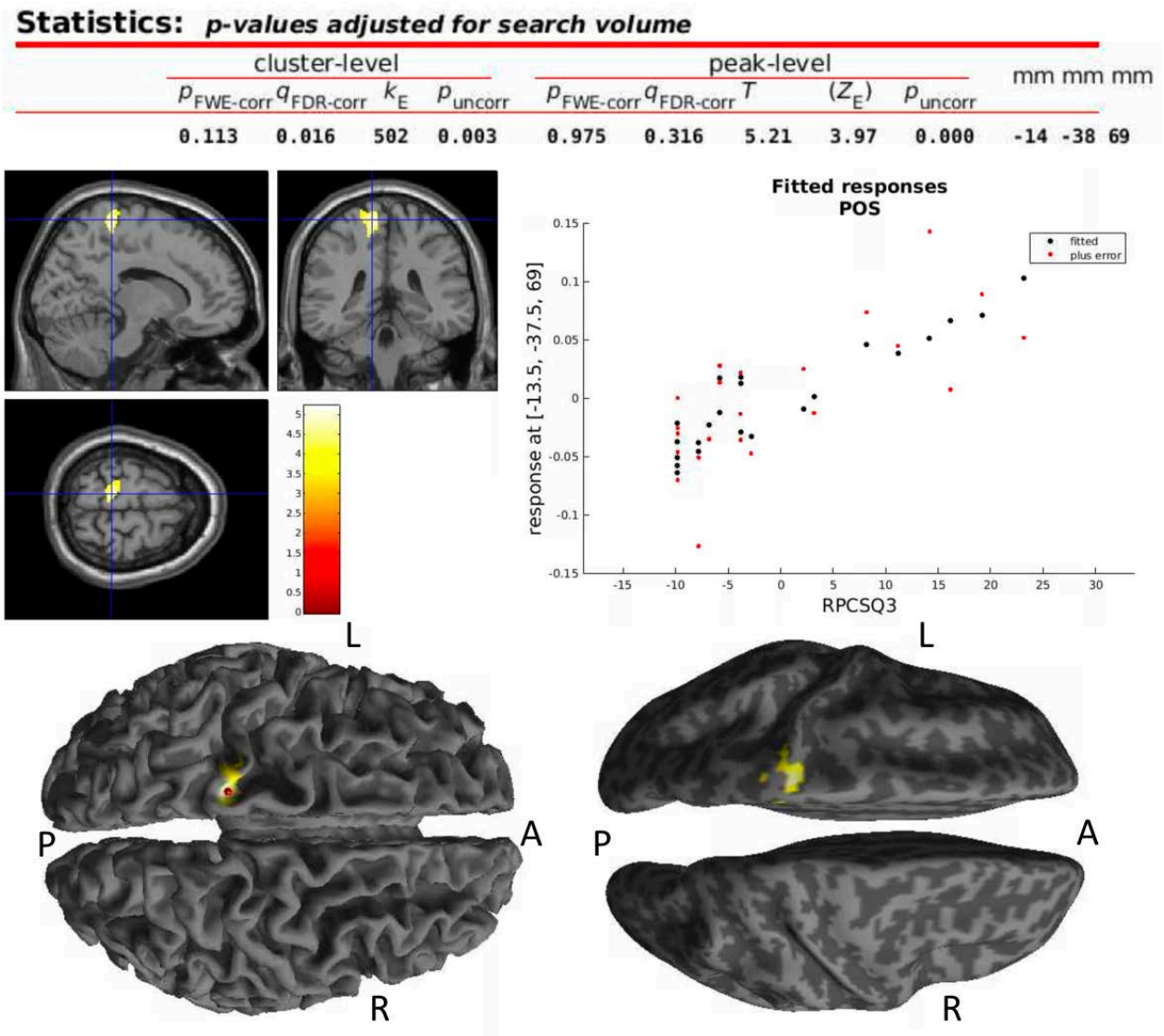


Figure S34. Gray matter volume (GMV) within a cluster of the left post-central gyrus/precuneus was positively correlated with scores on Late symptom scores on the RPQ-13 at 6-Months post injury. Top Left: x, y, z slices of the region of activation. Top Right: scatterplot of peak voxel correlation. Bottom Left: correlated regions on a cortical map of a standard brain. Bottom Right: regions of correlation overlaid on an inflated cortex map.

For completeness in reporting, we present the un-thresholded correlation maps for the 6-Month sample alone for RPQ-13 Late symptoms (Figure S35). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

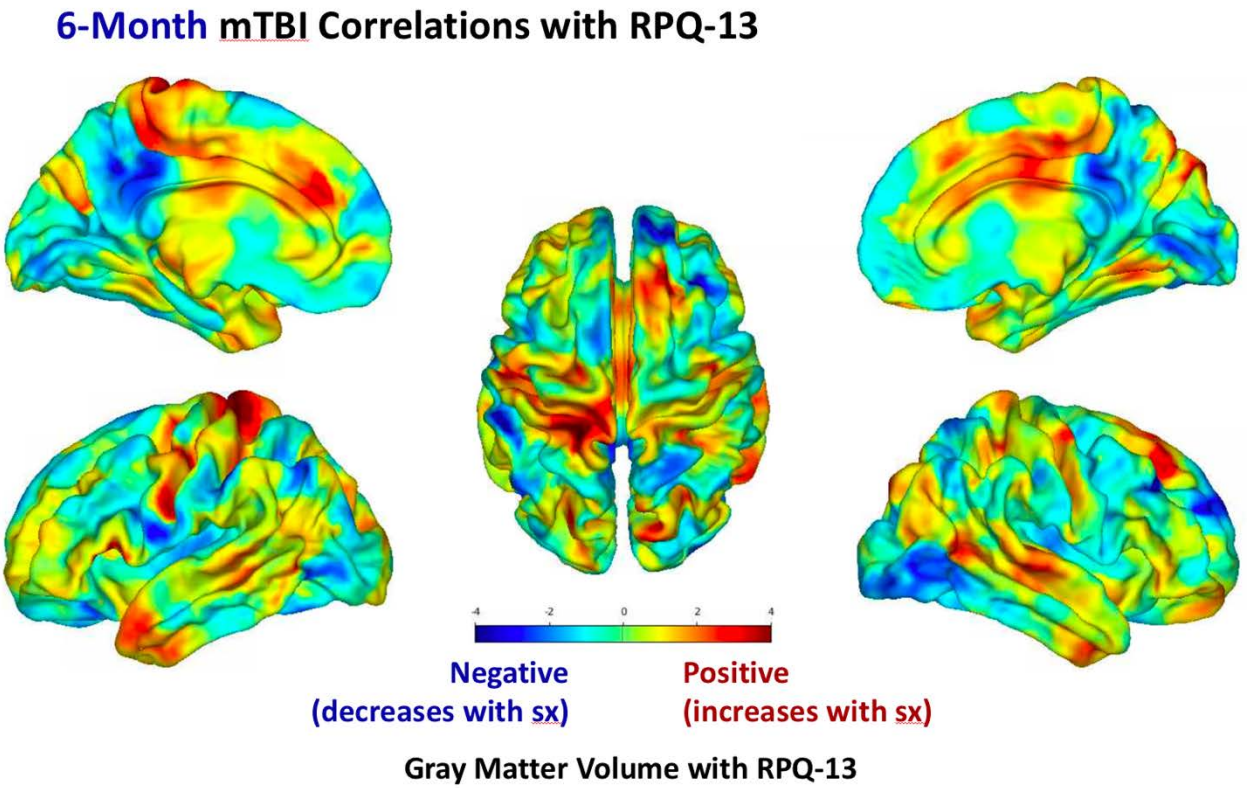


Figure S35. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **6-Month** pattern of correlations with RPQ-13 (Late) Symptoms. Warm colors reflect areas where GMV was greater with higher Late Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Late symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

12 Month Post-MTBI Participants. For the 12-Month post-injury group, we conducted a multiple regression analysis between GMV and the various cluster scores on the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ). We will examine correlations for each of these in the subsequent sections. All analyses included TIV, sex, and age as nuisance covariates.

Early Symptom Cluster (RPQ-3): After FDR whole-brain correction for multiple comparisons, there were no significant positive or negative correlations between GMV and the Early symptom cluster (RPQ-3). Nonetheless, we present the unthresholded correlation maps for the 6-Month sample alone for RPQ-13 Late symptoms (Figure S36). The values do not represent statistical significance. Rather they show the strength of the correlations based on T-maps. The maps are maintained at the same color scaling as the previous maps to facilitate ease of comparisons.

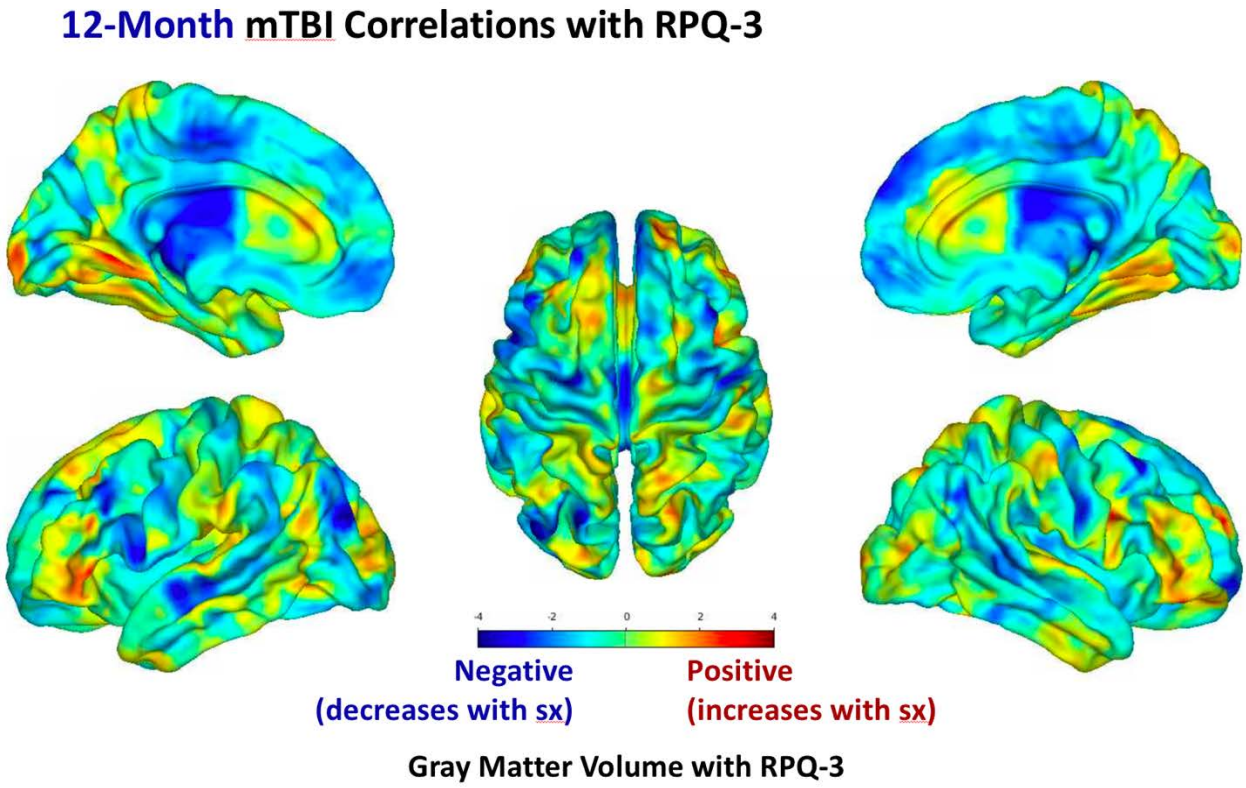


Figure S36. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **12-Month** pattern of correlations with RPQ-3 (Early) Symptoms. Warm colors reflect areas where GMV was greater with higher Early Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Early symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Late Symptom Cluster (RPQ-13): After FDR whole-brain correction for multiple comparisons, there was a *significant positive correlation* between the Late symptom cluster (RPQ-13) and greater GMV within a region of the left postcentral gyrus/precuneus (Figure S37). In contrast, no negative correlations were found after correction for multiple comparisons.

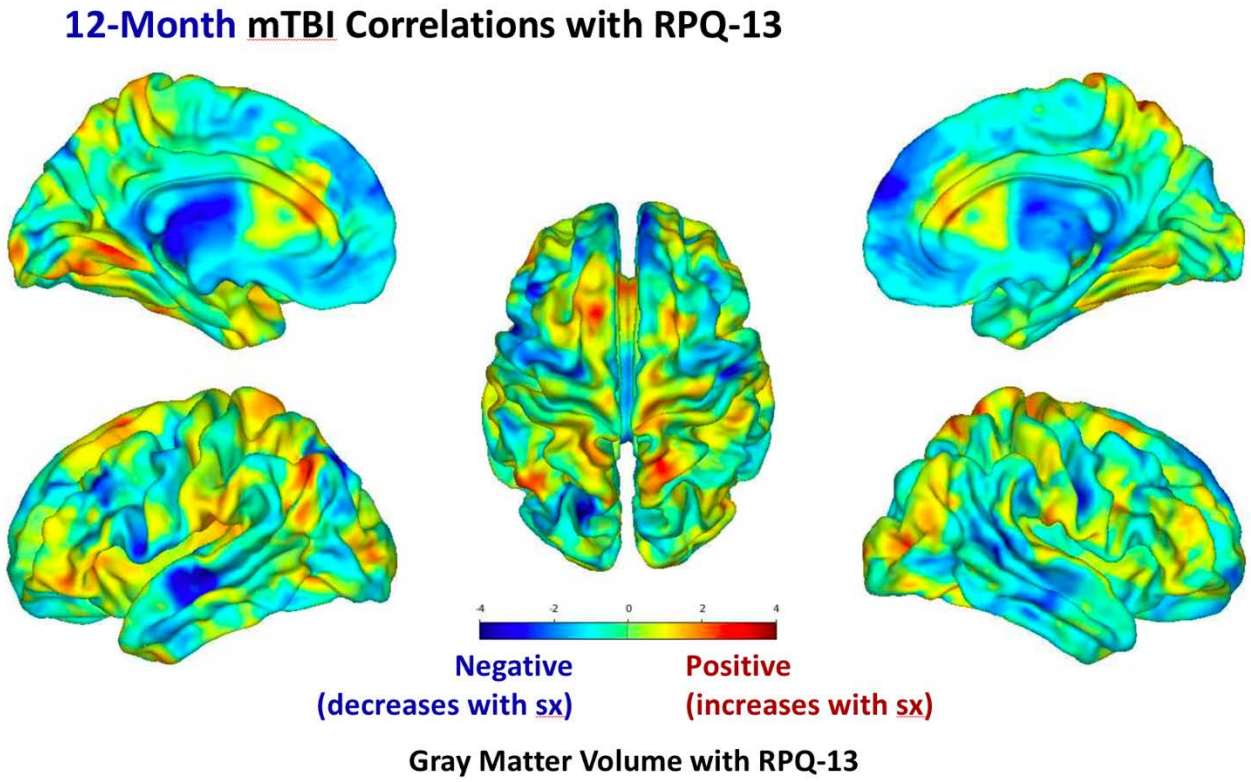


Figure S37. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the **12-Month** pattern of correlations with RPQ-13 (Late) Symptoms. Warm colors reflect areas where GMV was greater with higher Late Symptoms, while cooler colors reflect the negative correlations where GMV was reduced with higher Late symptoms. The colorbar shows the range of T-values, but does not reflect statistical significance.

Summary of Month-by-Month Associations Across Early and Late Symptom Clusters.
Given the large amount of data previously presented separately, below we consolidate the time-since-injury group associations together for Early RPQ-3) and Late (RPQ-13) symptom clusters of the RPCSQ. This is to facilitate further development of hypotheses regarding potential changes in the association between GMV and concussion symptom presentation at various timeframes following mTBI.

The figures that follow provide non-thresholded colormaps for the following: 1) Medial Left Hemisphere, 2) Lateral Left Hemisphere, 3) Superior aspect bilaterally, 4) Medial Right Hemisphere, and 5) Lateral Right Hemisphere (see Figures S38-S42):

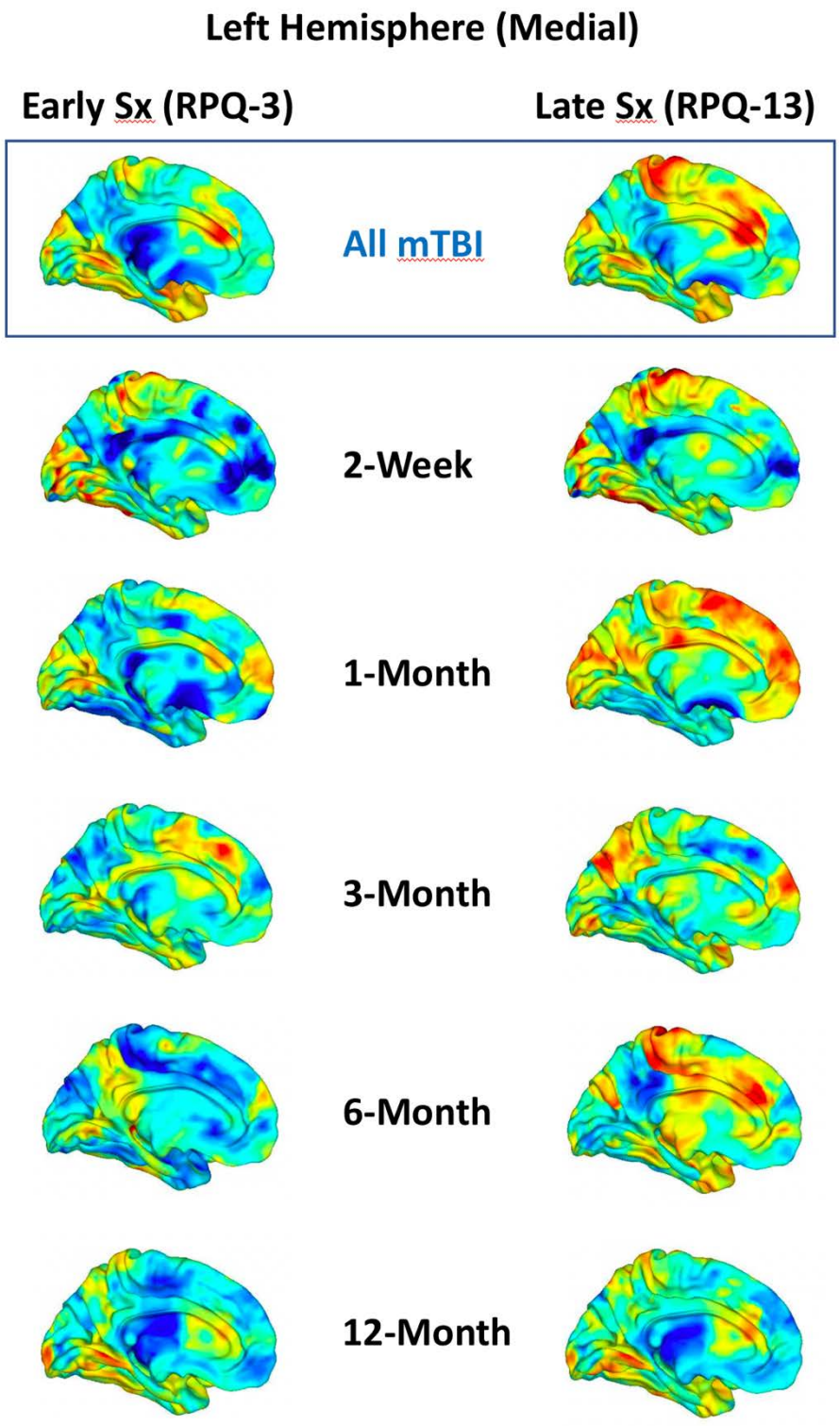


Figure S38. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the correlation between gray matter volume (GMV) and symptoms for each time-since-injury (TSI) group.

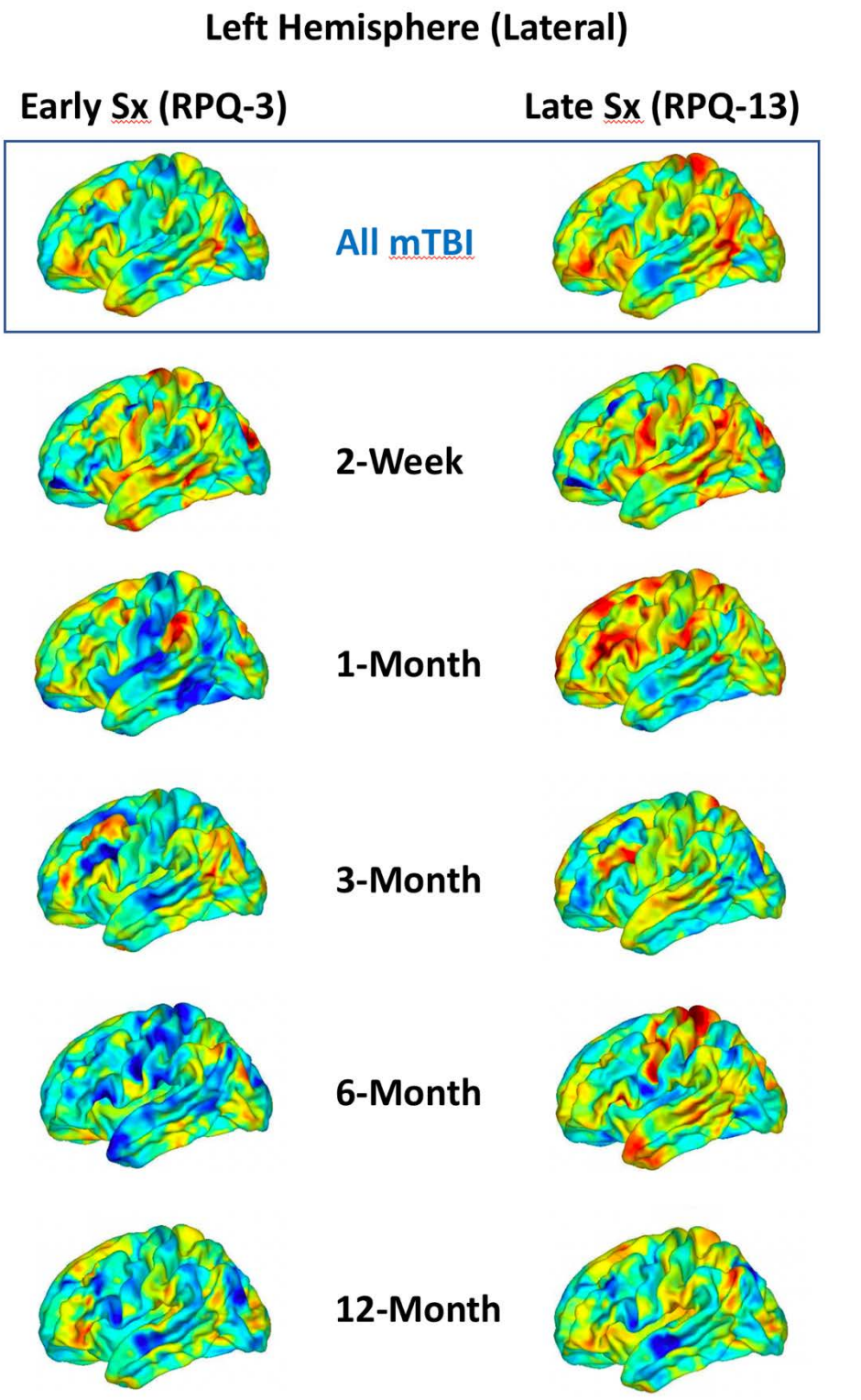


Figure S39. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the correlation between gray matter volume (GMV) and symptoms for each time-since-injury (TSI) group.

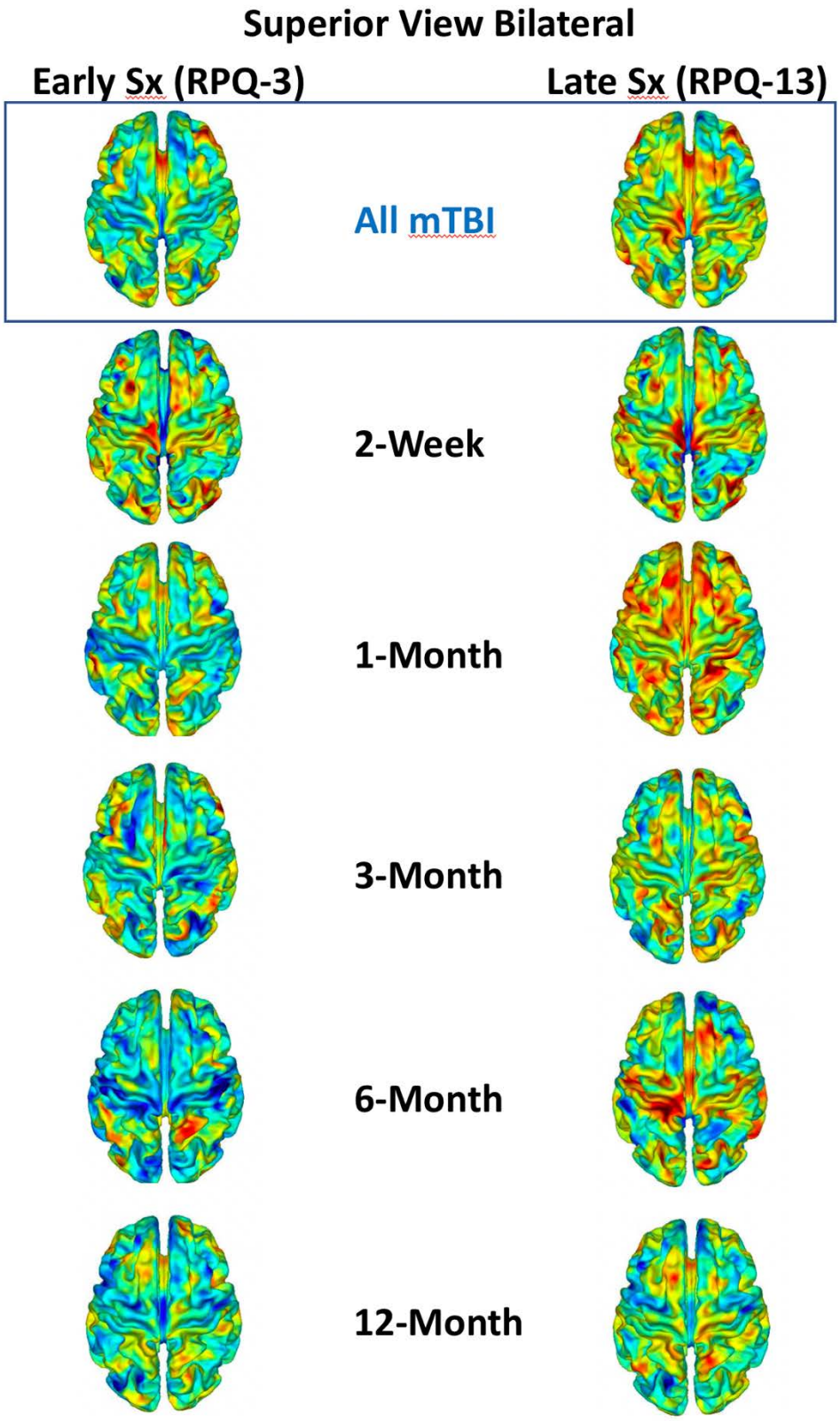


Figure S40. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the correlation between gray matter volume (GMV) and symptoms for each time-since-injury (TSI) group.

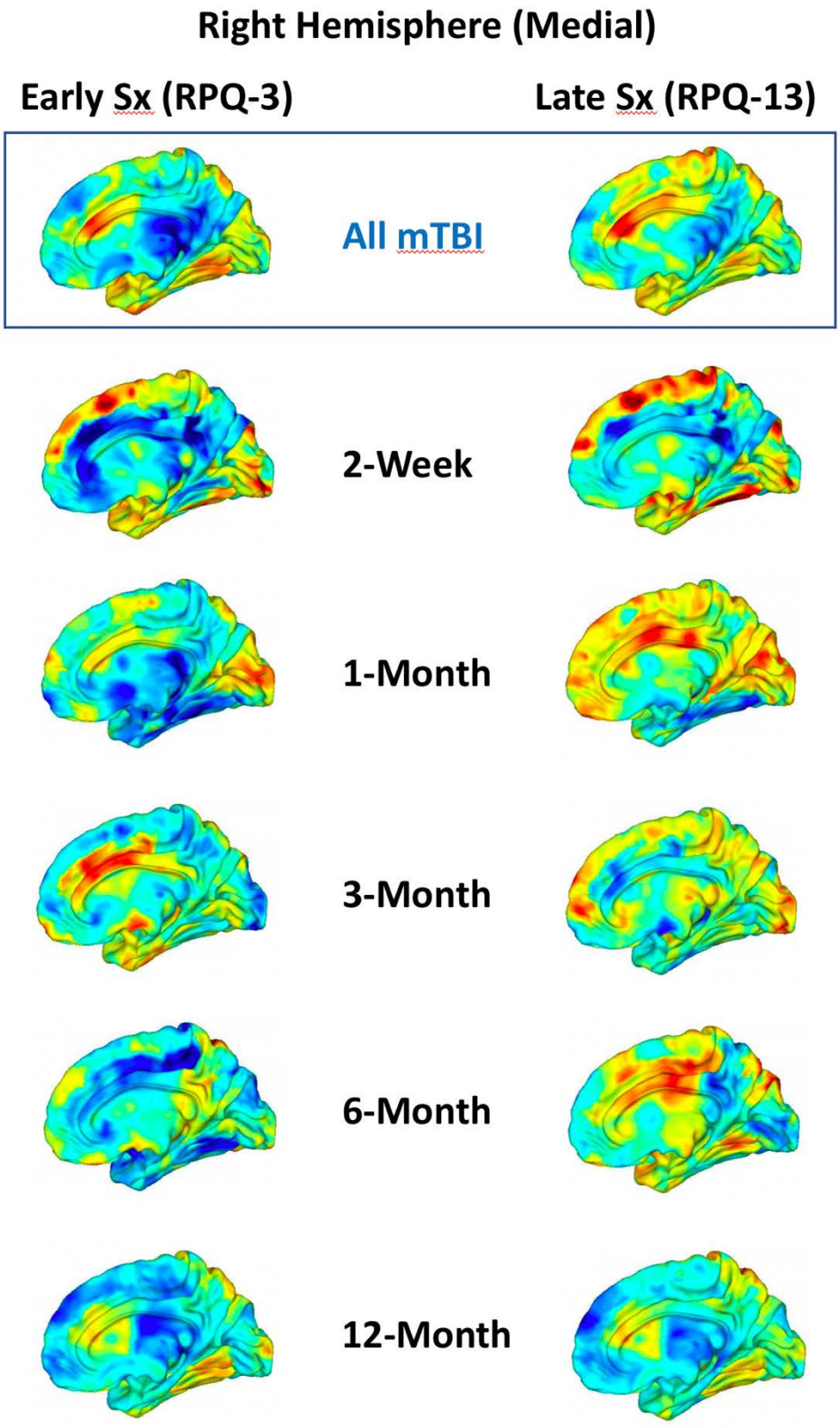


Figure S41. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the correlation between gray matter volume (GMV) and symptoms for each time-since-injury (TSI) group.

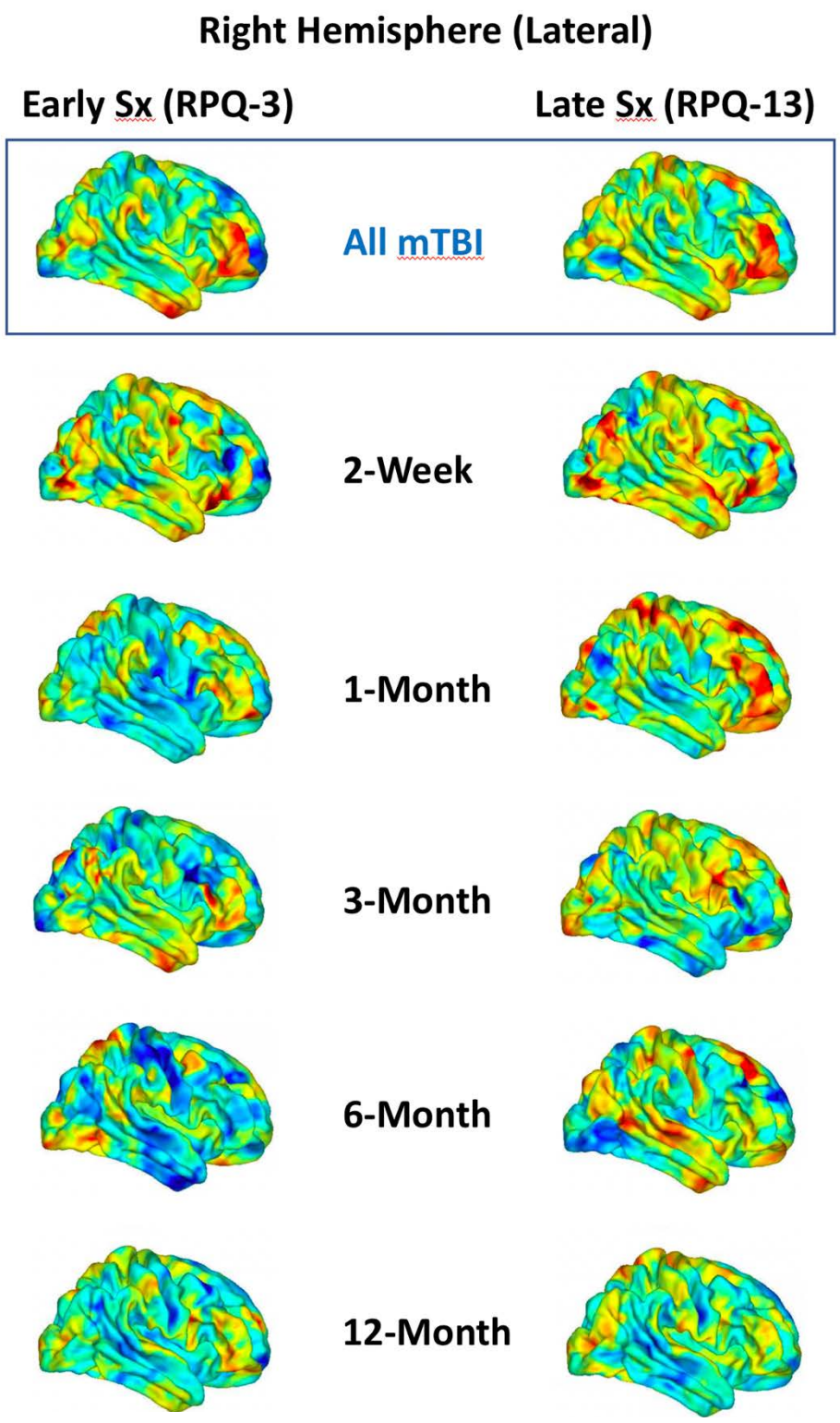


Figure S42. Voxel based morphometry (VBM) colormaps (not statistically thresholded) showing the correlation between gray matter volume (GMV) and symptoms for each time-since-injury (TSI) group.

Major GMV Clusters for Extraction:

As an additional approach to understanding the changes in brain-behavior associations at each time point following concussion, we first identified regions of the brain that were correlated with time-since-injury (TSI), excluding healthy control subjects (see previous section). However, to extract GMV clusters that might be associated with behavior, we used a more liberal height threshold for GMV ($p < .05$, uncorrected), followed by a cluster-wise whole brain FDR correction ($p < .05$, FDR corrected). As shown below, this initially yielded four large clusters where larger GMV was correlated with longer TSI. These four clusters were then extracted for subsequent correlation analysis. These clusters are illustrated along with associated statistics in Figures S43 through S45.

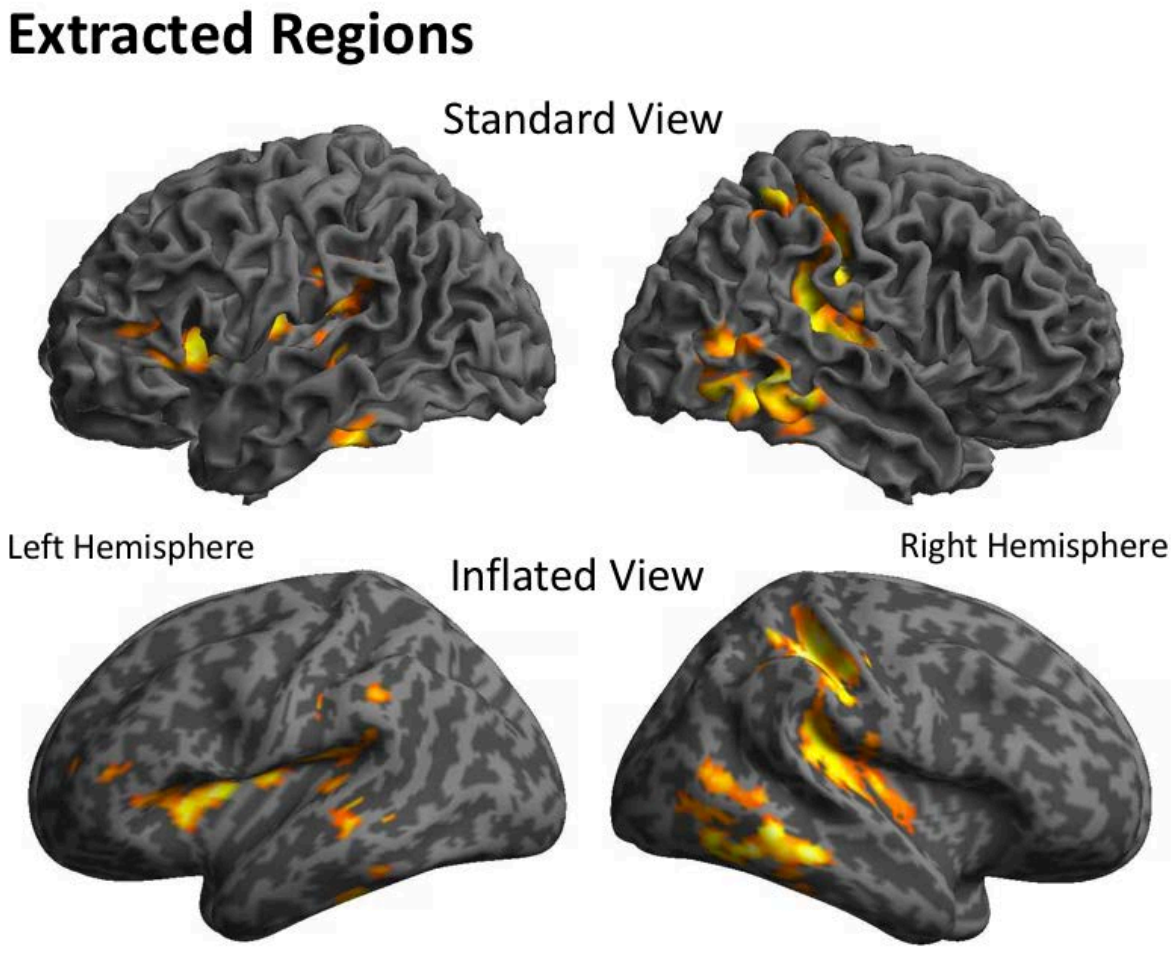


Figure S43. Voxel based morphometry (VBM) regions that showed significant positive correlation with time-since-injury in the mTBI group were extracted for further analysis. The figures show the cortical surface maps of the location of these gray matter volume clusters.

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm	mm	mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.001	**4**	**0.185**	**0.021**	**7972**	**0.001**	**0.745**	**0.570**	**4.24**	**4.08**	**0.000**	**-36**	**-42**	**-40**
						1.000	1.000	3.06	3.00	0.001	-18	-36	-48
						1.000	1.000	2.94	2.88	0.002	-50	-36	-26
		0.008	**0.002**	**14264**	**0.000**	**1.000**	**1.000**	**3.41**	**3.33**	**0.000**	**52**	**-48**	**-14**
						1.000	1.000	3.40	3.31	0.000	33	-42	-42
						1.000	1.000	3.30	3.22	0.001	70	-39	-9
		0.302	**0.026**	**7001**	**0.002**	**1.000**	**1.000**	**3.29**	**3.21**	**0.001**	**-28**	**6**	**8**
						1.000	1.000	3.29	3.21	0.001	-26	18	0
						1.000	1.000	3.14	3.07	0.001	-28	-8	15
		0.197	**0.021**	**7847**	**0.001**	**1.000**	**1.000**	**3.28**	**3.20**	**0.001**	**33**	**-38**	**45**
						1.000	1.000	3.10	3.04	0.001	44	-33	34
						1.000	1.000	3.05	2.99	0.001	56	-27	56

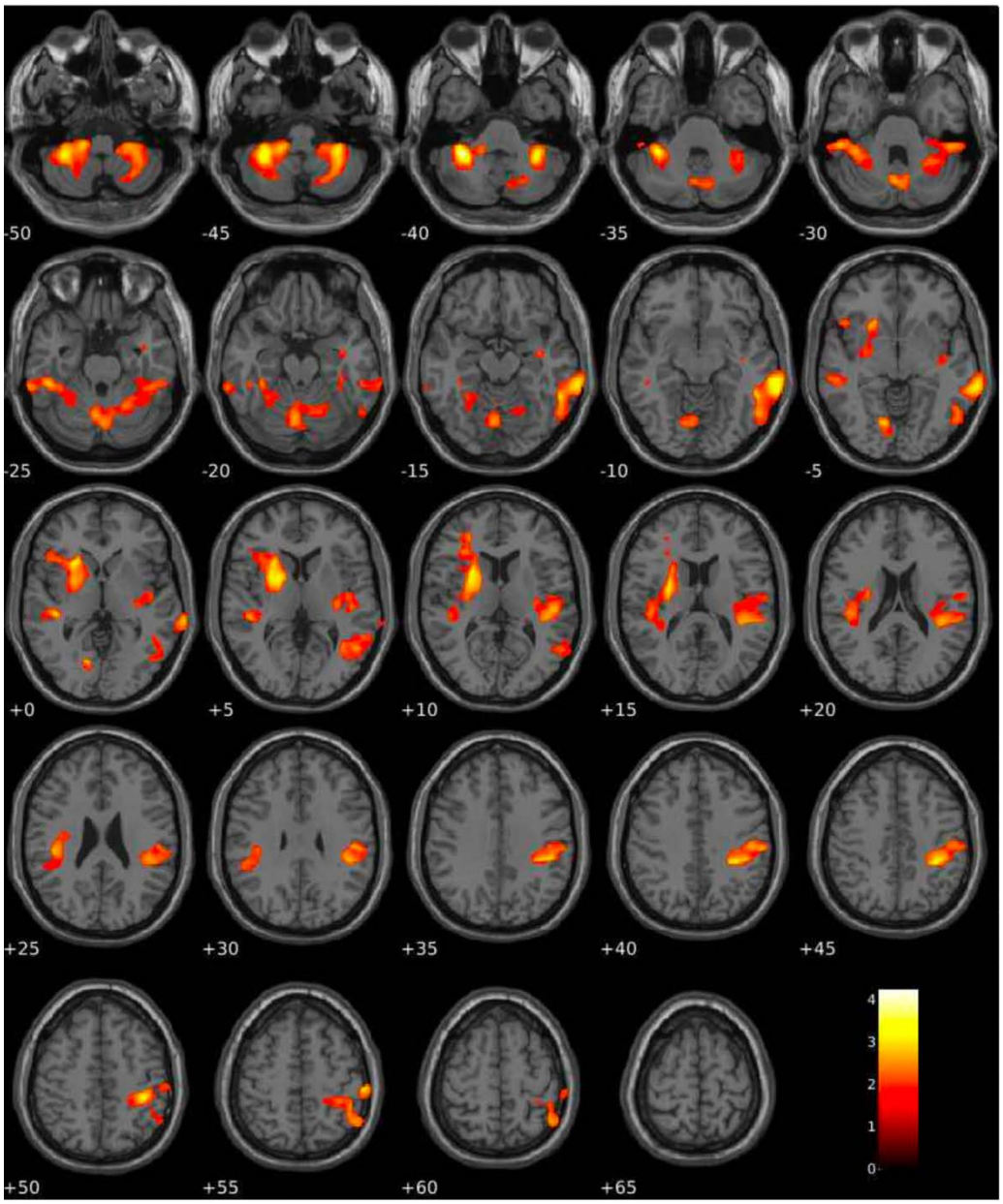
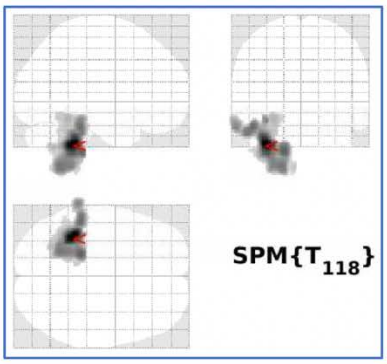


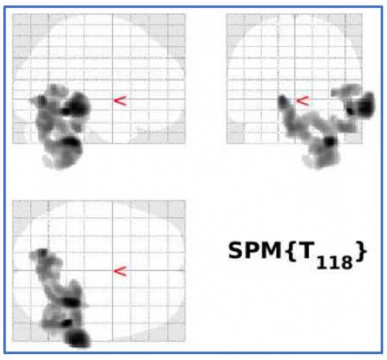
Figure S44. Initially, four primary regions of correlation with time-since-injury were observed and extracted for further analysis. The top table shows the significance level and regional coordinates for each cluster. The bottom figure shows the axial slices through these clusters. As shown in the next figure, the right cerebellar cluster was separated from the right inferior temporal cluster, resulting in a total of five clusters that were extracted.



Left Cerebellar Cluster

Statistics: ***p-values adjusted for search volume***

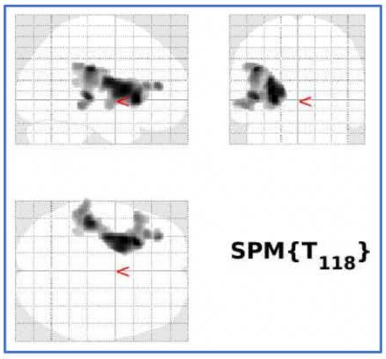
cluster-level				peak-level					mm	mm	mm
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.185	**0.021**	**7972**	**0.001**	**0.745**	**0.570**	**4.24**	**4.08**	**0.000**	**-36**	**-42**	**-40**
				1.000	1.000	3.06	3.00	0.001	-18	-36	-48
				1.000	1.000	2.94	2.88	0.002	-50	-36	-26



Right Inferior Temporal/Cerebellar Cluster

Statistics: ***p-values adjusted for search volume***

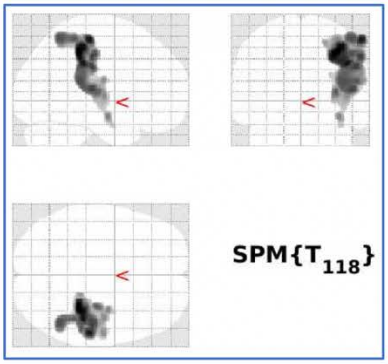
cluster-level				peak-level					mm	mm	mm
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.000	**0.000**	**14264**	**0.000**	**0.231**	**0.313**	**3.41**	**3.33**	**0.000**	**52**	**-48**	**-14**
				0.237	0.313	3.40	3.31	0.000	33	-42	-42
				0.302	0.313	3.30	3.22	0.001	70	-39	-9



Left Striatum Cluster

Statistics: ***p-values adjusted for search volume***

cluster-level				peak-level					mm	mm	mm
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.302	**0.026**	**7001**	**0.002**	**1.000**	**1.000**	**3.29**	**3.21**	**0.001**	**-28**	**6**	**8**
				1.000	1.000	3.29	3.21	0.001	-26	18	0
				1.000	1.000	3.14	3.07	0.001	-28	-8	15



Right Parietal Cluster

Statistics: ***p-values adjusted for search volume***

cluster-level				peak-level					mm	mm	mm
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}			
0.197	**0.021**	**7847**	**0.001**	**1.000**	**1.000**	**3.28**	**3.20**	**0.001**	**33**	**-38**	**45**
				1.000	1.000	3.10	3.04	0.001	44	-33	34
				1.000	1.000	3.05	2.99	0.001	56	-27	56

Figure S45. Four regions showing significant gray matter correlation with time-since-injury in the mTBI group were extracted for subsequent analysis. The left figures show the glass-brain maximum intensity projection (MIP) for each individual cluster. The tables to the right of each figure show the statistical significance of the cluster and the stereotaxic coordinates in MNI space.

Total Sample Correlations:

Exploratory analyses were undertaken to examine the associations between each of the four extracted GMV regions and neurocognitive performance factors for the entire sample as a whole (n = 158) regardless of injury status or time-since injury. Findings suggest that lager GMV of

		L Cerebellum	R Inf Temp	C3 L Striatum	R Parietal
F1 Verbal Memory	Pearson Correlation	-.151	-.098	-.025	-.102
	Sig. (2-tailed)	.058	.221	.751	.204
	N	158	158	158	158
F2 Atten Exec Control	Pearson Correlation	.049	.086	.186*	.108
	Sig. (2-tailed)	.545	.280	.019	.176
	N	158	158	158	158
F3 PCS/Emotion	Pearson Correlation	-.096	-.081	-.165*	-.137
	Sig. (2-tailed)	.232	.314	.038	.087
	N	158	158	158	158
F4 Aggression	Pearson Correlation	.268**	.309**	.300**	.238**
	Sig. (2-tailed)	.001	.000	.000	.003
	N	158	158	158	158
F5 Visual Memory	Pearson Correlation	-.016	-.061	-.132	-.083
	Sig. (2-tailed)	.846	.445	.098	.301
	N	158	158	158	158
F6 Sleep Quality	Pearson Correlation	.062	.020	-.018	-.025
	Sig. (2-tailed)	.437	.804	.822	.755
	N	158	158	158	158
F7 Motor Speed	Pearson Correlation	-.011	.014	.086	.052
	Sig. (2-tailed)	.892	.866	.281	.513
	N	158	158	158	158
F8 Vigilance	Pearson Correlation	.092	.059	.094	.092
	Sig. (2-tailed)	.252	.463	.240	.253
	N	158	158	158	158
F9 Cognitive Errors	Pearson Correlation	-.007	.048	.001	-.040
	Sig. (2-tailed)	.928	.546	.990	.621
	N	158	158	158	158
F10 Daily Functioning	Pearson Correlation	-.114	-.086	-.055	-.067
	Sig. (2-tailed)	.154	.281	.489	.400
	N	158	158	158	158
F11 Concept Formation	Pearson Correlation	.081	.145	.150	.119
	Sig. (2-tailed)	.312	.069	.060	.137
	N	158	158	158	158
F12 Impulsivity	Pearson Correlation	-.162*	-.168*	-.150	-.154
	Sig. (2-tailed)	.042	.034	.060	.054
	N	158	158	158	158
F13 Processing Speed	Pearson Correlation	.011	.057	.114	.169*
	Sig. (2-tailed)	.893	.478	.153	.034
	N	158	158	158	158

Table S1. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors detailed in the main results.

the left cerebellum was associated with greater aggression and lower impulsivity across the sample. Larger GMV of the right inferior temporal/cerebellar region was also associated with increased aggression and reduced impulsivity. Larger GMV of the striatum was associated with greater attention/executive control, reduced PCS symptoms and emotional disturbance, and greater aggression. Finally, larger GMV of the right parietal cortex was associated with greater aggression and faster processing speed across the sample as a whole.

Additionally, we divided the sample into the Injury Status/TSI groups and reran the analyses to identify potential associations that may differ at different times following injury. These are described in the subsequent sections.

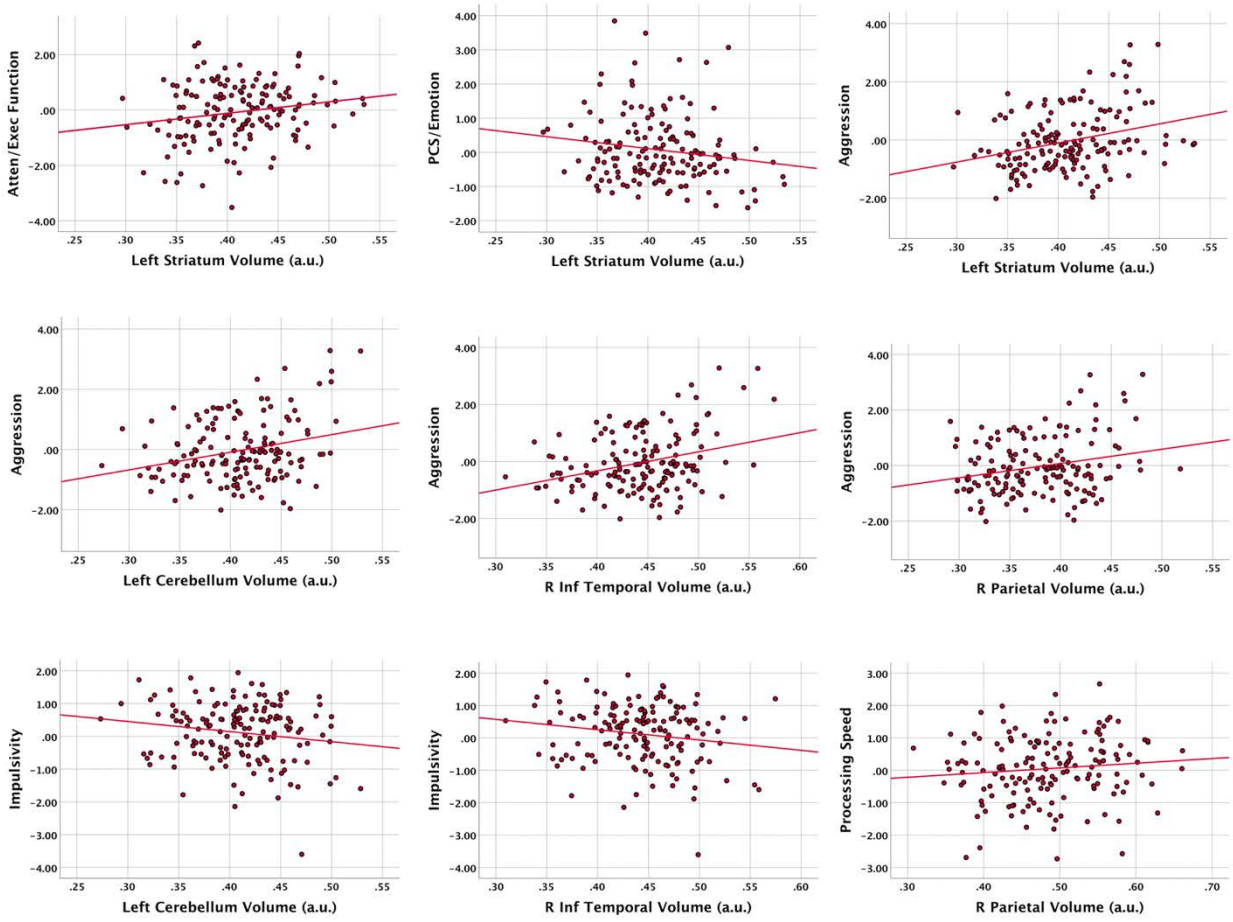


Figure S46. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the sample as a whole.

Healthy Control Correlations:

Exploratory analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factor variables. As shown in Table S2, there were no significant correlations between GMV within the four regions and the neurocognitive factors. This suggests that GMV variations are not meaningfully associated with neurocognitive performance among those who have not sustained an mTBI or other notable brain damage.

		L Cerebellum	R Inf Temp	L Striatum	R Parietal
F1 Verbal Memory	Pearson Correlation	-.267	-.151	-.101	-.081
	Sig. (2-tailed)	.121	.388	.564	.644
	N	35	35	35	35
F2 Atten Exec Control	Pearson Correlation	-.095	-.087	.038	.028
	Sig. (2-tailed)	.588	.618	.829	.874
	N	35	35	35	35
F3 PCS Emotion	Pearson Correlation	-.141	-.124	-.252	-.291
	Sig. (2-tailed)	.420	.479	.145	.090
	N	35	35	35	35
F4 Aggression	Pearson Correlation	.259	.333	.246	.105
	Sig. (2-tailed)	.133	.051	.154	.548
	N	35	35	35	35
F5 Visual Memory	Pearson Correlation	.120	-.040	.015	-.022
	Sig. (2-tailed)	.494	.821	.930	.901
	N	35	35	35	35
F6 Sleep Quality	Pearson Correlation	-.150	-.057	.071	.189
	Sig. (2-tailed)	.390	.743	.685	.278
	N	35	35	35	35
F7 Motor Speed	Pearson Correlation	-.130	-.132	-.109	-.210
	Sig. (2-tailed)	.456	.450	.532	.227
	N	35	35	35	35
F8 Vigilance	Pearson Correlation	-.032	-.078	-.001	.005
	Sig. (2-tailed)	.856	.657	.996	.978
	N	35	35	35	35
F9 Cognitive Errors	Pearson Correlation	.094	.184	.141	-.009
	Sig. (2-tailed)	.592	.290	.420	.960
	N	35	35	35	35
F10 Daily Functioning	Pearson Correlation	.038	.084	-.127	-.110
	Sig. (2-tailed)	.827	.631	.468	.529
	N	35	35	35	35
F11 Concept Formation	Pearson Correlation	.145	.247	.288	.318
	Sig. (2-tailed)	.406	.153	.094	.063
	N	35	35	35	35
F12 Impulsivity	Pearson Correlation	-.081	.001	.112	.121
	Sig. (2-tailed)	.645	.997	.520	.487
	N	35	35	35	35
F13 Processing Speed	Pearson Correlation	-.004	.049	.153	.272
	Sig. (2-tailed)	.982	.778	.381	.114
	N	35	35	35	35

Table S2. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors for Healthy Controls (HC) only.

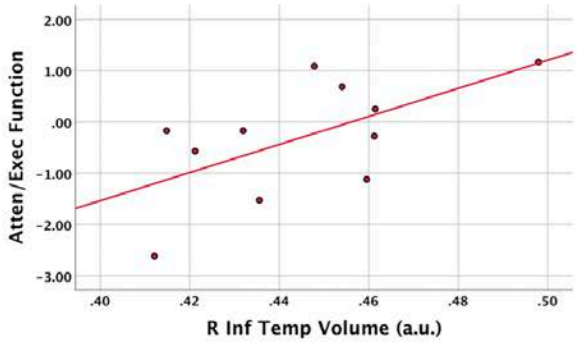
2-Week Post-Injury Correlations:

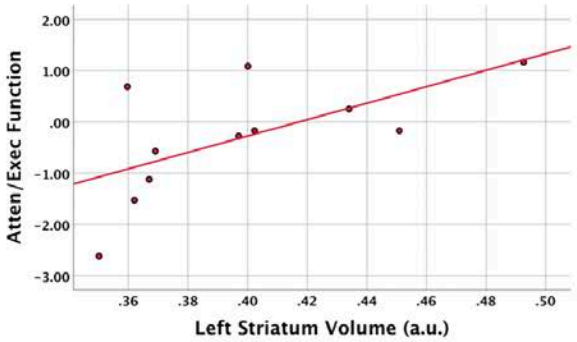
Exploratory analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factors within the sample of individuals who had sustained an mTBI in the 2-weeks preceding the assessment. As evident in Table S3, larger GMV within the right inferior temporal/cerebellar region and left striatum was associated with significantly better attention/executive control capacities. In this same group, larger GMV within all four regions was associated with faster motor speed performance. Finally, larger GMV of the right inferior temporal lobe was also associated with faster processing speed.

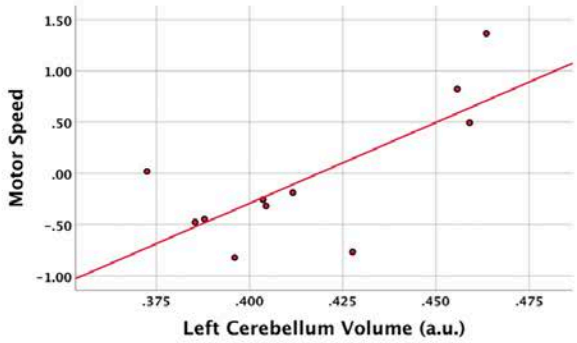
TSI_group			L Cerebellum	R Inf Temp	L Striatum	R Parietal
1	F1 Verbal Memory	Pearson Correlation	-.459	-.304	.264	-.274
		Sig. (2-tailed)	.156	.364	.433	.414
		N	11	11	11	11
	F2 Atten Exec Control	Pearson Correlation	.186	.610*	.627*	.591
		Sig. (2-tailed)	.585	.046	.039	.056
		N	11	11	11	11
	F3 PCS Emotion	Pearson Correlation	.242	.114	-.357	.114
		Sig. (2-tailed)	.474	.738	.281	.739
		N	11	11	11	11
	F4 Aggression	Pearson Correlation	-.278	-.316	.293	-.086
		Sig. (2-tailed)	.407	.343	.382	.801
		N	11	11	11	11
	F5 Visual Memory	Pearson Correlation	-.398	-.361	-.110	-.152
		Sig. (2-tailed)	.226	.275	.747	.655
		N	11	11	11	11
	F6 Sleep Quality	Pearson Correlation	.156	-.357	-.060	-.165
		Sig. (2-tailed)	.647	.281	.862	.628
		N	11	11	11	11
	F7 Motor Speed	Pearson Correlation	.737**	.726*	.666*	.718*
		Sig. (2-tailed)	.010	.011	.025	.013
		N	11	11	11	11
	F8 Vigilance	Pearson Correlation	.166	.247	.331	.494
		Sig. (2-tailed)	.625	.464	.320	.123
		N	11	11	11	11
	F9 Cognitive Errors	Pearson Correlation	-.396	-.206	-.004	-.217
		Sig. (2-tailed)	.228	.543	.991	.522
		N	11	11	11	11
	F10 Daily Functioning	Pearson Correlation	-.254	-.396	.137	-.245
		Sig. (2-tailed)	.450	.227	.687	.467
		N	11	11	11	11
	F11 Concept Formation	Pearson Correlation	.124	.444	.193	.441
		Sig. (2-tailed)	.717	.171	.570	.175
		N	11	11	11	11
	F12 Impulsivity	Pearson Correlation	-.270	-.572	.139	-.001
		Sig. (2-tailed)	.421	.066	.683	.997
		N	11	11	11	11
	F13 Processing Speed	Pearson Correlation	.356	.715*	.212	.489
		Sig. (2-tailed)	.282	.013	.531	.126
		N	11	11	11	11

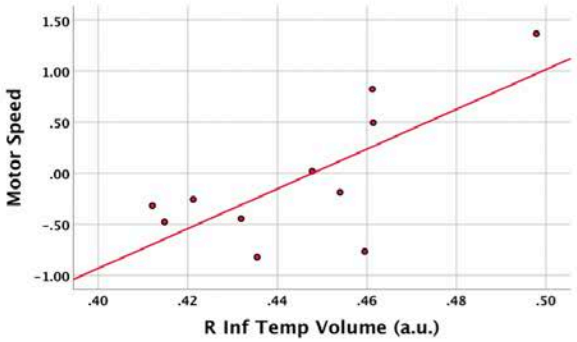
Table S3. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors for the 2-Week post-

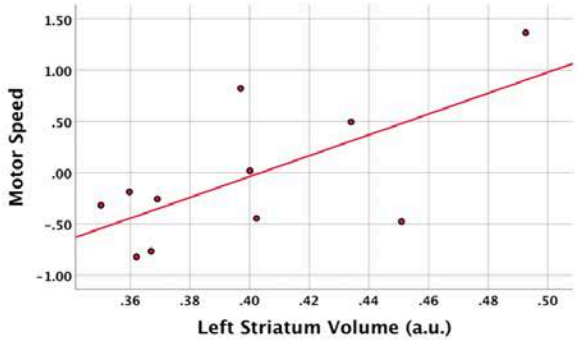
2-Week Post-Injury GMV Correlations











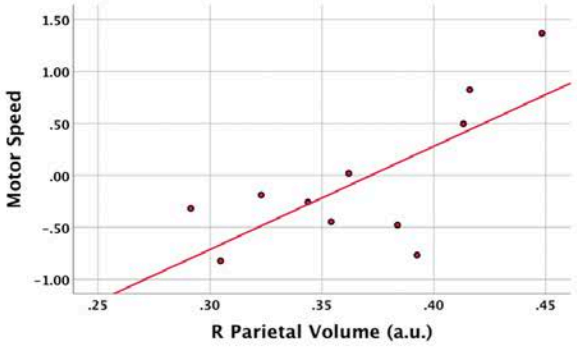
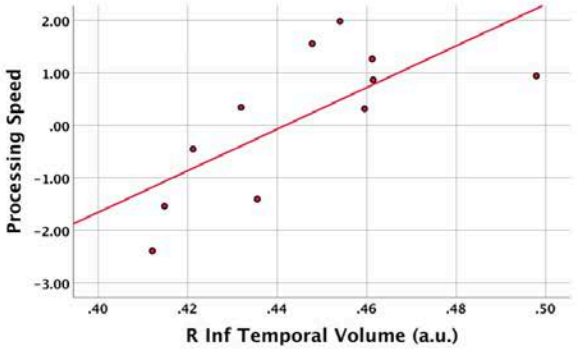


Figure S47. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the 2-Week Post-Injury group.



1-Month Post-Injury Correlations:

Exploratory analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factors within the sample of individuals who had sustained their mTBI a month prior to the assessment. As shown in Table S4, larger GMV of the left cerebellum and right inferior temporal/cerebellar regions was associated with fewer cognitive errors in this group. Additionally, larger GMV of the left striatum and right parietal regions was associated with worse self-reported daily functioning at 1-month post-injury. However, larger right parietal GMV was also associated with faster processing speed as well.

TSI_group			L Cerebellum	R Inf Temp	L Striatum	R Parietal
2	F1 Verbal Memory	Pearson Correlation	.068	.091	.308	.192
		Sig. (2-tailed)	.757	.679	.152	.381
		N	23	23	23	23
	F2 Atten Exec Control	Pearson Correlation	-.157	-.165	.129	-.025
		Sig. (2-tailed)	.474	.453	.557	.910
		N	23	23	23	23
	F3 PCS Emotion	Pearson Correlation	.170	.042	.133	.051
		Sig. (2-tailed)	.437	.848	.547	.817
		N	23	23	23	23
	F4 Aggression	Pearson Correlation	.217	.122	.392	.123
		Sig. (2-tailed)	.320	.580	.064	.575
		N	23	23	23	23
	F5 Visual Memory	Pearson Correlation	.276	.208	.099	.238
		Sig. (2-tailed)	.202	.342	.653	.274
		N	23	23	23	23
	F6 Sleep Quality	Pearson Correlation	.109	.063	.081	.290
		Sig. (2-tailed)	.622	.776	.715	.180
		N	23	23	23	23
	F7 Motor Speed	Pearson Correlation	-.280	-.199	.137	.250
		Sig. (2-tailed)	.195	.362	.532	.249
		N	23	23	23	23
	F8 Vigilance	Pearson Correlation	-.025	.039	-.038	-.151
		Sig. (2-tailed)	.910	.860	.863	.493
		N	23	23	23	23
	F9 Cognitive Errors	Pearson Correlation	-.416*	-.436*	-.392	-.207
		Sig. (2-tailed)	.048	.038	.065	.342
		N	23	23	23	23
	F10 Daily Functioning	Pearson Correlation	-.200	-.306	-.525*	-.468*
		Sig. (2-tailed)	.361	.155	.010	.024
		N	23	23	23	23
	F11 Concept Formation	Pearson Correlation	.213	.130	.251	-.036
		Sig. (2-tailed)	.328	.555	.247	.871
		N	23	23	23	23
	F12 Impulsivity	Pearson Correlation	.147	.172	.128	.051
		Sig. (2-tailed)	.504	.434	.561	.816
		N	23	23	23	23
	F13 Processing Speed	Pearson Correlation	.208	.192	.300	.438*
		Sig. (2-tailed)	.341	.379	.165	.036
		N	23	23	23	23

Table S4. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors for the 1-Month post-

1-Month Post-Injury GMV Correlations

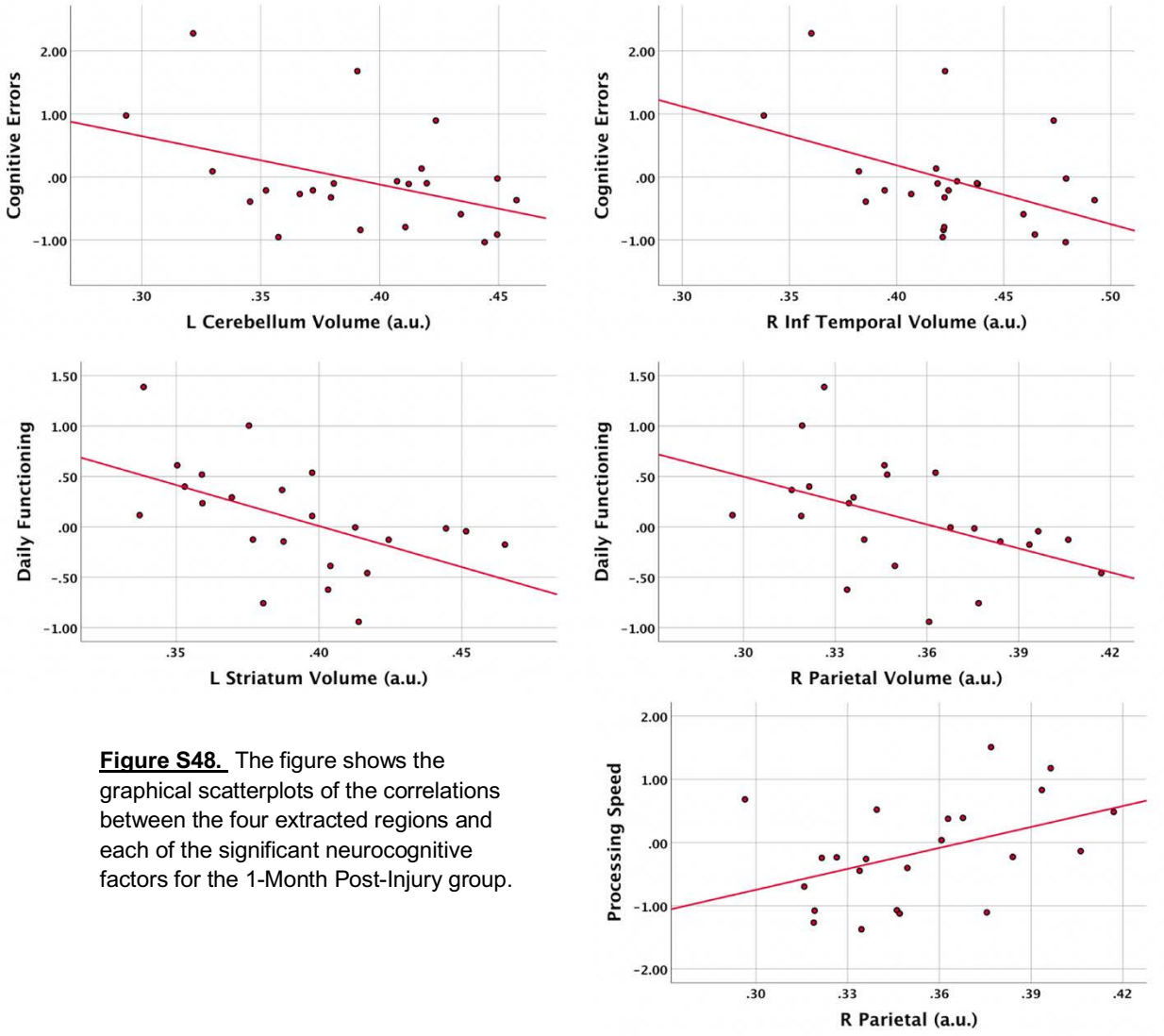


Figure S48. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the 1-Month Post-Injury group.

3-Month Post-Injury Correlations:

Analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factors within the sample of individuals who had sustained their mTBI 3 months prior to the assessment. As shown in Table S5, larger GMV of the left cerebellum and right inferior temporal/cerebellar region was associated with increased aggression. Additionally, larger gray matter volume in all four regions at this time point was associated with reduced impulsivity.

TSI_group			L Cerebellum	R Inf Temp	L Striatum	R Parietal
3	F1 Verbal Memory	Pearson Correlation	-.265	-.209	-.133	-.150
		Sig. (2-tailed)	.174	.286	.499	.446
		N	28	28	28	28
	F2 Atten Exec Control	Pearson Correlation	.059	-.019	-.024	-.101
		Sig. (2-tailed)	.764	.923	.903	.608
		N	28	28	28	28
	F3 PCS Emotion	Pearson Correlation	-.114	-.100	-.102	-.005
		Sig. (2-tailed)	.563	.612	.606	.981
		N	28	28	28	28
	F4 Aggression	Pearson Correlation	.454*	.452*	.252	.299
		Sig. (2-tailed)	.015	.016	.196	.122
		N	28	28	28	28
	F5 Visual Memory	Pearson Correlation	-.193	-.153	-.209	-.081
		Sig. (2-tailed)	.326	.438	.286	.682
		N	28	28	28	28
	F6 Sleep Quality	Pearson Correlation	.043	-.096	-.179	-.346
		Sig. (2-tailed)	.829	.628	.363	.071
		N	28	28	28	28
	F7 Motor Speed	Pearson Correlation	-.096	.021	-.065	-.186
		Sig. (2-tailed)	.626	.914	.743	.342
		N	28	28	28	28
	F8 Vigilance	Pearson Correlation	.071	.062	-.005	-.091
		Sig. (2-tailed)	.718	.753	.978	.647
		N	28	28	28	28
	F9 Cognitive Errors	Pearson Correlation	.229	.241	.086	.037
		Sig. (2-tailed)	.241	.216	.663	.852
		N	28	28	28	28
	F10 Daily Functioning	Pearson Correlation	-.198	-.134	.065	.188
		Sig. (2-tailed)	.311	.498	.743	.339
		N	28	28	28	28
	F11 Concept Formation	Pearson Correlation	-.252	-.190	-.145	-.189
		Sig. (2-tailed)	.196	.332	.463	.335
		N	28	28	28	28
	F12 Impulsivity	Pearson Correlation	-.496**	-.530**	-.463*	-.432*
		Sig. (2-tailed)	.007	.004	.013	.022
		N	28	28	28	28
	F13 Processing Speed	Pearson Correlation	-.137	-.080	.078	.133
		Sig. (2-tailed)	.487	.687	.694	.501
		N	28	28	28	28

Table S5. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors for the 3-Month post-

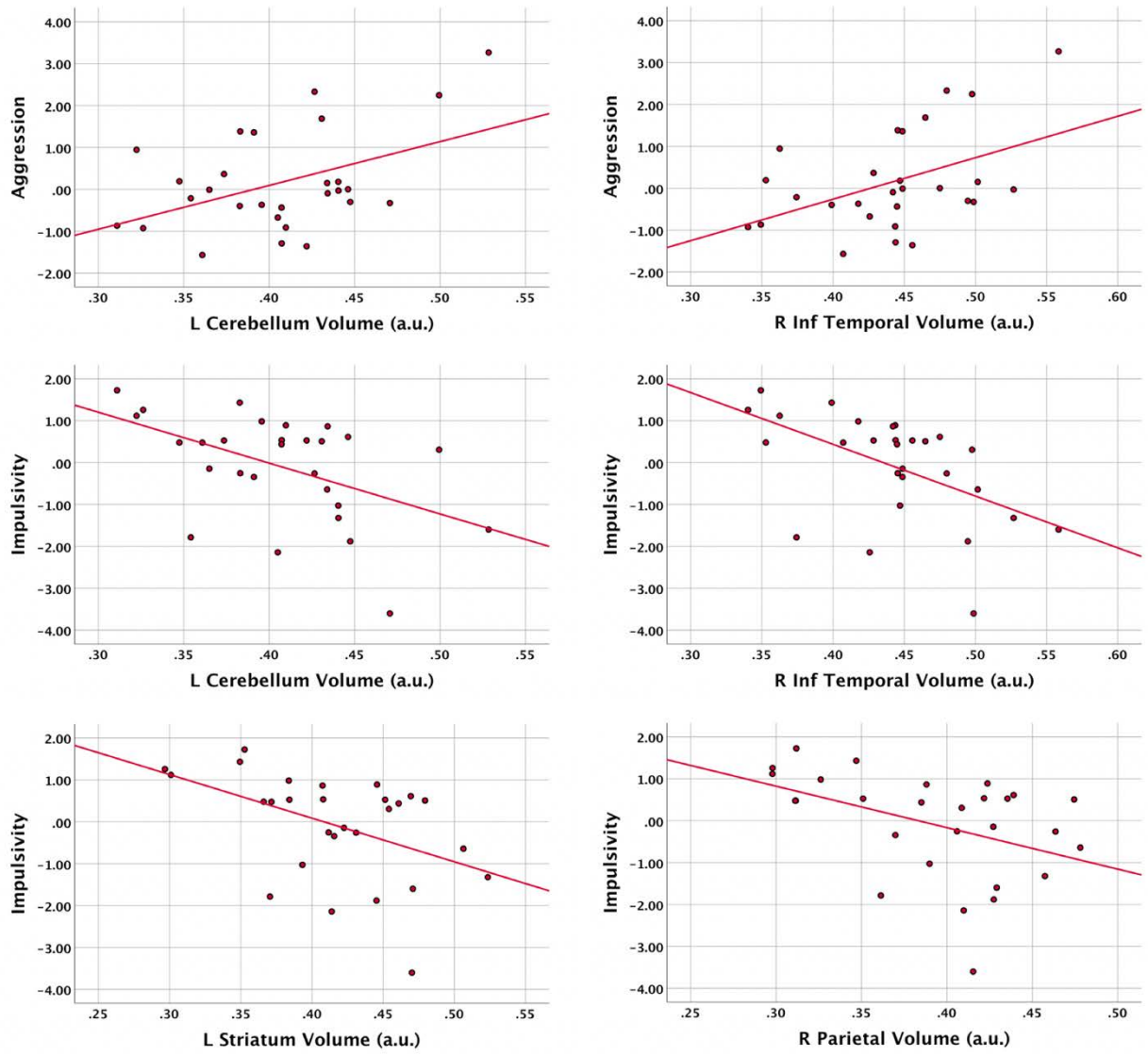


Figure S49. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the 3-Month Post-Injury group.

6-Month Post-Injury Correlations:

Analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factors within the sample of individuals who had sustained their mTBI 6 months prior to the assessment. As shown in Table S6, larger GMV of the right inferior temporal/cerebellar region, left striatum, and right parietal cortex was associated with better attention and executive function at 6-months post-injury. Additionally, larger gray matter volume of the left striatum and right parietal cortex was also significantly correlated with worse visual memory scores in this groups. However, these same regions were simultaneously associated with better vigilance performance at this time point.

TSI_group			L Cerebellum	R Inf Temp	L Striatum	R Parietal
4	F1 Verbal Memory	Pearson Correlation	.020	-.008	-.186	-.341
		Sig. (2-tailed)	.929	.973	.408	.121
		N	22	22	22	22
	F2 Atten Exec Control	Pearson Correlation	.383	.468*	.427*	.439*
		Sig. (2-tailed)	.079	.028	.047	.041
		N	22	22	22	22
	F3 PCS Emotion	Pearson Correlation	.023	.107	.067	-.009
		Sig. (2-tailed)	.917	.635	.766	.967
		N	22	22	22	22
	F4 Aggression	Pearson Correlation	.250	.214	.308	.259
		Sig. (2-tailed)	.263	.339	.164	.244
		N	22	22	22	22
	F5 Visual Memory	Pearson Correlation	-.223	-.367	-.557**	-.440*
		Sig. (2-tailed)	.319	.093	.007	.040
		N	22	22	22	22
	F6 Sleep Quality	Pearson Correlation	.258	.258	.217	.195
		Sig. (2-tailed)	.247	.247	.331	.385
		N	22	22	22	22
	F7 Motor Speed	Pearson Correlation	.230	.238	.393	.282
		Sig. (2-tailed)	.303	.285	.070	.203
		N	22	22	22	22
	F8 Vigilance	Pearson Correlation	.185	.266	.499*	.458*
		Sig. (2-tailed)	.409	.231	.018	.032
		N	22	22	22	22
	F9 Cognitive Errors	Pearson Correlation	.285	.298	.150	.104
		Sig. (2-tailed)	.199	.178	.506	.645
		N	22	22	22	22
	F10 Daily Functioning	Pearson Correlation	-.020	.019	-.001	.070
		Sig. (2-tailed)	.929	.933	.996	.756
		N	22	22	22	22
	F11 Concept Formation	Pearson Correlation	-.055	.095	.210	.175
		Sig. (2-tailed)	.808	.675	.347	.436
		N	22	22	22	22
	F12 Impulsivity	Pearson Correlation	-.173	-.240	-.229	-.099
		Sig. (2-tailed)	.441	.282	.305	.663
		N	22	22	22	22
	F13 Processing Speed	Pearson Correlation	-.066	-.004	-.046	-.116
		Sig. (2-tailed)	.771	.986	.839	.607
		N	22	22	22	22

Table S6. The table shows the correlations between the four extracted regions and each of the 13 neurocognitive factors for the 6-Month post-

6-Month Post-Injury GMV Correlations

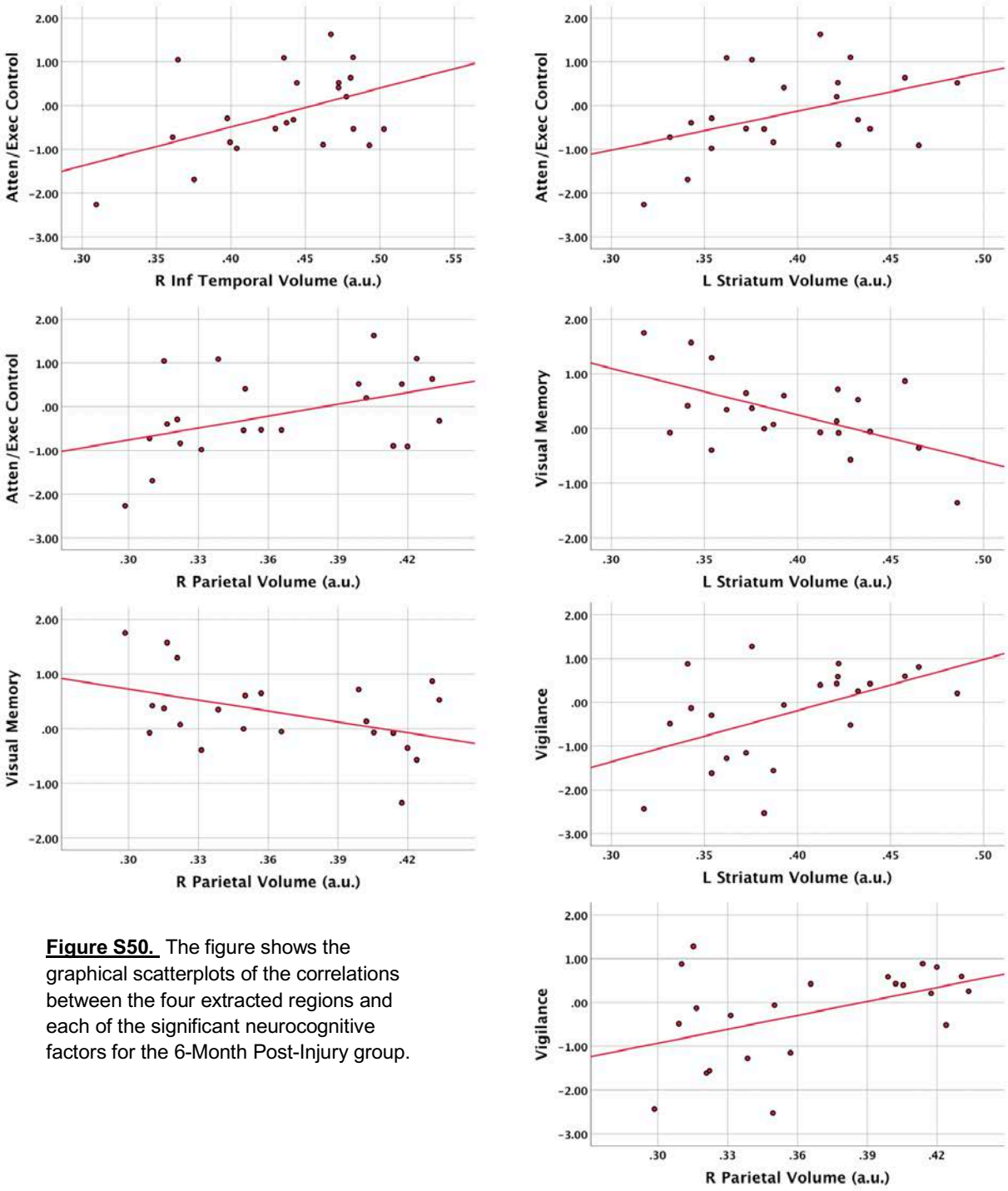


Figure S50. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the 6-Month Post-Injury group.

12-Month Post-Injury Correlations:

Analyses were undertaken to examine the associations between each of the four extracted brain clusters and the 13 neurocognitive factors within the sample of individuals who had sustained their mTBI 12 months prior to the assessment. As shown in Table S7, larger GMV of the right parietal cortex was associated with lower PCS and emotional disturbance symptoms. On the other hand, larger GMV within the right inferior temporal/cerebellar region was associated with greater aggression scores at this time point.

TSI_group			L Cerebellum	R Inf Temp	L Striatum	R Parietal
5	F1 Verbal Memory	Pearson Correlation	-.075	-.020	.022	.050
		Sig. (2-tailed)	.648	.903	.896	.762
		N	39	39	39	39
	F2 Atten Exec Control	Pearson Correlation	.117	.206	.303	.131
		Sig. (2-tailed)	.478	.208	.060	.428
		N	39	39	39	39
	F3 PCS Emotion	Pearson Correlation	-.281	-.244	-.289	-.347*
		Sig. (2-tailed)	.083	.134	.075	.030
		N	39	39	39	39
	F4 Aggression	Pearson Correlation	.243	.350*	.304	.275
		Sig. (2-tailed)	.136	.029	.060	.090
		N	39	39	39	39
	F5 Visual Memory	Pearson Correlation	.091	.113	-.028	.071
		Sig. (2-tailed)	.582	.492	.864	.667
		N	39	39	39	39
	F6 Sleep Quality	Pearson Correlation	-.096	-.177	-.216	-.206
		Sig. (2-tailed)	.559	.282	.187	.208
		N	39	39	39	39
	F7 Motor Speed	Pearson Correlation	.029	-.021	.022	.049
		Sig. (2-tailed)	.862	.899	.895	.766
		N	39	39	39	39
	F8 Vigilance	Pearson Correlation	.273	.112	.075	.161
		Sig. (2-tailed)	.093	.498	.651	.327
		N	39	39	39	39
	F9 Cognitive Errors	Pearson Correlation	-.206	-.150	-.150	-.119
		Sig. (2-tailed)	.207	.364	.362	.470
		N	39	39	39	39
	F10 Daily Functioning	Pearson Correlation	-.066	.003	-.094	-.119
		Sig. (2-tailed)	.688	.983	.570	.469
		N	39	39	39	39
	F11 Concept Formation	Pearson Correlation	.126	.213	.132	.163
		Sig. (2-tailed)	.446	.194	.423	.321
		N	39	39	39	39
	F12 Impulsivity	Pearson Correlation	.000	.065	-.076	-.119
		Sig. (2-tailed)	.999	.695	.644	.470
		N	39	39	39	39
	F13 Processing Speed	Pearson Correlation	-.106	-.043	-.014	-.053
		Sig. (2-tailed)	.521	.796	.935	.750
		N	39	39	39	39

Table S7. The table shows the correlations between the

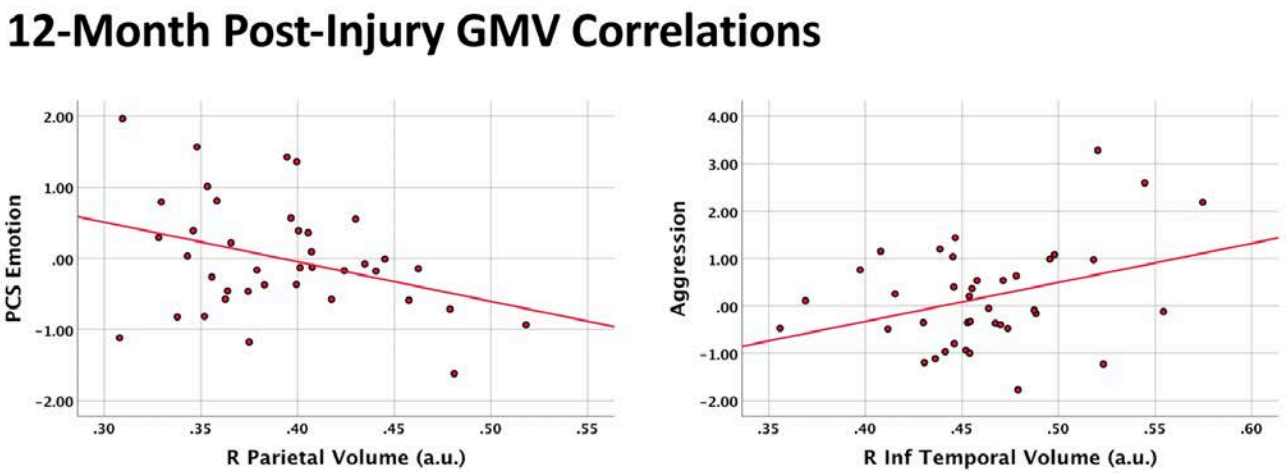


Figure S51. The figure shows the graphical scatterplots of the correlations between the four extracted regions and each of the significant neurocognitive factors for the 12-Month Post-Injury group.

3.F.II Archival Summary of Preliminary Work Over the Course of the Project

Over the multiple years of the project, we conducted numerous preliminary analyses as data became available. Many of these analyses have been superseded by more comprehensive analyses presented elsewhere in this report. Nonetheless, for comprehensiveness in reporting, we also include many of these early findings to document the course of work of the project over multiple years.

Early Preliminary Analyses (Years 1-3)

Early Voxel Based Morphometry (VBM) Findings

Quality of life/ Resilience post-injury and gray matter volume. The twenty-six mTBI participants (11 males, 15 females; mean age = 23.4), whose high-resolution T1 structural neuroimaging data were collected at McLean hospital, were used in VBM preliminary analyses. Using behavioral data from completed Satisfaction with Life Scale (SWLS) and the Connor-Davidson Resilience Scale assessments, we performed several multiple regression VBM analyses. After covarying for age, gender, time since injury and intra-cranial volume, a voxel-based morphometric (VBM) multiple regression analysis was conducted within Statistical Parametric Mapping (SPM8) to explore the association between gray matter volume in the frontal lobe and SWLS and CD-RISC scores. Greater GM volume in the left hemisphere of the superior frontal gyrus was positively correlated with SWLS scores (7 voxels, $p<0.05$, FWE corrected). No association was found in the right PFC. Consistent with the theory of lateralized affective processing, we found that greater volume of the left medial prefrontal cortex was associated with greater satisfaction with life among individuals with recent brain injuries.

Utilizing a small volume correction (SVC) for the frontal lobe, CD-RISC scores were found to be positively correlated with greater GMV in the left precentral gyrus (13 voxels, $p<.05$,

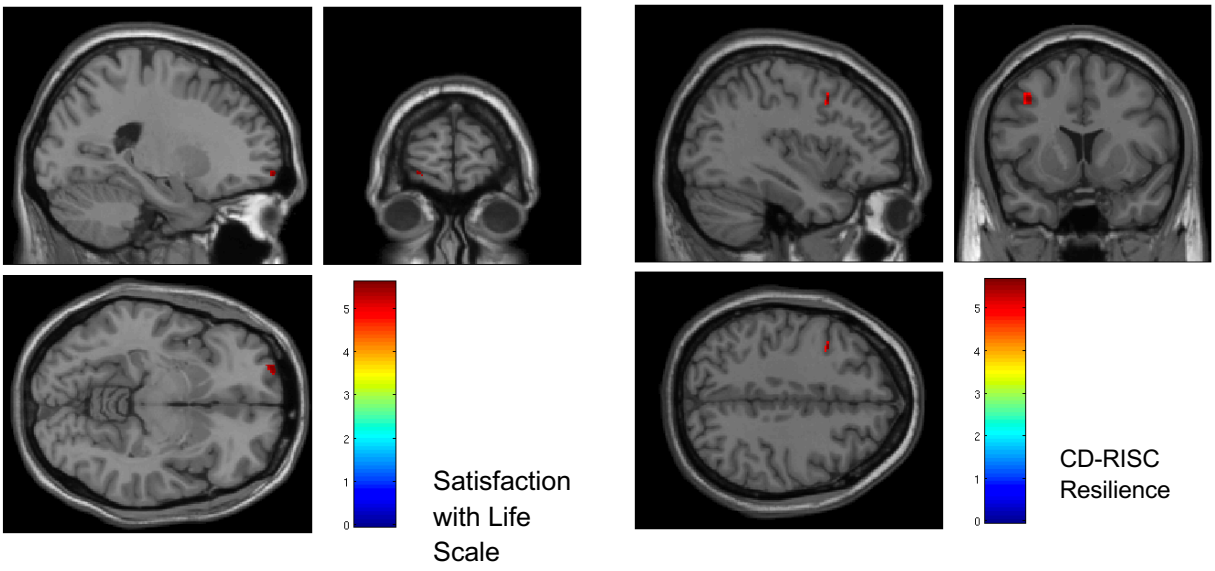


Figure S52. The figure on the left shows the association between prefrontal gray matter volume and the Satisfaction with Life Scale, while the figure on the right shows the positive association between prefrontal gray matter volume and the CD-RISC measure of resilience. All images are corrected at $p < .05$, family-wise error corrected.

FWE corrected). Exploratory analysis further revealed that this association is significantly more prominent in the acute (less than 3 months), as opposed to the chronic stage (between 3 and 12 months) following an mTBI. These findings suggest that GMV in the left precentral gyrus may predict cognitive resilience following an mTBI. Although the precentral gyrus is primarily thought to be responsible for voluntary movement, studies have shown that the left precentral gyrus may be associated with subthreshold depression risk and negative self-attributional bias in response to adverse life events. Early identification of gray matter deficits in this region following mTBI may therefore alert clinicians to the need to devote greater attention towards cultivating cognitive resilient skills.

Body Mass Index (BMI) and gray matter. mTBI participants were divided into groups of 12 healthy (BMI ≤ 25) and 12 overweight (BMI > 25). After controlling for age, gender, intra-cranial volume, and time since injury, gray matter volume was significantly greater ($p<0.005$) in the healthy group compared to the overweight group in a number of brain regions, including the bilateral caudate nucleus (head) regions, nucleus accumbens, bilateral parahippocampal gyrus, left inferior temporal gyrus, and left medial frontal gyrus. Significant differences in gray matter volumes were found between healthy and overweight individuals, particularly within regions involved in reward, executive functioning, memory, and emotion (see Figure S53). Interestingly, the direction of findings for the ventral striatum is opposite of that often reported for non-brain injured individuals, raising the possibility that mTBI might alter these associations.

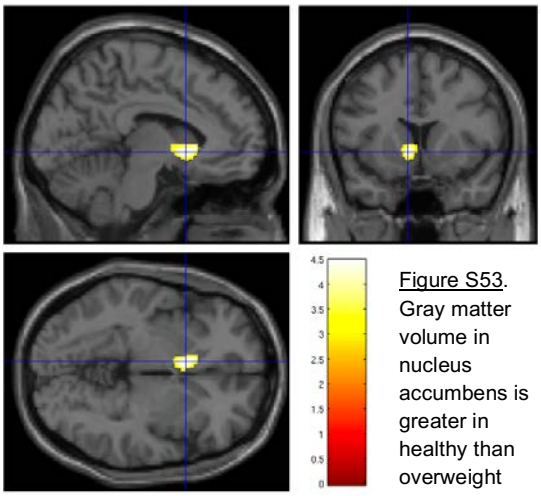


Figure S53. Gray matter volume in nucleus accumbens is greater in healthy than overweight

Gray matter in vMPFC and time since injury. Segmented images were used to create a custom DARTEL template, and then images were normalized and smoothed prior to analysis.

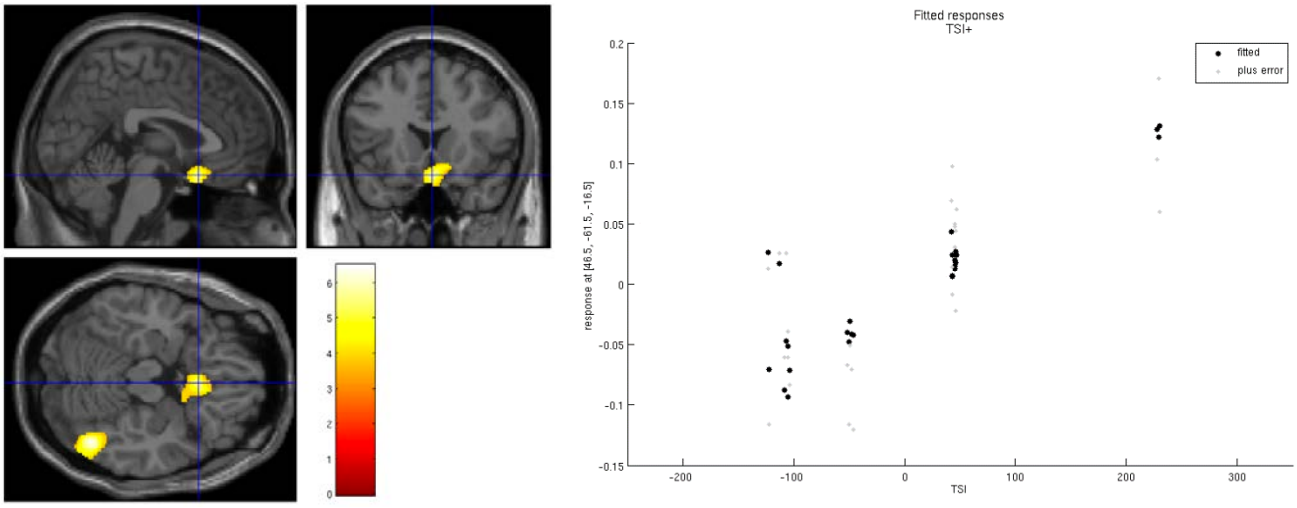


Figure S54. Gray matter volume within the ventromedial prefrontal cortex and inferior temporal cortex is positively correlated with days since injury.

VBM data were correlated with time since injury. The volume data from the resulting cluster were then extracted and correlated with metrics from the Delis-Kaplan executive function system (DKEFS). After controlling for age, gender and intracranial volume (ICV), GM volume in the right inferior temporal cortex and ventromedial prefrontal cortex (VMPFC) correlated positively with time since injury (cluster corrected, $p<0.05$ FDR, whole brain). VMPFC volume from this cluster were also found to be positively correlated with performance on several DKEFS tasks such as DKEFS-design fluency 1 (R^2 =0.177), DKEFS-design fluency 2 (R^2 = 0.164) and DKEFS-sorting test (R^2 = 0.230). VMPFC volume was greater with longer time since injury post mTBI. While causal inference cannot be made, we speculate that the greater volume in VMPFC with longer time since injury might reflect a compensatory phenomenon of neural plasticity aiding in recovery of cognitive functions post mTBI (see figure S54).

Early Diffusion Tensor Imaging (TBSS) Findings

In this preliminary analysis we investigated brain white matter (WM) integrity in 26 participants with mild traumatic brain injury (mTBI) (age M= 23.38, SD= 5.23; 15 females). First, we were interested to see whether mTBI is associated with WM changes regardless of the injury chronicity. We performed whole brain analysis using Tract Based Spatial Statistics (TBSS) across the entire group of participants while controlling for age, sex and time since injury. Correlational analysis showed that alterations in WM of participants with a recent history of mTBI were associated with performance metrics on a number of neuropsychological tests, as well as general health and wellbeing questionnaires. We used fractional anisotropy (FA) as a global measure to qualify changes within WM. There was a significant negative association ($p< .05$, corrected for multiple comparisons) between FA and the Aggression subscale of the Personality Assessment Inventory (PAI), indicating that reduced WM coherence was associated with increased physical aggression in this clinical population. WM fibers implicated in this association included the genu and splenium of the corpus callosum (CC), superior longitudinal fasciculus (SLF) and corona radiate (see figure at right).

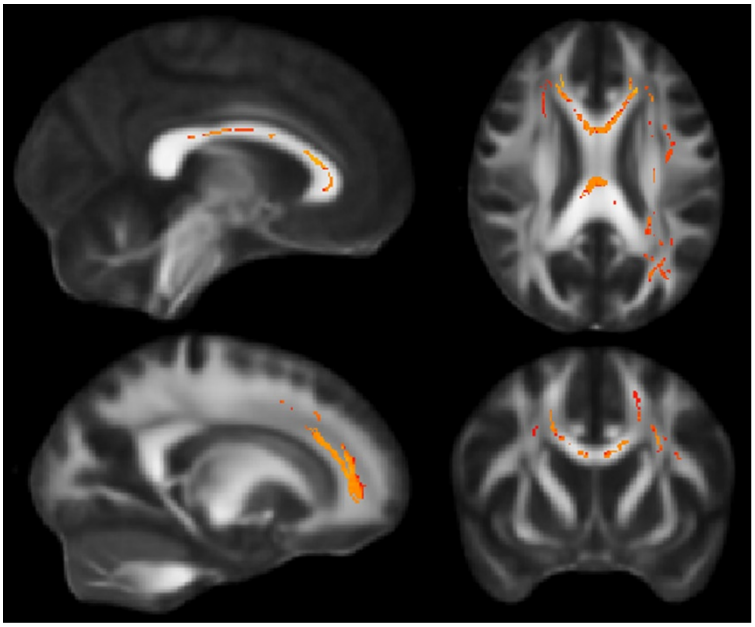


Figure S55. White matter FA in the corppus collosum were negatively correlated with the Aggression subscale of the PAI ($p < .05$, corrected).

Additionally, reduced FA in the external capsule and internal capsule in mTBI was significantly ($p < .05$, corrected for multiple comparisons) positively associated with performance on tests of vigilance, such as PVT Speed (i.e., 1/RT*1000). This result suggests that greater integrity of WM is associated with greater psychomotor vigilance speed (see figure S56).

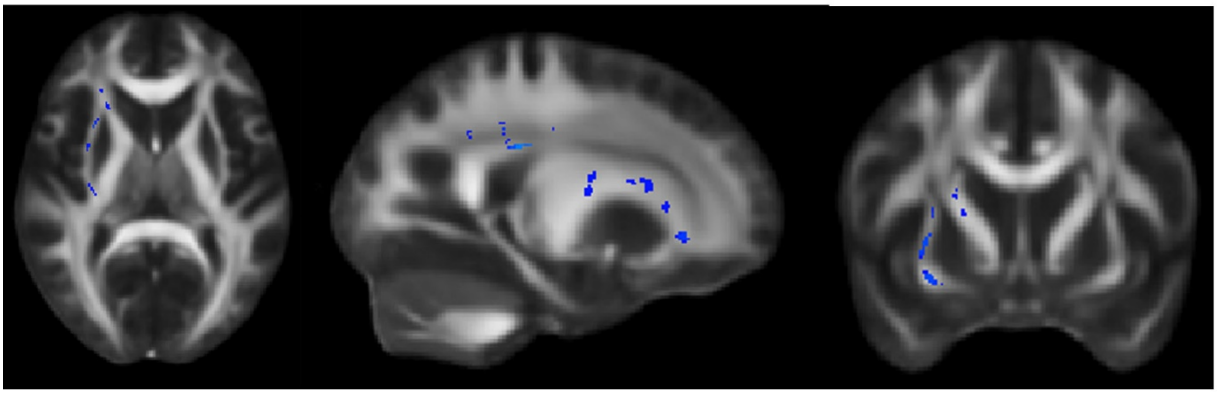


Figure S57. White matter FA in the external capsule and internal capsule was positively correlated with psychomotor vigilance speed.

Moreover, FA had a near significant association with a range of other cognitive measures. FA showed a negative association with Pittsburgh Sleep Quality Index (PSQI) and Rivermead Post- Concussion Symptoms Questionnaire (RPCSQ), thus suggesting that compromised WM coherence is associated with poorer sleep and greater post-concussive symptoms, respectively. In line with the observed negative association between FA and PAI aggression subscale, we also observed an association between FA and Buss Perry total aggression score. Interestingly, we found that these questionnaires also showed significant associations with time since injury. Overall, as shown in Figure S58, participants with a longer time since injury tended to have lower severity across several metrics of concussion (RPCSQ), anxiety, and aggression.

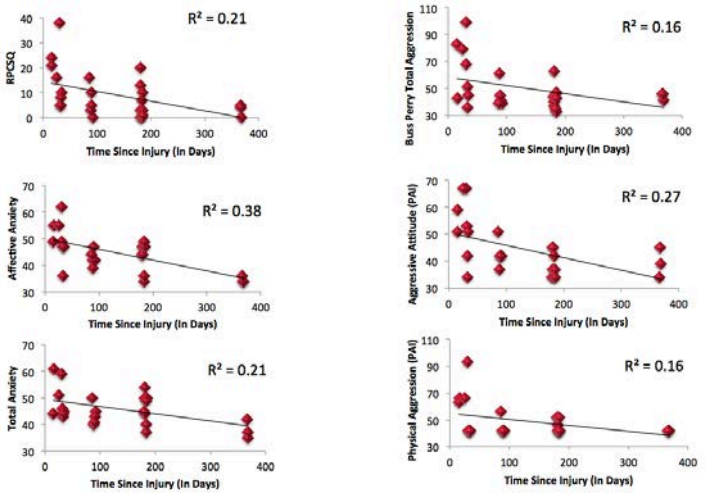
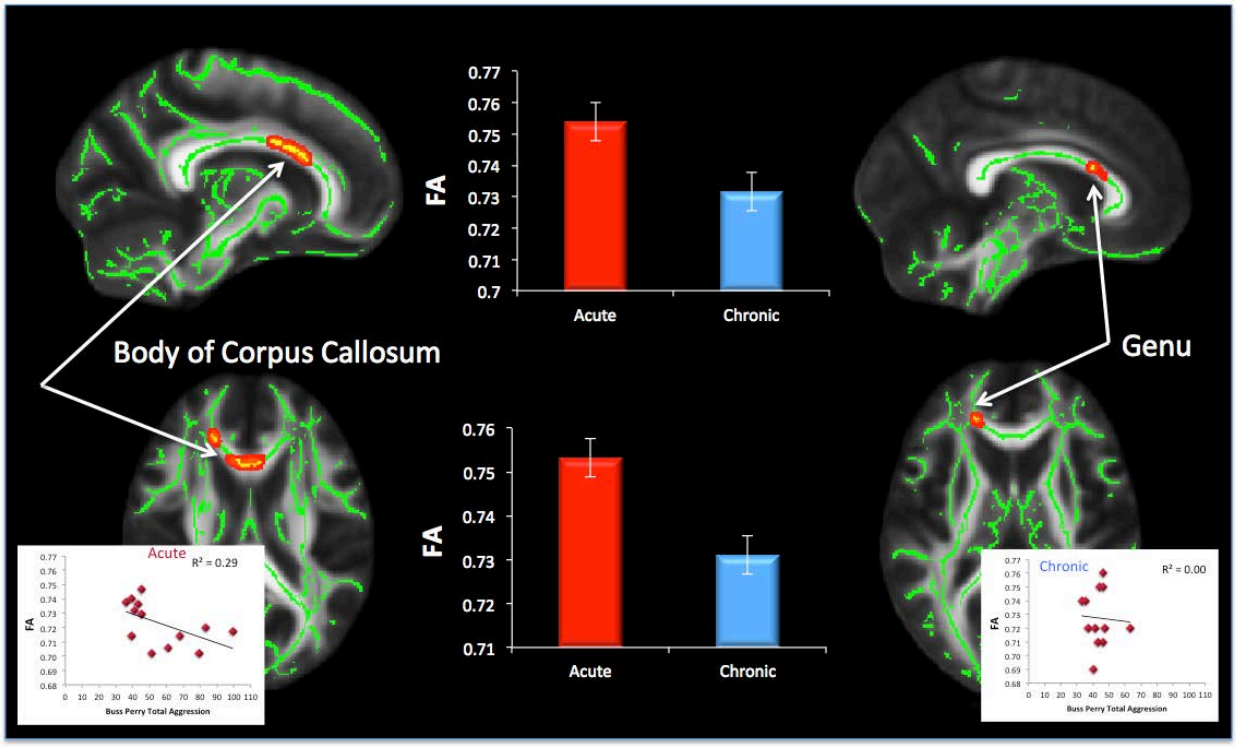


Figure S58. Longer time since injury is negatively correlated with several behavioral outcome measures, including the Rivermead Post-Concussion Symptom Checklist, several indices of anxiety, and several indices of aggression.

Finally, we were interested to see whether the associations observed across the entire mTBI group would differ when examined in acute (< 3 months) vs. chronic (> 6 months) mTBI subgroups. Our findings indicate that in the acute subgroup, PSQI measure of quality of sleep was negatively associated with FA in the genu, body and splenium of the CC, SLF, corona radiate and thalamic radiation ($p < .05$). There was also a near significant negative correlation between FA and Buss Perry total score in the acute group in the body of CC and SLF ($p < .1$). A

near significant negative correlation was also observed between performance on a vigilance test and FA in the corona radiate and internal capsule (see Figure S59.



FA Values: Acute mTBI > Chronic mTBI

Figure S59. FA values were compared between acute (0 to 3 months) and chronic (3 months to 1 year) mTBI. The body and genu of the corpus collosum showed significant differences in FA values, with lower FA observed in the Chronic group. Separate correlations between FA and Aggression scores for each group showed that FA was negatively correlated with aggression for the Acute group, but not the Chronic group.

Early Resting State Functional Connectivity Findings

In order to further explore the functional aspects, we used resting-state functional MRI (rsfMRI) data collected from mTBI survivors to identify different neural networks distributed throughout the whole brain. Depending on the time since mTBI onset from the date of scan, we divided our data set in two categories: (1) 'Early Stage (ES)' for mTBI survivors who suffered a TBI within the last 3 months and (2) 'Late Stage (LS)' for mTBI survivors who suffered a TBI more than 3 months ago.

The primary focus of rsfMRI is on spontaneous low frequency (< 0.1 Hz) oscillations. For the current study, we opted for rsfMRI data over task-based MRI data because clinically it is important to assess the functional role of different brain networks whereas task based MRI data allows to explore the functionality of specific networks depending on the type of stimulus.

In previous studies, using various approaches, several major resting state functional networks were detected and analyzed (Greicius, Krasnow, Reiss, & Menon, 2003; Lee et al., 2012; Raichle, 2011). In a study by Raichle in 2011 (Raichle, 2011), using a seed-based approach, seven major resting-state networks were reported. So before comparing and detecting the significant differences between functional connectivity measures for healthy controls and mTBI survivors, we first validated the resting-state networks for healthy-controls using the seed-voxel approach. In seed-voxel approach, a specific brain area is selected as a seed-region and the mean time-series over the voxels of the seed is correlated with each voxel of the brain. Here, we selected seven seed-regions based on a previous study (Raichle, 2011).

Data collection. As of 08/31/2016, we had collected functional MRI data from (i) 24 mTBI survivors (13F, 11M, mean age = 23.5±5.4 years, 12 ES and 12 LS mTBI survivors with mean age of 21.4±1.7 and 25.6±7 years respectively) (functional MRI data from 2 mTBI survivors out of a total of 26 were discarded as the data were not saved correctly) and 3 healthy controls (all females, mean age = 24.3±2.3 years) - collected at McLean hospital and (ii) 19 mTBI patients (10F, 9M, mean age = 23.5±6.7 years, 13 ES, 6 LS mTBI survivors with mean age of 21±1.1 and 24.7±7.9 years respectively) and 15 healthy controls (9F, 6M, mean age = 22.8±3.4 years) - collected at University of Arizona (UA), comprising a total data collected from 43 mTBI survivors (23F, 20M, mean age = 23.5±5.9 years, 25 ES and 18 LS mTBI survivors with mean age of 21.2±1.5 and 25.1±7.4 respectively) and 18 healthy controls (12F, 6M, mean age = 23.0±3.3 years).

Along with brain imaging data, we also collected behavioral data during cognitive screening of participants, such as: Epworth Sleepiness Scale (ESS), which is a measure of participant's sleepiness (measured during day-time), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) attention index, which is a measure of participant's attention (coding and digit span indices).

Approach. Based on a previous study, for resting-state functional connectivity analysis, we selected seven seed regions: PCC (posterior cingulate cortex), DMPFC (dorsal medial prefrontal cortex), DAC (dorsal anterior cingulate), LMC (left motor-cortex), LV1 (left primary visual), LA1 (left primary auditory) and LFEF (left frontal eye field) (Table 1), which are well known for generating seven individual resting-state functional networks. For seed-voxel functional connectivity analysis, we used MATLAB and SPM (Statistical Parametric Mapping: http://www.fil.ion.ucl.ac.uk/spm/) based functional connectivity toolbox: CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012), which also involves basic fMRI data preprocessing steps.

Our goal here was to first validate previously known resting-state networks (RSNs) for healthy controls. Further, for each of the RSN, our goal is to compare and detect the significant difference for strength of functional connectivity between (i) healthy controls and ES mTBI survivors, (ii) healthy controls and LS mTBI survivors and (iii) ES and LS mTBI survivors. In this report, we are reporting the functional connectivity differences for only one of the seven resting-state networks we detected for healthy controls, followed by detecting any behavioral differences between HCs, ES and LS mTBI survivors.

Findings: Resting state functional networks (RSNs)

Healthy controls (HCs): For validation of resting-state networks (RSNs), we performed seed-voxel functional connectivity analysis for 15 healthy controls whose data was collected at University of Arizona (UA). Table S8 and Figure S60 show a summary of seven resting-state functional networks detected for validation purpose. We found that all the RSNs were consistent with previously reported networks (Raichle, 2011).

Table S8

Resting-state Network (RSN)	Networks	Seed Region (MNI co-ordinates)
RSN01	Default mode network	PCC (0, -52, 27)
RSN02	Executive control network	DMPFC (0, 24, 46)
RSN03	Salience network	DAC (0, 21, 36)
RSN04	Sensorimotor network	LMC (-39, -26, 51)
RSN05	Visual network	LV1 (-7, 83, 2)
RSN06	Auditory network	LA1 (-62, -30, 12)
RSN07	Dorsal attention network	LFEF (-29, -9, 54)

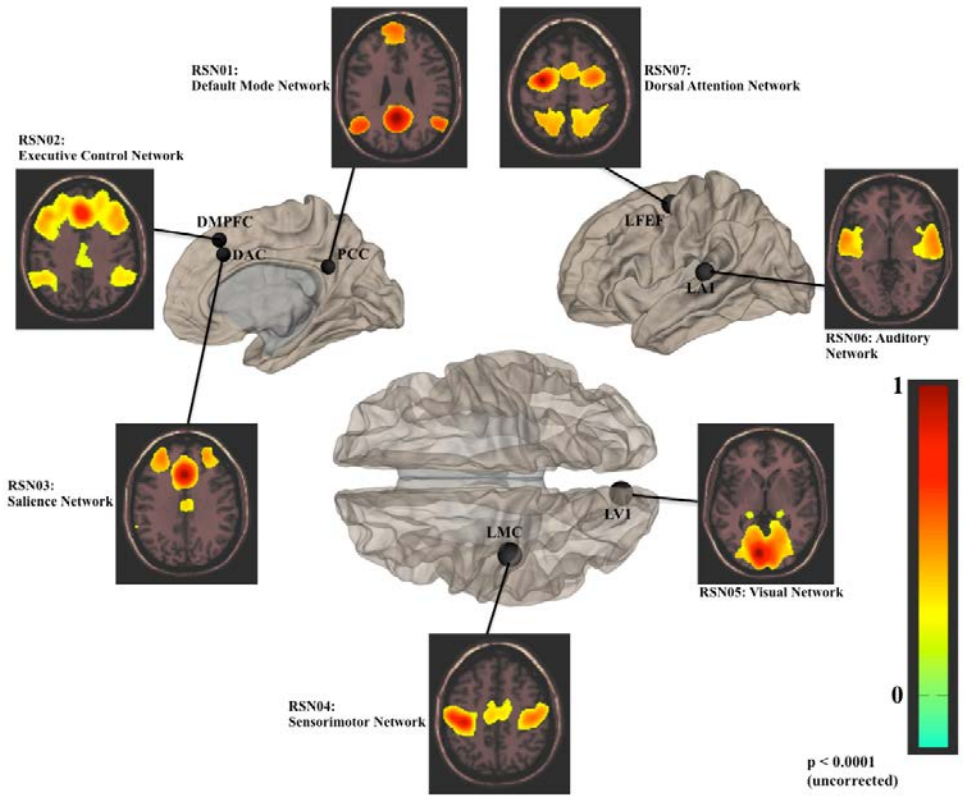


Figure S60. Here we summarize seven RSNs, corresponding to seven seed regions (Table 1) detected for healthy controls.

Resting-state functional connectivity: Healthy controls (HCs), Early Stage (ES) and Late Stage (LS) Traumatic Brain Injury (TBI) survivors

For HCs, figure 61A shows the significant functional connectivity patterns on brain surface for RSN01: default mode network (DMN), considering PCC as a seed region. In table S9, we report the sites in detail showing these functional connectivity patterns.

Table S9

Sites of significant functional connectivity*	**Peak MNI Co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: HCs					
Precuneus (28%) and posterior cingulate gyrus (37%)	0	-50	28	2892	29.59
Left angular gyrus (28%) and left lateral occipital cortex (9%)	-46	-60	32	782	13.84
Right angular gyrus (20%) and right lateral occipital cortex (4%)	56	-62	28	568	12.91
Left medial frontal cortex (37%) and left paracingulate gyrus (5%)	-6	40	-18	521	10.31
Left middle temporal gyrus (anterior, 48% and posterior, 4%)	-50	-6	-26	349	9.94
Paracingulate gyrus (left, 4% and right, 5%)	-10	48	20	221	8.77
Right middle temporal gyrus (anterior, 17% and posterior, 3%)	56	-8	-22	144	9.63
Right insular cortex (4%)	34	16	-2	57	-8.08
Right insular cortex (3%)	46	6	-6	35	-8.56

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

(a) ES mTBI survivors

For ES mTBI survivors, figure 2B shows the significant functional connectivity patterns on brain surface. In table 3, we report the sites in detail showing these functional connectivity patterns

Table S10

Sites of significant functional connectivity*	**Peak MNI Co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: ES mTBI					
Left medial frontal cortex (88%), paracingulate gyrus (left, 59% and right, 46%), left superior frontal gyrus (39%), frontal pole (left, 32% and right 20%), left anterior cingulate gyrus (29%), left middle frontal gyrus (21%) and left subcallosal cortex (47%)	-2	60	-16	13541	17.56

Posterior cingulate gyrus (78%), precuneous (59%), left posterior parahippocampal cortex (58%) and left hippocampus (30%)	0	-52	26	8310	26.03
Right inferior frontal gyrus (57%), right frontal operculum cortex (80%) and right insular cortex (38%)	36	50	34	3272	-10.02
Left middle temporal gyrus (anterior, 67% and posterior, 84%)	-66	-18	-20	2843	15.85
Left angular gyrus (52%) and left lateral occipital cortex (26%)	-44	-70	38	2243	16.22
Right middle temporal gyrus (anterior, 98%, posterior, 44%), right temporal pole (17%), and right inferior temporal gyrus (anterior, 25%)	60	0	-26	1977	14.48
Right angular gyrus (33%) and right lateral occipital cortex (18%)	56	-64	34	1735	12.48
Left frontal operculum cortex (66%) and left insular cortex (33%)	-40	-8	-16	1383	-9.98
Right supramarginal gyrus (anterior, 48% and posterior, 35%)	66	-42	34	1183	-10.10
Left supramarginal gyrus (anterior, 61% and posterior, 10%)	-52	-38	52	957	-8.96
Right parahippocampal gyrus (50%) and right hippocampus (28%)	24	-14	-20	537	8.68

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

(b) LS mTBI survivors

For LS mTBI survivors, figure 2C shows the significant functional connectivity patterns on brain surface. In table 4, we report the sites in detail showing these functional connectivity patterns.

Table S11

Sites of significant functional connectivity*	**Peak MNI Co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: LS mTBI					
Frontal pole (left, 22% and right, 15%), superior frontal gyrus (left, 22% and right, 14%), paracingulate gyrus (left, 44% and right, 34%), left medial frontal cortex (56%), left anterior cingulate gyrus (7%) and left subcallosal cortex (12%)	-8	58	34	7186	16.79
Precuneous (35%), posterior cingulate gyrus (57%)	0	-52	28	3974	23.50
Left middle temporal gyrus (anterior, 76% and posterior, 61%) and left temporal pole (16%)	-66	-12	-20	1998	14.22
Right temporal pole (22%), right middle temporal gyrus (anterior, 85% and posterior,	44	20	-38	1494	11.85

23%) and right inferior temporal gyrus (anterior, 16%)					
Left angular gyrus (29%) and left lateral occipital cortex (20%)	-44	-56	32	1464	15.23
Right angular gyrus (16%) and right lateral occipital cortex (11%)	50	-62	32	991	14.11
Left middle frontal gyrus (10%)	-36	12	54	305	12.46
Left supramarginal gyrus (anterior, 24%)	-56	-36	48	266	-8.68
Right frontal operculum cortex (24%) and right insular cortex (9%)	38	20	-2	194	-8.29
Left hippocampus (9%) and left parahippocampal cortex (anterior, 7% and posterior 7%)	-22	-18	-30	166	9.01
Left frontal operculum cortex (16%) and left insular cortex (4%)	-28	16	6	111	-7.97
Right supramarginal gyrus (anterior, 6% and posterior, 1%)	56	-36	52	78	-6.96
Right inferior frontal gyrus (9%)	52	8	8	72	-8.57

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

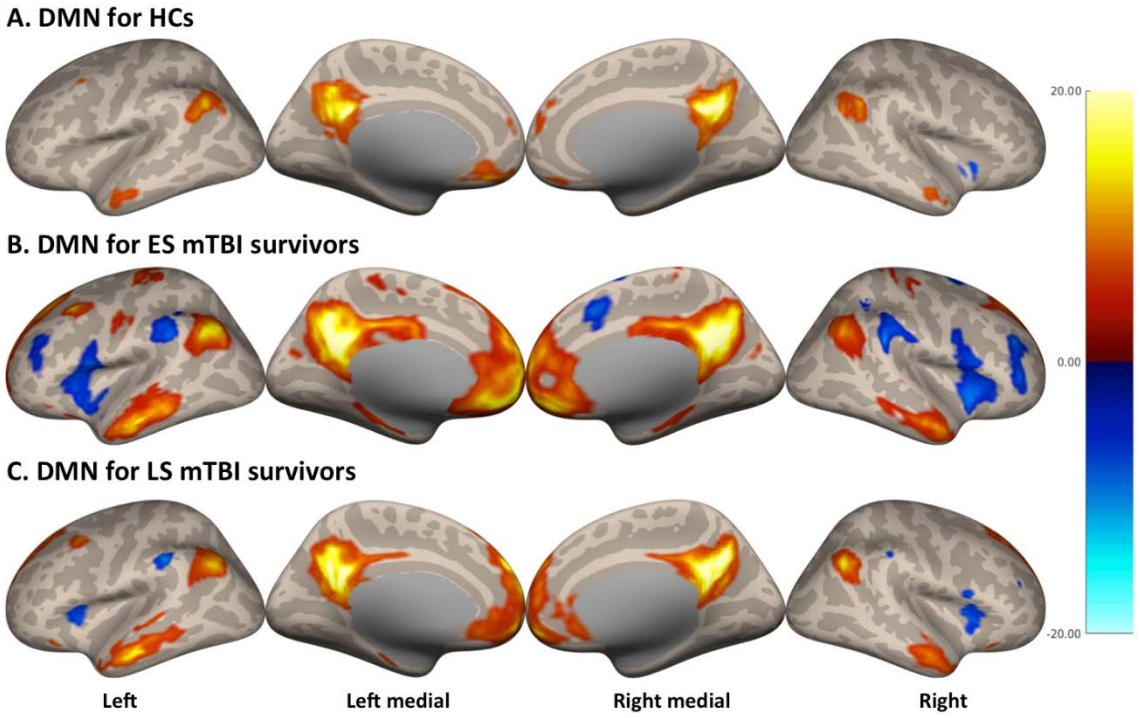


Figure 61. Functional connectivity maps generated for DMN (height threshold, $p < 0.001$, FD-corrected; extent threshold, $p < 0.001$, FDR-corrected), considering posterior cingulate cortex (PCC) as seed region for (A) Healthy Controls (HCs) (B) ES and (C) LS mTBI survivors.

In tables S9, S10, and S11 above, we report the common functional connectivity maps (i) among HCs, ES and LS mTBI survivors in 'green' color, (ii) between ES and LS mTBI survivors in

'blue' color whereas the functional connectivity maps which are not common in any case are colored in 'red'. Here, we noticed hyper connectivity (large percent of functional connectivity maps) in ES mTBI case, but with time this percent decreases with time (LS case) and tends towards normal percent connectivity maps (HCs case) (Figure 62A). In figure 62A, we showed the percent involvement of only those regions, which were common between HCs, ES and LS mTBI survivors but showed at-least 25% involvement in HCs. On the other hand, in figure 62B, we showed the decrease in percent involvement of only those regions, which were common between ES and LS mTBI survivors but showed at-least 20% involvement in LS mTBI survivors.

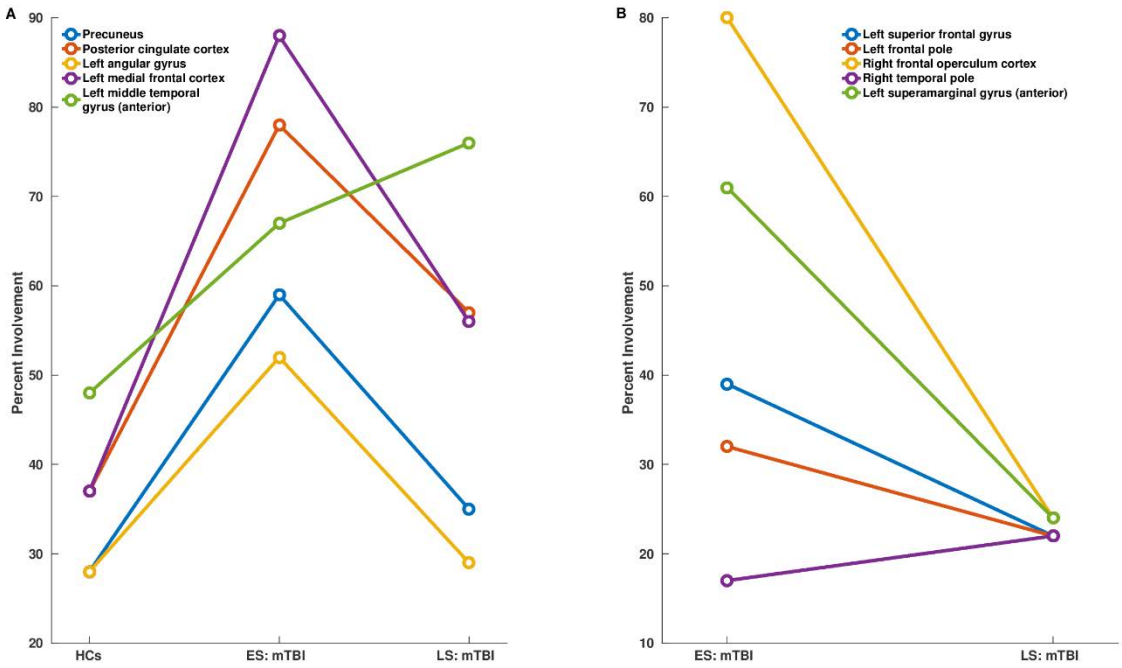


Figure 62. Comparison of percent involvement of regions involved significantly (tables S9, S10, and S11) in functional connectivity maps of DMN between (A) healthy controls (HCs), ES and LS mTBI survivors and (B) ES and LS mTBI survivors.

(c) HCs versus ES mTBI survivors

Further, we computed the significant differences between functional connectivity patterns of HCs and ES mTBI survivors for DMN. Figure 63A shows these significant differences on brain surface. In table S12, we report the sites in detail showing these significantly different functional connectivity clusters.

Table S12

Sites of significant functional connectivity*	**Peak MNI co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: ES > HCs					
Right supplementary motor cortex (3%), anterior cingulate cortex (1%),	14	0	44	75	5.38

Left insular cortex (2%), left central opercular cortex (1%)	-32	-16	12	50	5.36
Anterior cingulate cortex (1%), left supplementary motor cortex (1%)	-6	-6	40	34	5.03
Right post-central gyrus (1%), right pre-central gyrus (11 voxels),	46	-16	34	33	4.21
Left pre-central gyrus (17 voxels)	-22	-24	76	19	4.29
Right inferior temporal gyrus (posterior, 2%)	58	-36	-20	19	4.10
Left hippocampus (2%)	-28	-12	-18	16	5.17
Left pre-central gyrus (12 voxels), left post-central gyrus (1 voxel)	-44	-12	36	13	4.11
Left middle temporal gyrus (anterior, 2%)	-58	-10	-14	11	-4.14

*Height threshold, $p < 0.001$, FDR un-corrected; *Cluster size > 10.

(d) HCs versus LS mTBI survivors

Further, we computed the significant differences between functional connectivity patterns of HCs and LS mTBI survivors for DMN. Figure 63B shows these significant differences on brain surface. In table S13, we report the sites in detail showing these significantly different functional connectivity clusters.

Table S13

Sites of significant functional connectivity*	**Peak MNI Co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: LS > HCs					
Right precentral gyrus (1%), right middle frontal gyrus (12 voxels)	54	10	40	59	4.66
Left insular cortex (1%)	-34	-6	-6	14	4.32
Left central opercular cortex (1%), left insular cortex (2 voxels)	-38	-8	18	11	4.19

*Height threshold, $p < 0.001$, FDR un-corrected; *Cluster size > 10.

(e) ES versus LS mTBI survivors

Next, we also computed the significant differences between functional connectivity patterns of ES and LS mTBI survivors for DMN. Figure 63C shows these significant differences on brain surface. In table S14, we report the sites in detail showing these significantly different functional connectivity clusters.

Table S14

Sites of significant functional connectivity*	**Peak MNI Co-ordinates**			**Cluster size (number of voxels)**	**T-score**
	X	Y	Z		
Seed PCC: ES > LS					
Left pre-central gyrus (2%), left post-central gyrus (11 voxels)	-24	-26	68	133	4.47
Right temporal pole (3%)	40	16	-38	75	-4.85

Right middle temporal gyrus (posterior, 2% and temporo-ccipital, 1%), right superior temporal gyrus (posterior, 3%), right supramarginal gyrus (posterior, 1%)	58	-32	4	62	-4.40
Left middle temporal gyrus (anterior, 9% and posterior, 3 voxels)	-56	-10	-12	46	-4.70
Left inferior frontal gyrus 3%), left pre-central gyrus (4 voxels), left central opercular cortex (4 voxels), left frontal opercular cortex (1 voxel)	-50	6	4	41	-5.05
Left temporal pole (1%), left superior temporal gyrus (anterior, 3 voxels)	-46	6	-16	35	-5.14
Right supramarginal gyrus (posterior, 1% and anterior, 3 voxels)	66	-38	30	23	-4.28

*Height threshold, $p < 0.001$, FDR un-corrected; *Cluster size > 10.

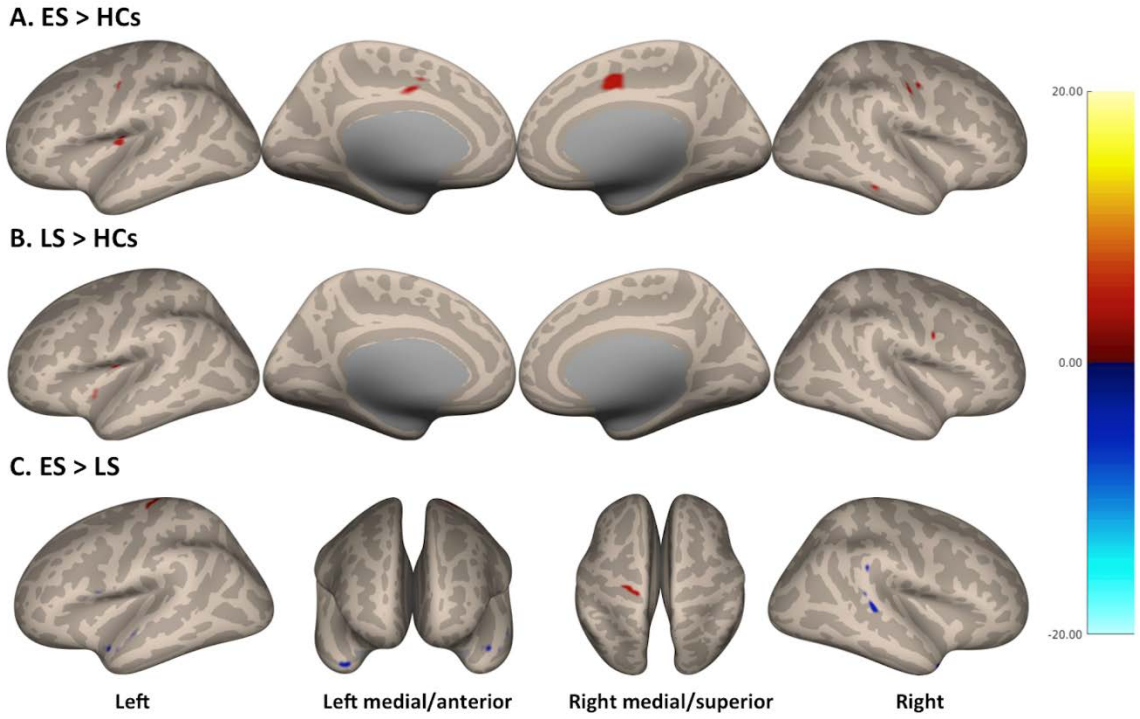


Figure 63. Significant differences between functional connectivity maps generated for DMN (height threshold, $p < 0.001$, FDR un-corrected; cluster size > 10), considering posterior cingulate cortex (PCC) as seed region for (A) ES mTBI survivors > HCs (B) LS mTBI survivors > HCs and (C) ES mTBI survivors > LS mTBI survivors.

Behavioral differences between HCs, ES and LS mTBI survivors

We compared ESS and RBANS scores between HCs, ES and LS mTBI survivors (Figure 64).

ESS scores: We found strong significant difference between ESS scores for HCs and ES mTBI survivors (two-sample t-test, $p < 0.01$). There was also significant difference between ESS scores for HCs and LS mTBI survivors (two-sample t-test, $p < 0.05$) but less strong than between HCs and ES mTBI survivors, although there was still no significant difference between ESS scores for ES and LS mTBI survivors (two-sample t-test, $p > 0.05$).

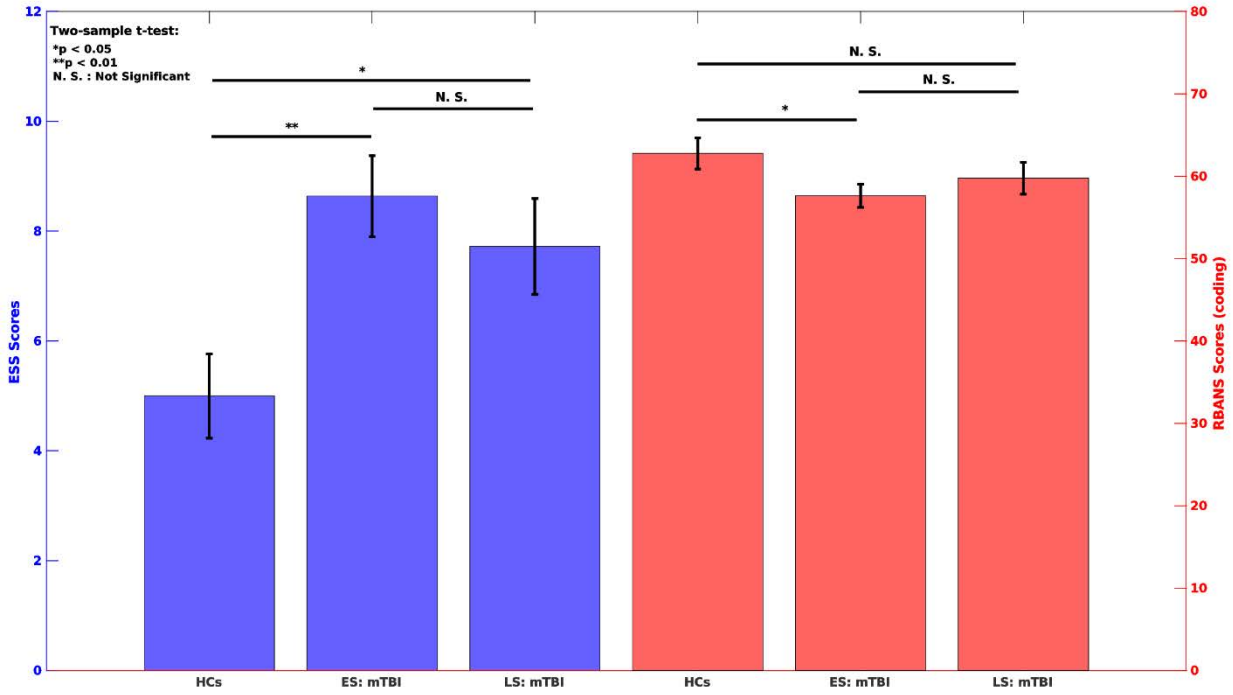


Figure 64. Comparison of ESS and RBANS scores (coding) between HCs, ES: mTBI and LS: mTBI survivors.

RBANS scores: We did not find any significant difference between RBANS digit span scores for HCs, ES or LS mTBI survivors. But there was significant difference between RBANS coding scores (two-sample t-test, $p < 0.05$) for HCs and ES mTBI survivors and there was no significant difference (two-sample t-test, $p > 0.05$) between RBANS coding scores for HCs and LS mTBI survivors.

Preliminary Functional Connectivity Analysis Conclusions

From functional connectivity maps of HCs and mTBI survivors, we found that there was hyper connectivity within default mode network following the brain injury (within 3 months of the onset of injury) but with time this hyper connectivity tends to be normal towards HCs for the mTBI survivors who had brain injury onset since more than 3 months.

From direct calculation of significant functional connectivity differences between HCs and mTBI survivors, we also noticed that there was clear abnormally high hyper connectivity at the

early stage of mTBI survivors, compared to HCs and late stage mTBI survivors but there were also very few small sized clusters found with percent involvement of around 1% or lesser which showed stronger functional connectivity for late stage mTBI survivors compared to HCs. This could either be a sign of neural plasticity or could still reflect abnormal hyper connectivity for LS mTBI survivors.

Comparison of ESS and RBANS scores also confirmed our findings from functional connectivity analysis. We found that there was significant improvement in ESS scores with time i.e. late stage mTBI survivors were found to be less sleepy during daytime, along with being more attentive than mTBI survivors who were in their early stage.

Middle Range Preliminary Analyses (Years 4-6)

By the middle period of the project, it became possible to conduct more extensive preliminary analyses with a larger sample. The data below were analyzed from Year 5 onward in the project and provide further assessment of the role of white matter connectivity, functional connectivity, and gray matter volumetrics in outcomes following mTBI. While more extensive than the preceding outcomes collected during the first four years of the project, these findings should also be considered as preliminary and superceded by the finalized outcomes presented in the main report. These are presented below for archival purposes.

White Matter Pathways Associated with Post-Concussion Aggression

We have been particularly interested in the association between mTBI and aggression, as this has particular applicability to Service members who must work closely in small teams and also may find themselves expressing aggression in inappropriate circumstances with family or fellow Service members. Aggression is one of the most commonly reported post-concussive symptoms, with upwards to 40% of individuals reporting increased levels of aggression hostility, and/or irritability after sustaining a mTBI.

Initial Sample: In an initial analysis, we examined the association between white matter axonal changes and aggression in patients at different stages of time since sustaining their injury. Specifically, we compared aggression in healthy controls (n = 16) and chronic mTBI (n = 10) using the Buss-Perry Aggression Questionnaire (BPAQ) and the Personality Assessment Inventory (PAI). Our preliminary analysis revealed elevated levels of total aggression, physical aggression, anger on the BPAQ, and elevated aggressive attitude, verbal aggression and total aggression on the PAI, in the mTBI compared to healthy control group. White matter integrity between the two groups was measured using DTI, revealing significantly reduced integrity in the bilateral anterior thalamic radiation (ATR) and corpus callosum (CC) in the mTBI compared to health control group. Finally, we examined the relationship between white matter integrity and aggression. Preliminary findings showed reduced white matter in the anterior thalamic radiation was associated with higher levels of aggression (see Figure 001). Our results suggest disrupted

frontal pathways could be part of the underlying neural mechanisms associated with impaired emotional processes. Furthermore, our findings highlight the potentially persistent nature of post-concussive symptoms in mTBI.

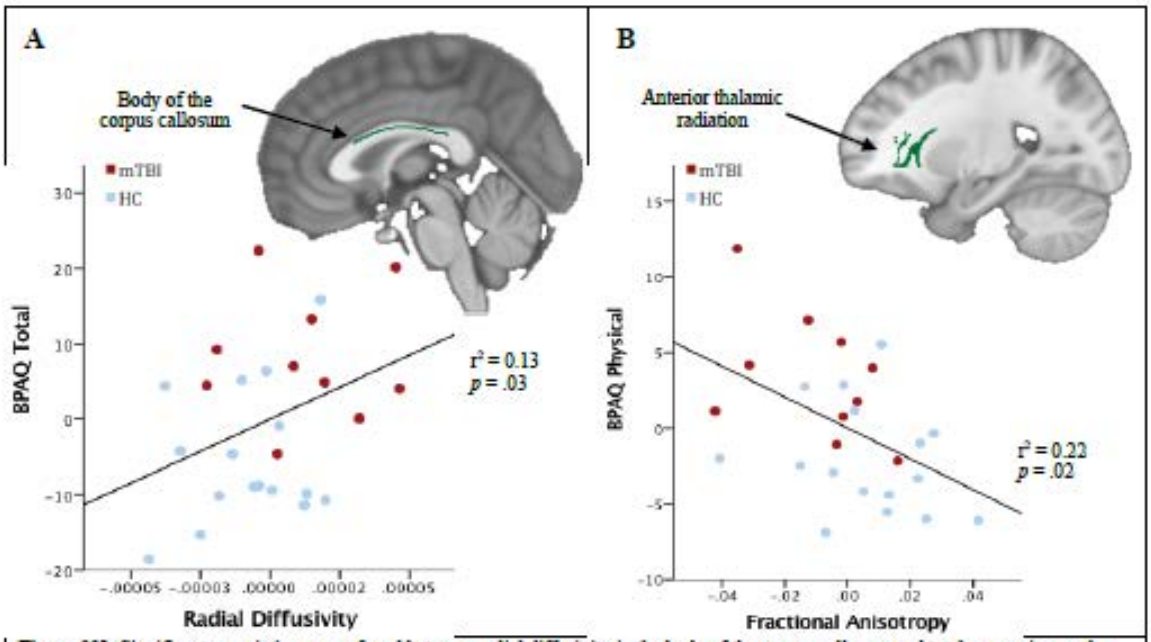


Figure 001. Significant associations were found between radial diffusivity in the body of the corpus callosum and total aggression on the Buss-Perry Aggression Questionnaire (BPAQ) (A) and fractional anisotropy in the left anterior thalamic radiation and physical aggression on the Buss-Perry Aggression Questionnaire (BPAQ) (B). Targeted tract is shown in green, overlaid on standard brain template using FSL.

Expanded Sample: We subsequently followed up with additional comparisons in larger samples as more data were acquired over this past year, which allowed us to examine data in the post-acute stage as well. It was hypothesized that individuals with mTBI would report higher levels of aggression, which would be associated with reduced white matter integrity in four, bilateral frontal pathways. For this analysis, 37 individuals participate, including 16 healthy controls, 11 mTBI patients in the post-acute stage (1-month or less since injury), and 10 mTBI patients in the chronic stage (6 months or longer since injury). Demographic data are listed in the table below:

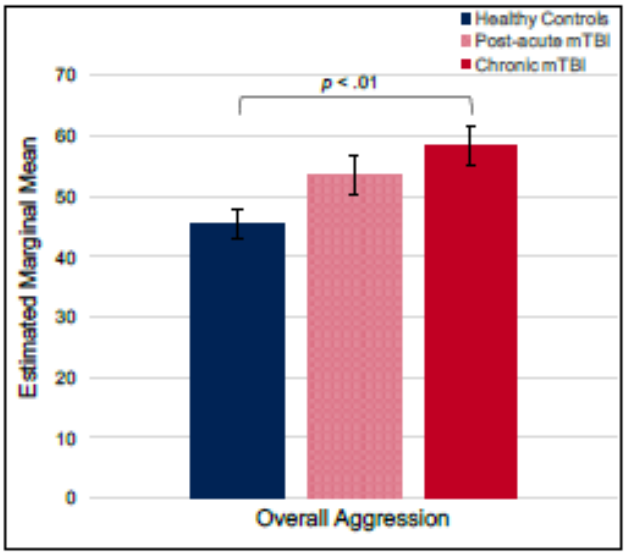
Table 1. Demographic characteristics of all groups

	HCs (n=16)	Post-acute (n=11)	Chronic (n=10)	Statistic
Age, in years	22.69 (3.40)	25.91 (8.68)	22.40 (6.38)	*F*
Sex – M/F	8/8	6/5	3/7	χ^2
Education	14.19 (2.43)	14.82 (2.86)	12.80 (1.55)	*F*
WASI-II IQ	111.31 (9.69)	115.09 (16.54)	111.90 (12.90)	*F*

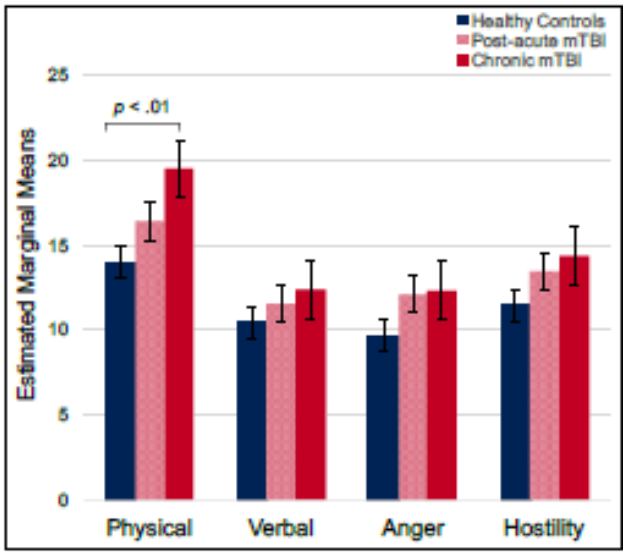
Note: Values are Mean (Standard Deviation) unless otherwise noted. WASI-II = Wechsler Abbreviated Scale of Intelligence – 2nd Edition; * p < .05

Participants completed the Buss-Perry Aggression Questionnaire (BPAQ) and underwent diffusion tensor imaging (DTI) at 3T. The Buss-Perry Aggression Questionnaire (BPAQ) is a 29-item self-report measure of overall aggression and 4 sub-scales including physical aggression, verbal aggression, anger, and hostility. Diffusion Tensor Imaging (DTI) was collected using single-shot echo planar imaging (EPI) with 78 directions using b-value of 0 and 1000 s/mm^2 (thickness = 2mm; voxel size = 2x2x2mm; TR = 9600ms; TE = 88ms; FOV = 100; matrix = 128 x 128 x 74). Binary masks were created for frontal pathways using the JHU ICBM-DTI-81 atlas, and targeted the corpus callosum, cingulum, uncinate fasciculus, and anterior thalamic radiation.

Buss-Perry Aggression Questionnaire (BPAQ). An ANCOVA, controlling for age and gender, showed significant group differences for overall aggression ($F(2,32) = 5.52$, $p < .01$, d = 1.19) and physical aggression ($F(2,32) = 5.83$, $p < .01$, d = 1.22). As shown in the figures below, the chronic mTBI group scored significantly higher on total aggression than the healthy controls. There was a trend toward greater aggression among chronic relative to post-acute mTBI, but this difference did not reach significance in the current analysis. We further explored the different facets of aggression and found that the differences were driven primarily by Physical Aggression, which was significantly higher among those in the chronic group versus the healthy controls. Other differences were not significant, but the sample sizes are still too small to draw reliable inferences, and we await confirmation as the sample sizes are increased.



The chronic mTBI group reported significantly higher overall aggression, compared to HCs ($p < .01$).



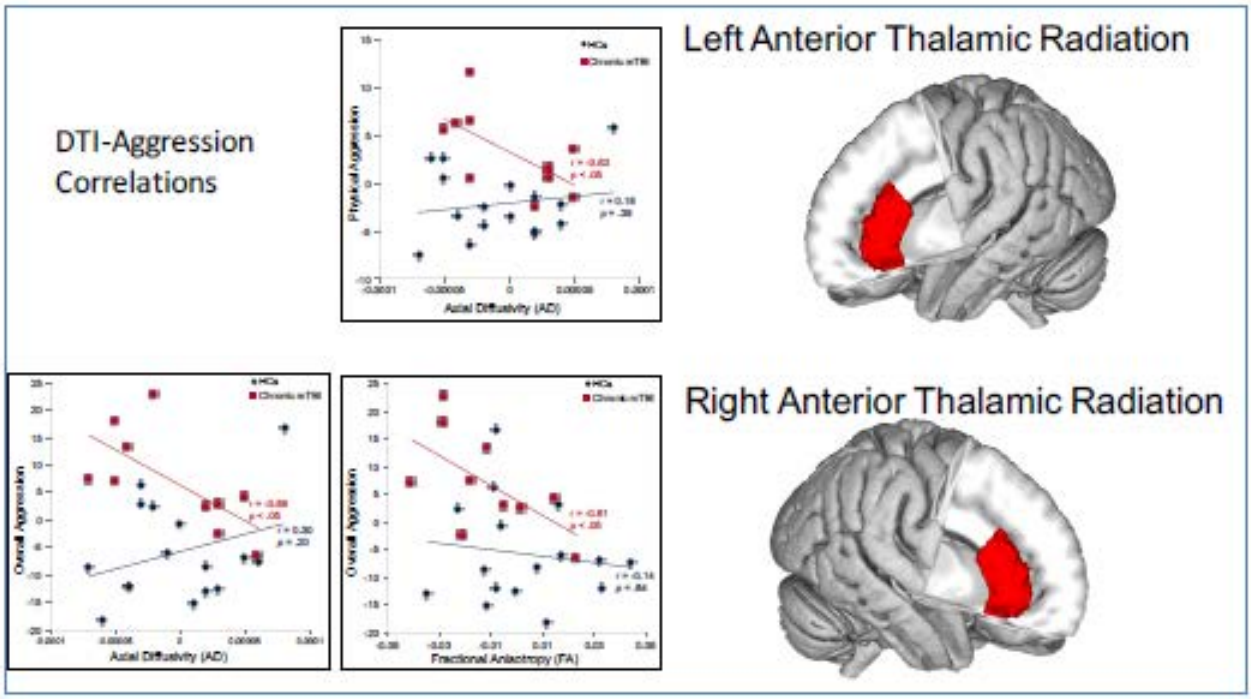
The chronic mTBI group reported significantly higher physical aggression, compared to HCs ($p < .01$).

Tract-Based Spatial Statistics (TBSS). TBSS was used for non-linear registration to standard space and projection to an alignment-invariant 4D mean skeleton (threshold .2) on an individual subject level. Mean DTI metrics were derived from the 4D skeleton for each participant, including Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AD). Anatomical masks were used to extract mean DTI metrics for all fiber pathways of interest, for each subject. MANCOVAs (controlling for age and gender)

were calculated for each pathway and DTI metric. No significant between-group effects were found for FA, MD, RD, or AD.

Neural Correlates of Aggression. Partial correlations, controlling for age and gender, were calculated between the BPAQ measures of aggression and white matter integrity of targeted pathways. Correlations were restricted to physical aggression and overall aggression, based on behavioral findings.

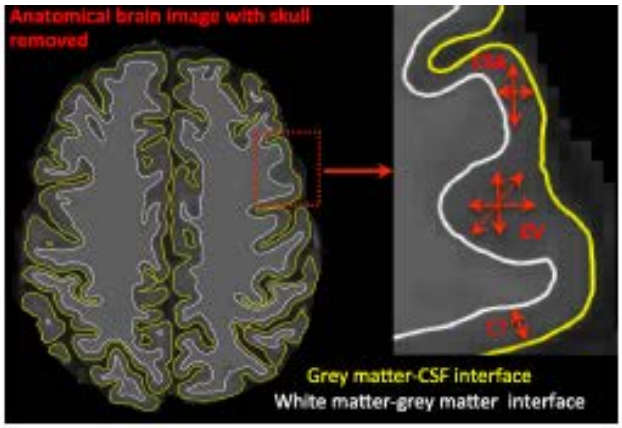
As shown below, in the chronic mTBI group, increased physical aggression was significantly correlated with lower AD in the left anterior thalamic radiation ($p < .05$). In the chronic mTBI group, increased overall aggression was significantly correlated with lower AD ($p < .05$) and FA ($p < .05$) in the right anterior thalamic radiation. Overall, of individuals with a mTBI, only those in the chronic stage of recovery reported elevated levels of aggression, which was associated with reduced white matter integrity in the anterior thalamic radiation. These findings suggest that the associations between tract myelination and emotion behaviors are complex and dynamic *across* the recovery process.



Gray Matter Morphology Differences Across Time Since Injury

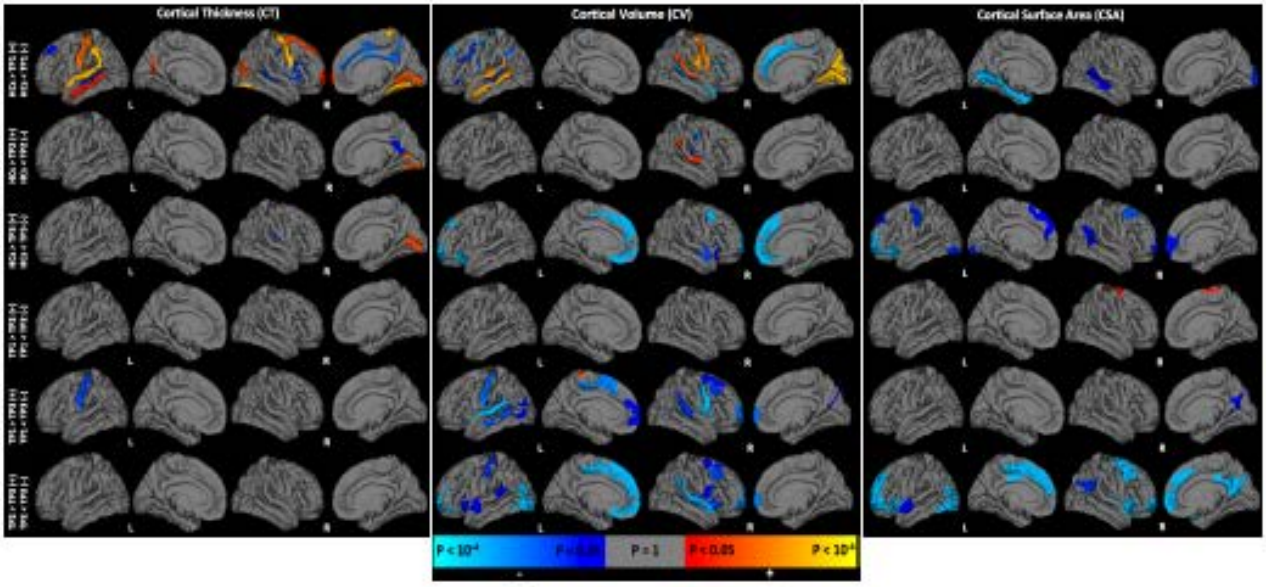
One goal of this project is to identify structural changes in the brain over time following an mTBI, including changes in both white matter axonal tracts, as well as changes on gray matter morphology. Therefore, we also conducted preliminary analyses examining changes in gray matter at different time points since injury, focusing on three inter-related but distinct metrics. We compared differences in brain structure, specifically cortical thickness (CT), cortical volume (CV) and cortical surface area (CSA) in 54 individuals (mean age = 22.40±4.60 years, 33 female) who sustained a recent mTBI and 33 healthy-controls (HCs) (mean age = 24.52±3.03

years, 19 female). The figure shows a representation of these three types of morphological data. Briefly, CT reflects the two-dimensional distance between the inner and outer edge of the cortex, CSA reflects the two-dimensional area reflected at the surface of the cortex, and CV reflects the three-dimensional volume of gray matter at a particular location within the brain.



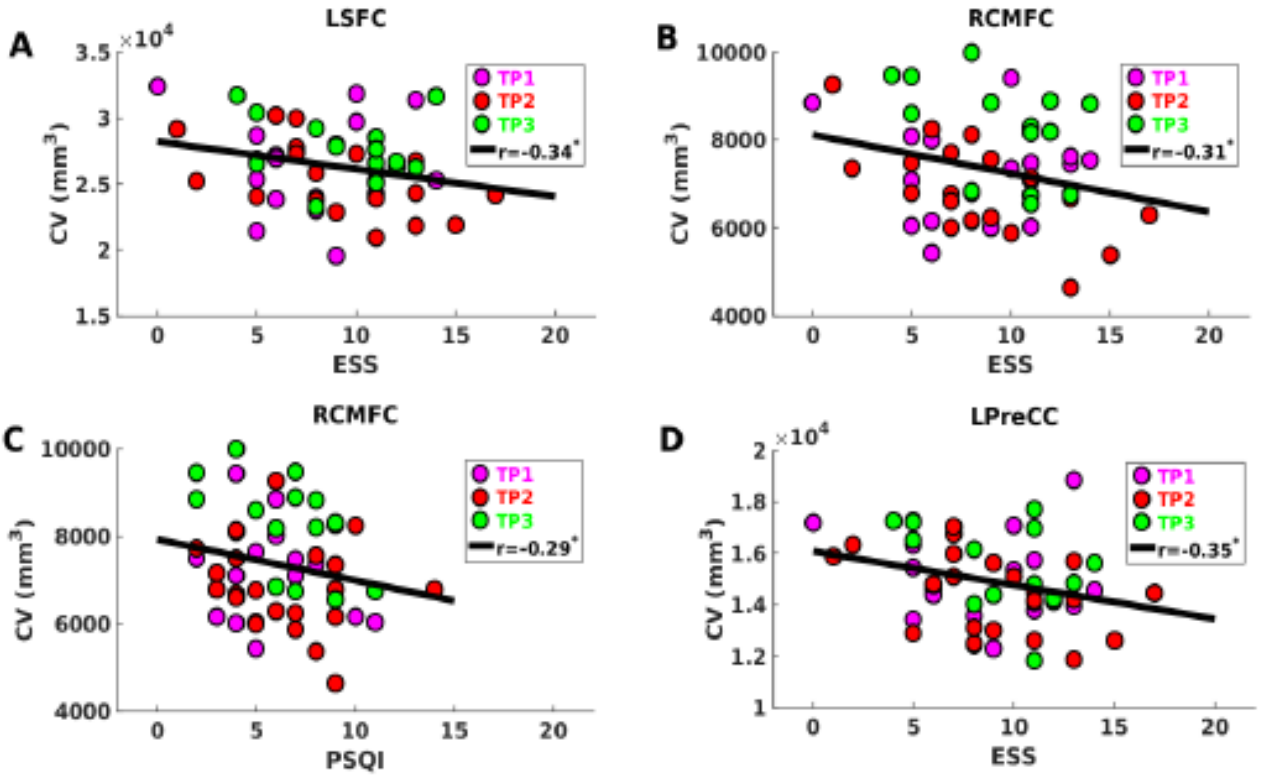
In this study, eligible individuals with mTBI were grouped into one of three sub-categories based on time-since injury - less than 3 months, between 3 to 6 months and between 6 to 18 months. Eighteen individuals experienced an mTBI (mean age = 24.56±6.09 years, 11 female) within the preceding 3 months (TP1), 22 experienced an mTBI (mean age = 21.77±3.53 years, 14 female) between 3 to 6 months prior to evaluation (TP2) and 14 experienced an mTBI (mean age = 20.61±2.56 years, 8 female) between 6 to18 months prior to the evaluation (TP3).

By comparing structural measures between individuals with mTBI and HCs, differences in (a) CT and CV reflected brain damage in more acute stages of mTBI, and (b) CV and CSA reflected possible partial recovery in the most chronic stage of mTBI. By comparing structural measures across three mTBI groups, we identified several brain areas showing significant differences in CV and CSA.



We also examined sleep complaints among patients in this sample and found negative correlations between (a) daytime sleepiness and CV as well as CSA for the left superior frontal cortex (LSFC), (b) daytime sleepiness and CV, sleep problems and CV, and daytime sleepiness and CSA for the right caudal middle frontal cortex (RCMFC), and (c) daytime sleepiness and CV for the left precentral cortex (LPreCC). However, after correction for multiple comparisons,

these correlations were either not significant or showed a trend towards significance ($p = 0.07$). These associations are displayed in the scatterplots below:



Our findings also demonstrate the role of each structural measure in identifying brain damage during the early post-acute period and compensatory recovery during the more chronic stages of mTBI.

Gray Matter Volume of the Cerebellum is Associated with Poor Sleep Quality in mTBI

While cortical insults are common in mTBI, few studies have actually examined the role of cerebellar damage from mTBI and its association with sleep problems. To follow up on the above-mentioned sleep issues, we conducted additional analyses on the cerebellum using voxel-based morphometry. In the present study, we correlated whole-brain grey matter with Pittsburgh Sleep Quality Index (PSQI) total scores in individuals within one year of an mTBI.
Here, 39 right-handed individuals with a self-reported history of mTBI (14 males; mean age: 24.17 ± 7.11y) were administered the PSQI as part of a larger on-going study. Additionally, we obtained T1 high-resolution structural scans, which were segmented and normalized (CAT12) and smoothed (SPM12) prior to voxel-based morphometric analysis. Whole-brain grey matter volume (GMV) was correlated with total PSQI scores, after controlling for age, sex, total intracranial volume, and time since most recent mTBI. GMV in significant clusters was exported for further analysis. We found that GMV in a cluster including portions of the left cerebellum's lobules 7 and 8 positively correlated with total PSQI score (FWE corrected, $p = 0.019$), indicating worse sleep. GM volume in this cluster was additionally significantly negatively correlated with faster psychomotor vigilance task mean reaction time ($R^2 = 0.099$) and positively with PVT reaction time coefficient of variation ($R^2 = 0.137$). PSQI total scores did not correlate with any PVT measures and prevented further mediation analysis. Thus, these preliminary

findings suggest that individuals with mTBI who reported lower sleep quality had greater GMV in the left cerebellum. The lack of correlation between total PSQI and PVT performance metrics suggests that increased GMV in the cerebellum may be a compensatory mechanism for maintaining task performance in spite of perceived sleep decrement following mTBI.

Gray Matter Volume Differences Associated with Greater Number of Concussions

While our aforementioned preliminary data, and that of others, suggests that mTBI may, in fact, be associated with changes in gray matter (GM) volume, the direction, timing, and extent of these changes remain unclear. One important factor that may play a role on military concussion outcome is the number of prior concussions. Few studies have investigated the relationship between the number of past mTBIs and GM volume changes. Therefore, we attempted to quantify differences in GM volume with respect to the number of prior head injuries. In this analysis, the T1 high-resolution structural scans of 39 right-handed individuals with a self-reported history of mTBI (14 males; mean age: 24.17 ± 7.11y) were used for volume-based morphometric analysis (CAT12). Images were segmented and normalized following an automated procedure in CAT12 and smoothed prior to analysis. GM volume was correlated with the total number of self-reported past mTBIs, after controlling for age, sex, total intracranial volume, and time since most recent mTBI. Volumetric data from the single surviving cluster were exported for additional analyses. We found that GM volume in a single cluster encompassing areas of the left superior temporal and supramarginal gyri (proximal to Wernicke's Area) positively correlated with total number of mTBIs (FWE corrected, $p = 0.035$). GM volume in this cluster was additionally significantly positively correlated with Delis-Kaplan executive function system (DKEFS) tasks, including letter fluency ($R^2 = 0.102$) and category switching ($R^2 = 0.106$). Thus, our preliminary findings suggest that in individuals with a history of mTBI, GM volume in the left superior temporal and supramarginal gyrus was greater with increasing numbers of mTBIs. This increase in volume may reflect an adaptive neuroplastic response to increasing numbers of mTBIs that preserves aspects of language-based executive function. Longitudinal studies are needed to identify a causal relationship between mTBI and adaptive neuroplastic processes in the gray matter.

Verbal Fluency Deficits in Post-Concussion Subjects with Associated Sleep Disturbance

Changes in neuropsychological status was evaluated in mTBI to investigate the relationship between post-concussive symptom severity, associated sleep problems, and executive function abilities in a semantic memory task. We conducted a preliminary analysis on 26 mTBI volunteers who underwent a battery of neuropsychological testing including the DKEFS verbal fluency task, a questionnaire about self-perceived sleep difficulties, and a questionnaire about post-concussive symptom severity (RPCSQ). The most prevalent sleep problems included *greater sleepiness during the day* and greater feelings of drowsiness when concentrating. Overall, we found a significant *negative* correlation between category fluency and symptom severity ($r = -.47$, $p < .01$) in patients with mTBI. However, the association only reached significance among those reporting sleep disturbances ($r = -.38$, $p = .03$), but not in those with no sleep disturbances ($r = -.26$, $p = .22$). While preliminary, these results raise the possibility that some executive function deficits following concussion may be secondary to sleep-related issues. Furthermore, the relationship between category fluency and symptom severity was only significant when individuals experienced sleep disturbance, providing additional support that

deficits in category fluency may relate more to sleep disturbance than post-concussive symptom severity. This will need to be explored further once the full sample has been collected.

Late Stage Preliminary Analyses (Years 7-9)

A primary aim of this study is to evaluate different diffusion tensor imaging (DTI) metrics across various stages of recovery following mild traumatic brain injury (mTBI). As the sample size increases, we are examining these associations in greater depth. Each DTI metric provides slightly different information about underlying changes to the microstructure of white matter pathways in the brain. Selected metrics include fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). While FA provides a measure of anisotropic diffusion of water molecules and MD provides a measure of overall water diffusion, RD and AD are predicted to be more sensitive measures of pathology related to demyelination and axonal injury, respectively. We conducted a preliminary analysis of data from **50 individuals**: 34 with mTBI and 16 with no history of mTBI (HC). 1) Beck Depression Inventory (BDI) scores were significantly higher for the mTBI group than the HC group; 2) After controlling for age, sex, and time since injury FA was negatively correlated with BDI scores in the mTBI group, and 3) MD and RD were positively correlated with BDI scores in the mTBI group. Correlations (see Fig. S65A-C) were primarily observed in the left and right anterior thalamic radiations. These findings suggest that higher levels of depressive symptoms may be associated with demyelination of these regions in individuals with mTBI. Another preliminary analysis of DTI data from 52 individuals (34 post-mTBI, 18 HC) yielded, for the mTBI group, 1) a negative correlation between FA and Pittsburgh Sleep Quality Index (PSQI) scores, and 2) a positive correlation between RD and PSQI scores (See Fig. S65D-E). Similarly to the results summarized above, these findings suggest that demyelination in white-matter tracts might contribute to the development of sleep disturbance post-mTBI.

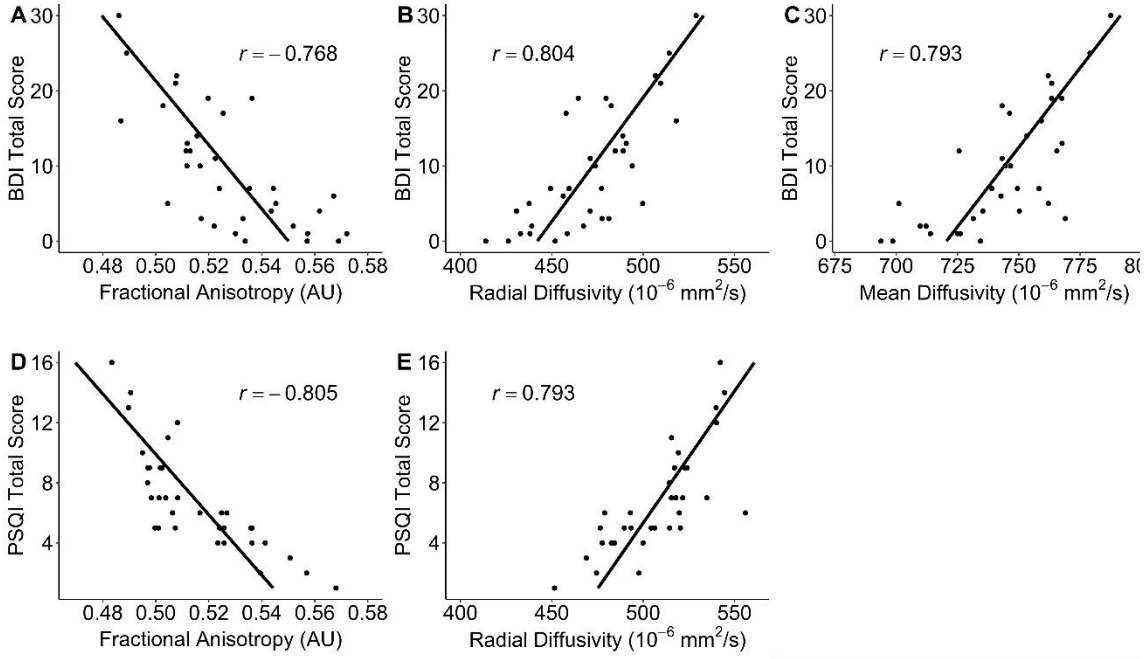


Figure S65. Relationship between white-matter integrity, sleep, and depression. In individuals

with a prior mTBI, white matter integrity exhibited a positive relationship with sleep quality and depression symptoms. Lower FA and higher RD, indices of myelin-related damage, were associated with worse depression symptoms and lower sleep quality.

Another aim of the study was to examine the relationship between functional connectivity and neuropsychological measures. To this end, we conducted a preliminary analysis including 34 participants (n = 17 mTBI, 10 females, mean age = 23.49 ± 3.36 years; n = 17 HC, 13 females, mean age = 22.88 ± 5.14 years). Participants in the mTBI group were in the chronic stage of recovery (at least 6-months post-mTBI). Our previous analyses revealed increased aggression in mTBI was associated with reduced *structural connectivity* in the anterior thalamic radiation.

Expanding upon these finding, we hypothesized *functional connectivity* would be lower in the executive control network (ECN), a large-scale network implicated in emotional regulation, in the mTBI group compared to healthy controls (HCs). Functional connectivity was calculated between six functionally defined regions of interest (ROIs) including the thalamus. We found lower functional connectivity between the thalamus and inferior/middle temporal gyrus (ITG/MTG) in those with a mTBI compared to HCs (see Figure S66). Furthermore, thalamic-ITG/MTG functional connectivity was inversely related to physical aggression. As these ECN regions are implicated in voluntary emotion regulation processes, our preliminary findings indicate mTBI may disrupt large-scale network connections important for regulating anger/aggression.

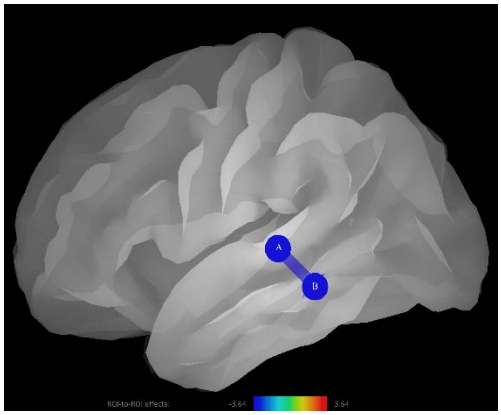


Figure S66. Strength of functional connectivity between regions of interest in the executive control network. Lower connectivity was found between the thalamus (A) and inferior/middle temporal gyrus (B) for individuals with mTBI.

Cortical Measures following MTBI

We continued to conduct preliminary analyses on the available data. Our preliminary findings were recently published in peer-reviewed journal *Human Brain Mapping*. Major findings from these analyses indicated an association between alterations in the cortical thickness and neuropsychological assessments during the early stages of mild traumatic brain injury (mTBI), whereas alterations in cortical surface area indicated compensatory physical recovery during the chronic stage of mTBI (see figure below).

The upper left figure above shows a representation of cortical thickness (CT), cortical volume (CV) and cortical surface area (CSA) within an original anatomical brain image. The upper right figure shows 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 post central gyrus (R. PostCG) ($r = -0.44$, $p = 0.03$) and (B) the left rostral middle frontal gyrus (R. RMFG) ($r = -0.41$, $p = 0.05$). The lower left figure shows 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 (0-3 months following injury) and 2 (3-6 months following injury). The lower right figure shows 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 (6-18 months following injury).

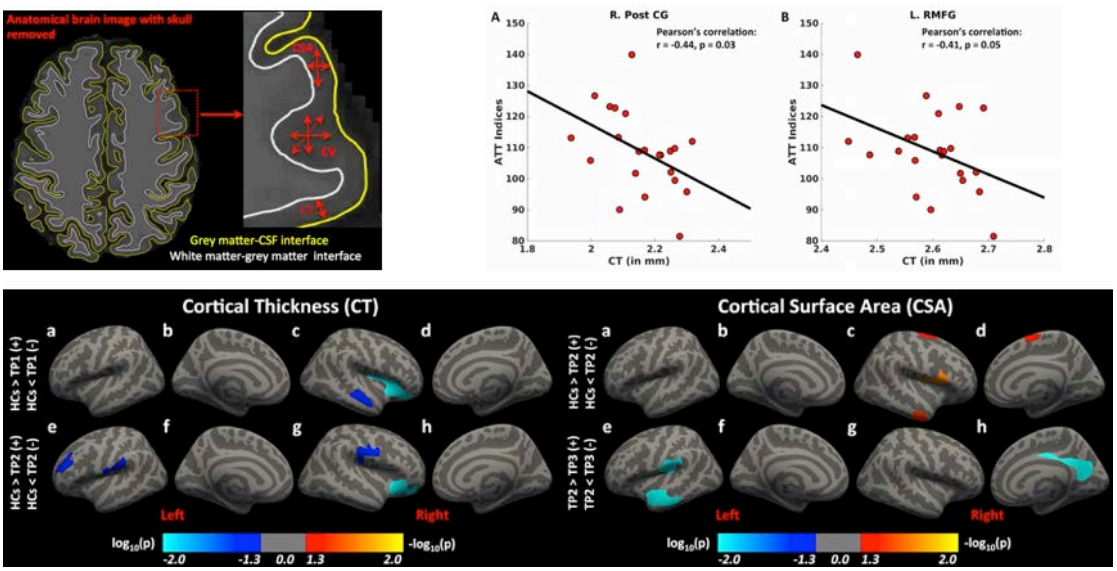


Figure S68. Cortical metrics.

Gray Matter Correlates of Insomnia following MTBI

Numerous studies have identified both self-reported and objective evidence of sleep disruption following mild traumatic brain injury (mTBI), with self-reported insomnia being the most common. To date, no structural brain correlates of post-mTBI self-reported insomnia have been identified. The purpose of this study was to identify gray matter volume (GMV) differences between healthy and post-mTBI individuals with and without self-reported insomnia.

We analyzed data from 40 mTBI patients and 18 healthy controls. Within the post-mTBI group, those with self-reported insomnia exhibited greater GMV in the cerebellum than those without insomnia. Those with insomnia also showed greater GMV than healthy controls in the superior temporal gyrus (STG). GMV in these clusters was positively associated with psychomotor vigilance stimulus-to-stimulus response time variability (cerebellum, STG) and chronic mTBI symptom endorsement (cerebellum)(Figure S68).

As previous work on post-injury brain structure has tended to report GMV reductions, the present findings highlight the potential importance of examining within-group symptom differences (such as insomnia) in these clinical groups. We suggest that greater GMV in post-mTBI with insomnia may reflect compensatory mechanisms for maintaining overall sustained and vigilant attention, at the expense of stable performance, in the presence of perceived sleep disruption (Figure S69).

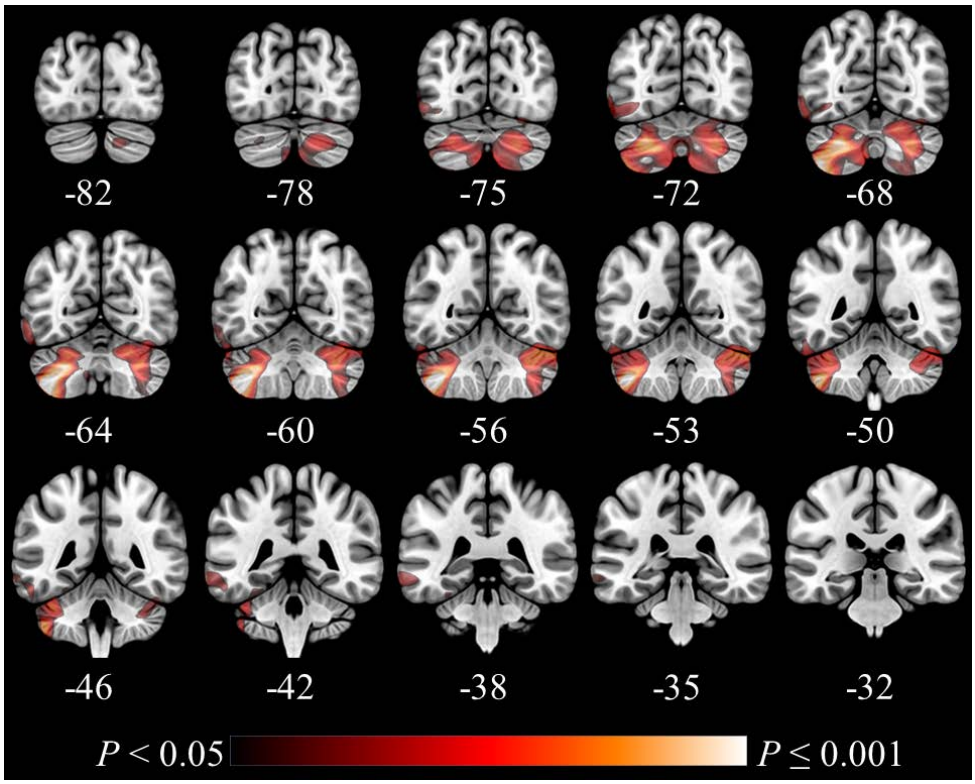


Figure S68. Gray Matter Volume Clusters correlated with insomnia.

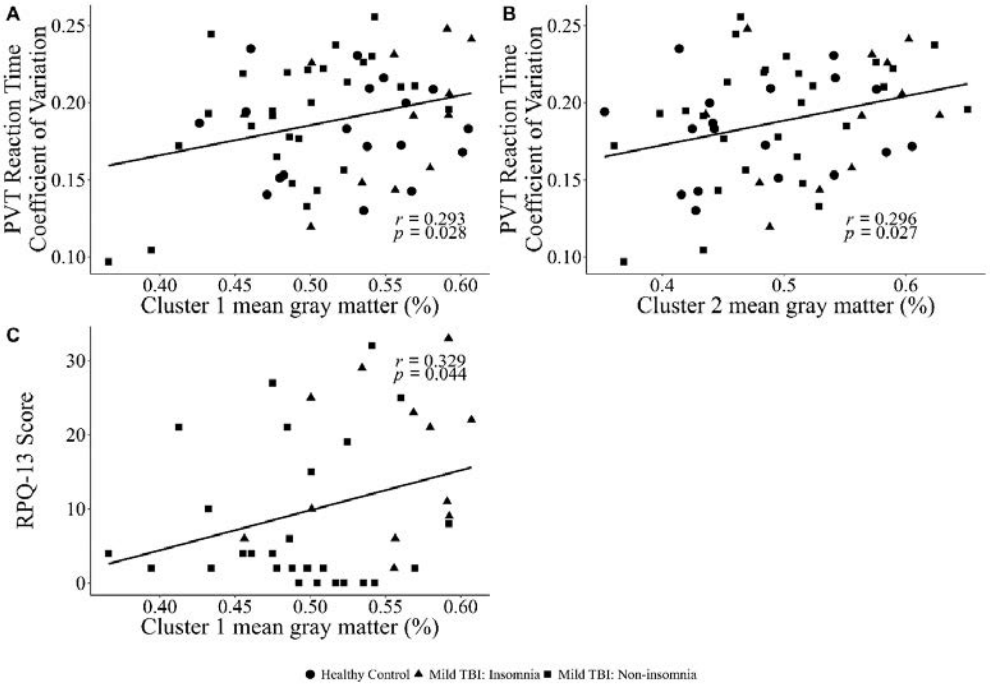


Figure S69. Gray Matter Volume correlates with psychomotor vigilance and concussion Scores on the RPQ-13

Aggression and White Matter Tracts following MTBI

We examined the association between DTI disruption and aggression in the preliminary sample of mTBI patients. The findings are briefly summarized below:

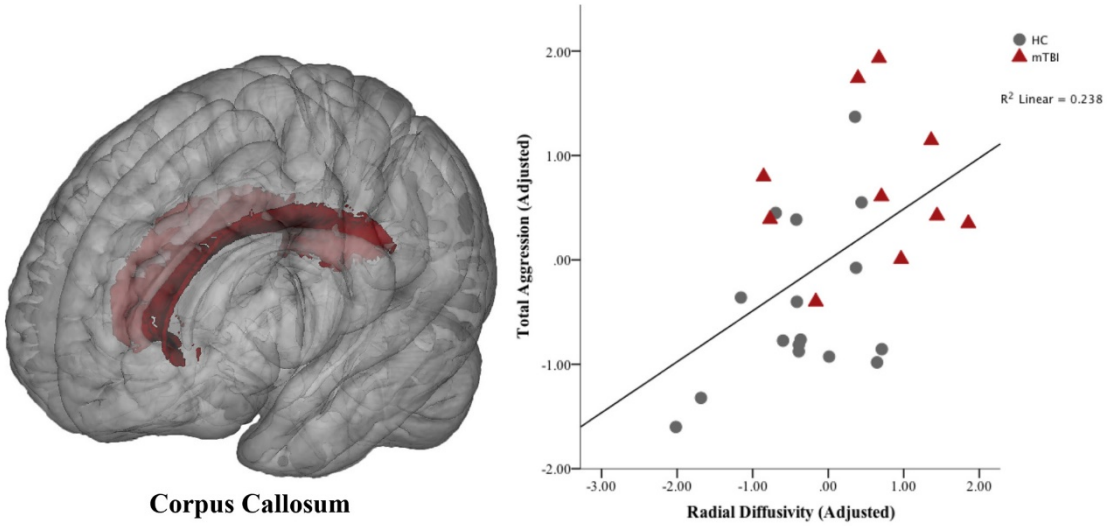


Figure S70. Gray Matter Volume correlates with aggression

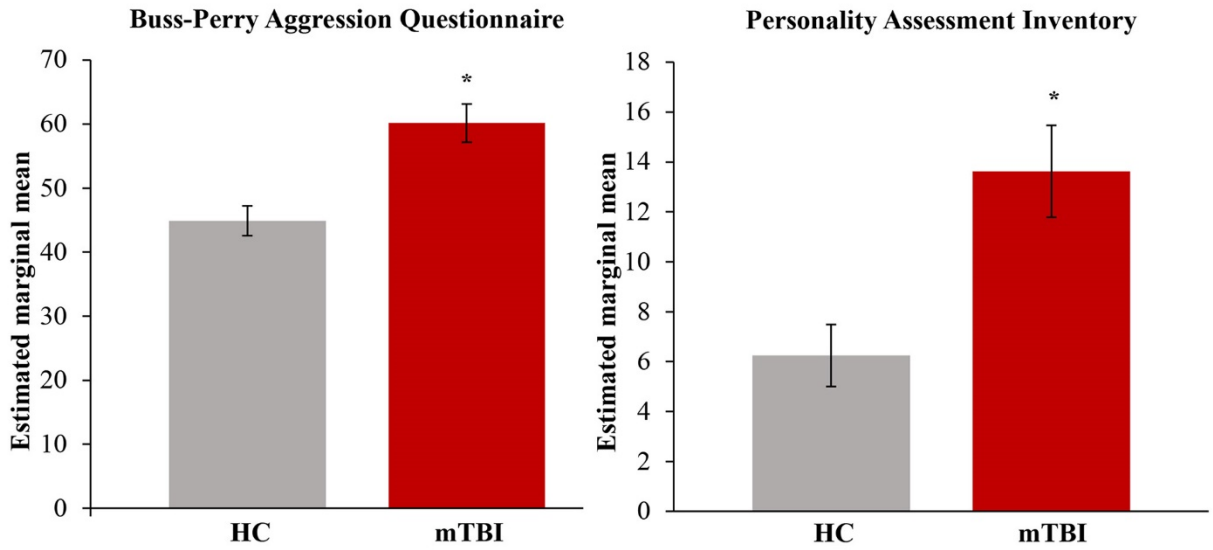


Figure S71. Aggression scores by group

We investigated the association between white matter integrity and aggression in mTBI using diffusion tensor imaging (DTI). Twenty-six age-matched adults participated in the study, including 16 healthy controls and 10 individuals in the chronic stage of recovery (either 6-months or 12 months post-mTBI). Psychological measures of aggression included the Buss-Perry Aggression Questionnaire and the Personality Assessment Inventory. Axonal pathways

implicated in affective processing were studied, including the corpus callosum, anterior thalamic radiation, cingulum, and uncinate fasciculus, and measures of white matter integrity included fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. We found that adults with mTBI in the chronic stage of recovery had higher levels aggression.

Individuals with mTBI also had greater radial diffusivity in the corpus callosum compared to healthy controls, indicating reduced fiber integrity. Furthermore, we observed a significant association between reduced white matter integrity in the corpus callosum and greater aggression. Our findings provide additional evidence for underlying neuroanatomical mechanisms of aggression, although future research will be necessary to characterize the specific relationship between aggression and the white matter pathways we identified.

Functional Connectivity following MTBI

We have extended our previous work on the association between connectivity and aggression in individuals with mTBI. Our initial work explored structural connectivity and aggression, identifying reduced structural integrity in the corpus callosum and increased aggression in adults with mTBI. Our most current research expands upon previous findings, exploring the relationship between functional connectivity and aggression. Preliminary findings are briefly summarized below:

We investigated the association between functional connectivity within the default mode network and aggression using resting-state functional magnetic resonance imaging (rs-fMRI). Thirty-four adults participated in the study, including 17 healthy controls and 17 individuals in the chronic stage of recovery (i.e. at least 6-months post-mTBI). Aggression was measured using the Buss-Perry Aggression Questionnaire and depression, a common co-morbid disorder, was measured using the Beck Depression Inventory. The default mode network (DMN) is an intrinsic brain network that has been shown to be disrupted following mTBI. Furthermore, the DMN is has been implicated in emotion regulation. Therefore, we hypothesized that functional connectivity within the DMN would be disrupted in those with mTBI, compared to healthy controls, and that within-network connectivity would be associated with previously reported increased aggression in mTBI. Overall, within the DMN, functional connectivity was similar between healthy controls and adults with mTBI (see Figure S72 below).

We found significant differences between healthy controls and those with mTBI when we explored the relationship between aggression and DMN connectivity. In the mTBI group, increased connectivity between the hippocampus and midcingulate cortex was significantly associated with increased levels of aggression.

Consistent with previous reports of disrupted DMN connectivity following mTBI, the present findings highlight the potential importance of the DMN in emotional regulation. We suggest that elevated aggression in those with mTBI may reflect impaired emotion regulation due to disrupted large-scale intrinsic neural networks.

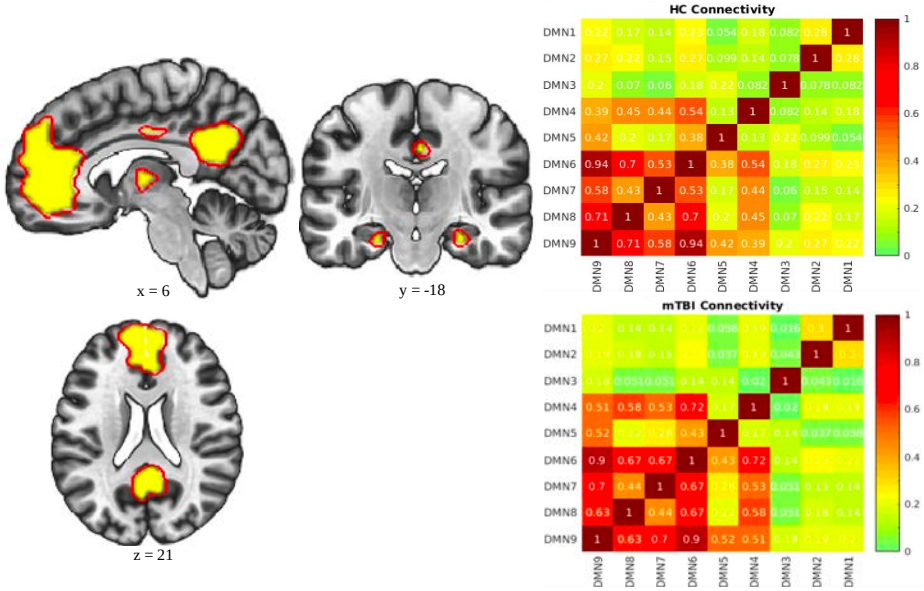


Figure S72. Left: Functionally defined regions of interest masks are depicted in yellow for the default mode network. Within-network connectivity was calculated between each region of the default mode network. Right: Matrices show within-network functional connectivity between each seed and target region of the default mode network for healthy controls (top) and individuals with mild traumatic brain injury (bottom).

Predictors of Verbal Fluency following MTBI

We continued to explore cognitive abilities at different stages post-mTBI, to better understand the dynamic recovery process of mTBI. We conducted preliminary analyses to investigate verbal fluency following mTBI, a language-based skill that could be impacted by executive function deficits often reported in mTBI. Therefore, we aimed to identify lexical-semantic and/or executive function factors that best predict verbal fluency following mTBI.

Fifty-three participants were included in the preliminary analyses, including 20 healthy controls and 33 individuals with mTBI. Of those with mTBI, 16 individuals were in the acute phase and 17 individuals were in the chronic phase of recovery. Verbal fluency was measured using the Delis-Kaplan Executive Functions System (D-KEFS). In our preliminary analyses, we found that individuals in the chronic stage of recovery constructed significantly fewer unique clusters on the verbal fluency task, as compared to healthy controls. Furthermore, we found that digit span significantly predicted verbal fluency switching, while the number of reported mTBIs significantly predicted verbal fluency clustering, following mTBI.

Findings from preliminary analyses suggest individuals with mTBI exhibit an overreliance on a single clustering strategy to maintain sufficient verbal fluency performance. Following mTBI, predictors of verbal fluency include executive function and number of injuries, as opposed to lexical-semantic factors. These findings indicate that observed language-based deficits following mTBI may result from underlying damage to executive functions.

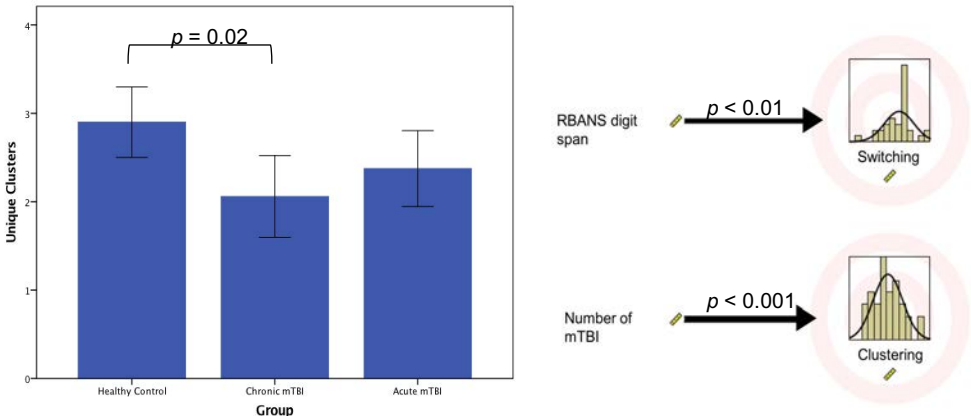


Figure S73. Unique clustering by group.

Cortical Measures Across Time Since Injury

Previous investigations have extensively studied the functional and structural recovery of the brain following mild traumatic brain injury (mTBI). Despite prior work, the field still lacks a consistent larger picture of brain recovery over a longer time-period. The primary goal of this study was to better understand the complex brain mechanisms that unfold over a time-period of 18 months following mTBI. Therefore, we sub-categorized mTBI participants from the present study, as well as another sample of mTBI patients with injuries extending out to 18 months into three groups depending on their time since injury (i.e., at time-point (TP) 1: 0-3 months, TP2: 3-6 months and TP3: 6-18 months) followed by an estimation and comparison of cortical measures within the three groups as well as compared to healthy controls (HCs).

Cortical thickness (CT): We identified several brain areas, which showed significantly thicker cortex in mTBI individuals (at TP 1 and 2) compared to HCs. We also found that the CT within two areas – the right post central gyrus (R.PostCG) and the left rostral middle frontal gyrus (L.RMFG) – showed significant differences in CT between HCs and mTBI individuals at TP2, and was negatively associated with attention abilities (R.PostCG: r = -0.44, p = 0.03 and L.RMFG: r = -0.41, p = 0.05). These findings are summarized in **Figure S74A**.

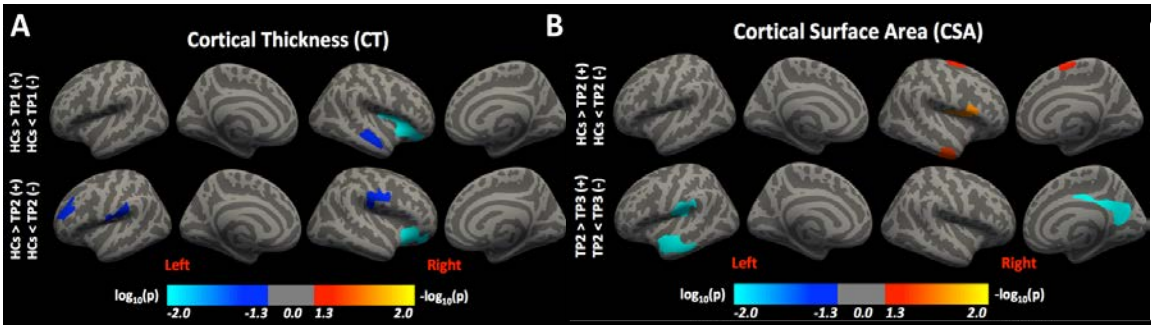


Figure S74. Comparison of cortical thickness (A) and cortical surface area (B) between HCs and individuals with mTBI at different time-points post-injury.

Cortical surface area (CSA): We found that at TP2, individuals with mTBI had significantly lower CSA within several areas as compared to HCs. However, at TP3, mTBI individuals showed greater surface area within several regions as compared to mTBI individuals at TP2. These findings are summarized in **Figure S74B.**

Summary: Overall, our findings suggest that the differences in CT and associated attention abilities may be prominent during the acute stage of mTBI, however, differences in CSA may indicate compensatory structural recovery during the later stages of mTBI. These findings were recently published in the peer-reviewed journal, *Human Brain Mapping (2018).*

Functional Connectivity as a Biomarker of Aggression in mTBI

In addition to disrupted structural connectivity, previous research has reported disrupted functional connectivity within the default mode network (DMN). However, the majority of research focuses on the acute and subacute recovery stages (i.e. less than 3-months post-injury). The goal of this preliminary study was to explore the association between DMN function and aggression in individuals in the chronic stage of recovery (i.e. at least 6-months post-injury). For this preliminary analysis, we analyzed a subset of the data, including 17 individuals with mTBI and 17 healthy controls completed the Buss-Perry Aggression Questionnaire and a resting-state functional magnetic resonance imaging scan.

Network Connectivity: Functional connectivity strength between each of the nine regions of the DMN was measured. We found similar DMN connectivity strength in those with mTBI compared to healthy controls. The metrices in **Figure S75** show within-network DMN connectivity between seed and target regions in healthy controls and individuals with mTBI, separately.

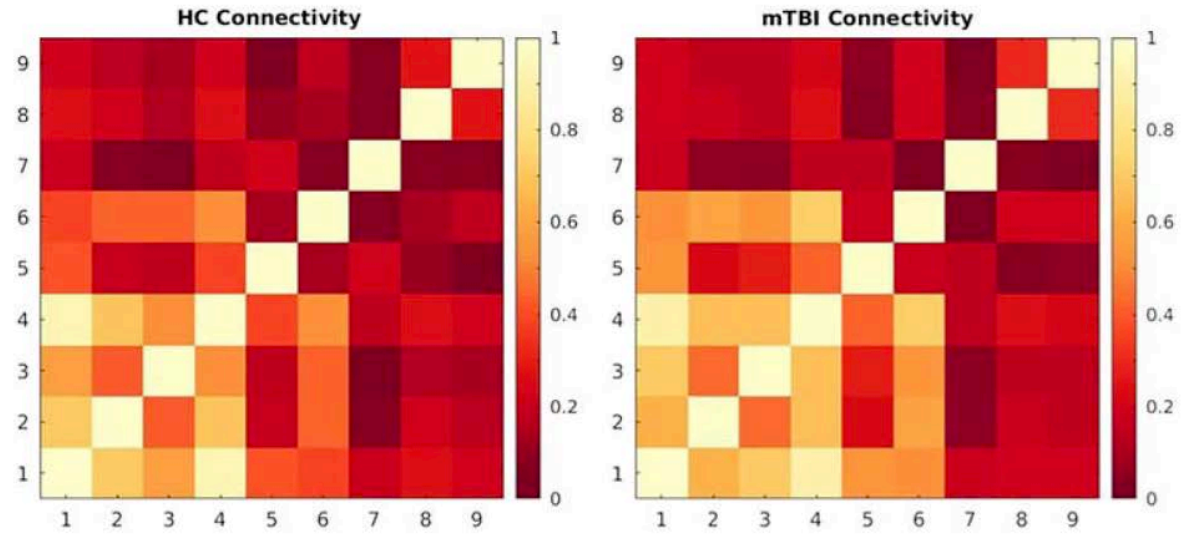


Figure S75. Functional connectivity within regions of the default mode network for healthy controls and individuals with mild traumatic brain injury.

Aggression: We found significant group differences in the association between DMN connectivity and aggression. Connectivity between aggression and the right hippocampus (rHPC) to midcingulate cortex (MCC), as well as the rHPC to medial prefontal cortex (mPFC)was significantly greater in those with mTBI relative to healthy controls (see **Figure S76**).

Summary: Our preliminary findings suggest that mTBI-related aggression may be associated with altered DMN connectivity, a large-scale intrinsic neural network. These findings were recently published in the peer-reviewed journal, *NeuroReport (2018).*

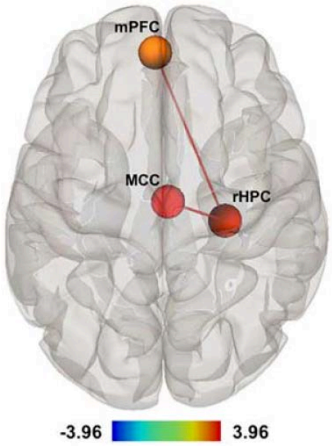


Figure S76. Significant between-group differences in DMN connectivity associated with aggression. Contrast mTBI>HC.

Learning and Memory Abilities in Acute and Chronic Recovery Stages

Impaired cognitive functioning is frequently reported after mTBI. However, little is known about neurocognitive performance throughout various stages of the recovery processes. The cross-sectional design of the study enables us to compare performance in initial and later stages of recovery following mTBI. These preliminary analyses were conducted to assess verbal recall in acute and chronic stages of mTBI recovery, relative to healthy controls. Serial and semantic clustering are two types of self-initiated recall strategies that can improve performance on verbal recall tasks. The California Verbal Learning Test (CVLT) were used to assess verbal recall strategies in those with mTBI. Serial clustering refers to the tendency to recall items that were located together in the same order they were learned from a list, while semantic clustering refers to the tendency to recall items together based on their conceptual associations (e.g., fruits, furniture, etc.), regardless of serial position in the list.

Serial Clustering: We found significantly lower scores on serial clustering in the acute mTBI group, compared to the healthy control and the chronic mTBI groups. This finding suggests the acute mTBI group was unable to recall words in the order in which the words were presented. These findings are summarized in **Figure S77A**. Furthermore, we calculated the percentage of correct words recalled from the beginning, middle, and end of the list. In our preliminary analyses, we found that the acute mTBI group recalled significantly more words from the middle of the list compared to the chronic mTBI group.

Semantic Clustering: Through these preliminary analyses, we observed a tendency for those in the acute mTBI group to rely more heavily on semantic clustering (see **Figure S77B**). These preliminary findings suggest that individuals in the acute recovery stage employ a different self-initiated recall strategy compared to healthy controls and individuals in the chronic recovery stage.

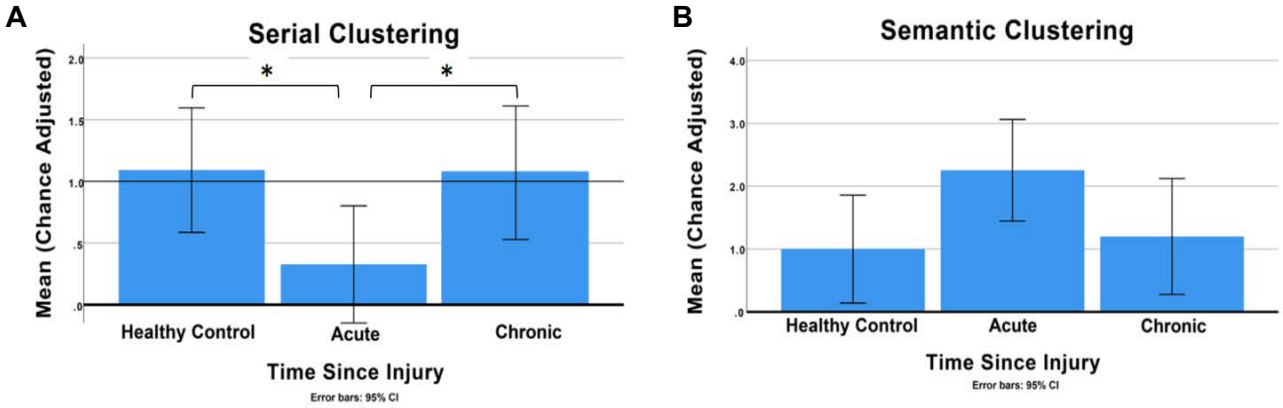


Figure S77. Raw scores on serial (A) and semantic (B) clustering for healthy control, acute mTBI, and chronic mTBI groups.

Neural Correlates: The neural mechanisms of serial and semantic clustering were investigated in a subset of the participants included in the aforementioned analyses. The superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF) were targeted and separate stepwise linear regressions were calculated to determine the relationship between white matter integrity and time since injury on the use of serial and semantic clustering. Serial clustering was associated with reduced white matter integrity in the left SLF, and increased integrity in the right UF, whereas semantic clustering was associated with increased integrity in the left UF.

Summary: Overall, these preliminary findings suggest individuals in the acute and chronic recovery stages employ different verbal recall strategies. Furthermore, these strategies appear to rely on different pathways in the brain, suggesting the potential use of compensatory mechanisms during learning and memory.

Information Processing and Attention in mTBI

A primary aim of the ongoing study is to determine whether cognitive deficits are present throughout various stages of recovery. We used the Psychomotor Vigilance Test (PVT) to measure information processing speed and sustained attention of individuals with mTBI in the acute and chronic stages of recovery. We predicted reduced processing speed and attention in adults with mTBI compared to healthy controls. For those with mTBI, we hypothesized that adults in the acute stage of recovery (i.e. 3-months or less post-injury) would exhibit greater deficits in processing speed and sustained attention, compared to adults in the chronic stage of recovery (i.e., 6-months or more post-injury).

Results: In our preliminary analyses, there were a significant effect of group on reaction time ($F(2,27) = 4.99$, $p = .01$, $\eta^2 = .27$). Post hoc analyses revealed significantly longer reaction times in the chronic mTBI group (M = 323.91; SD = 63.02) compared to healthy controls (M = 280.20;

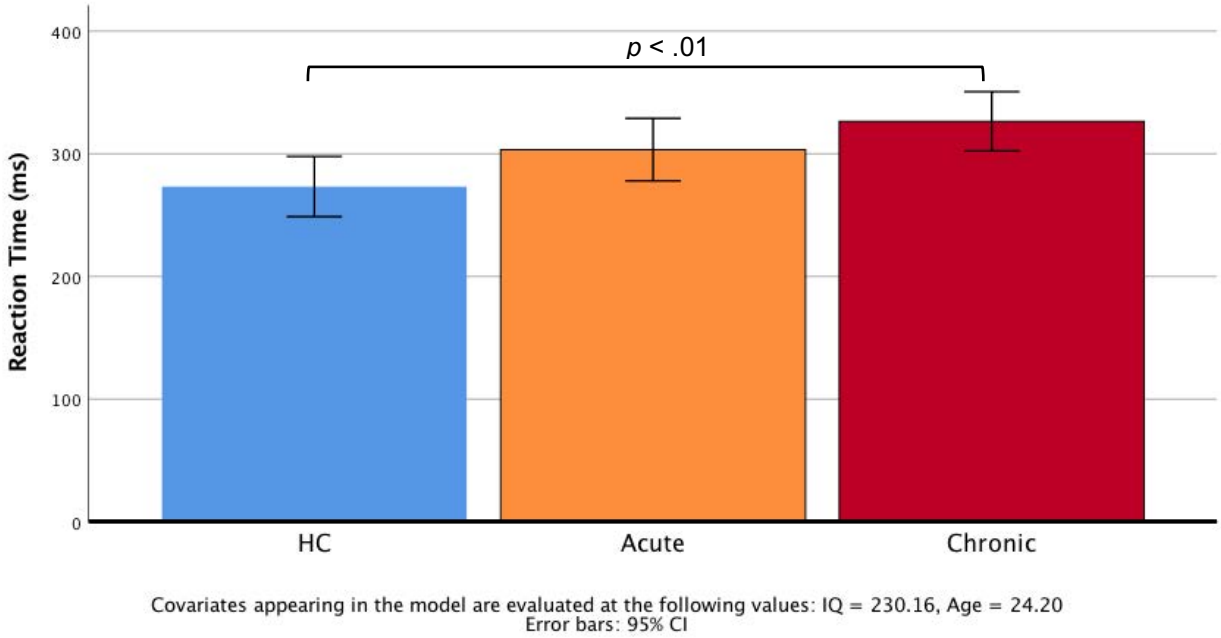


Figure S78. Reaction time on the Psychomotor Vigilance Test (PVT) for healthy control (HC), acute mTBI, and chronic mTBI groups. Significantly longer reaction times were observed in the chronic mTBI group compared to healthy controls (*$p < .01$).

SD = 43.54) (see **Figure S78**). All groups performed similarly on the measure of attention.

Summary: Overall, we found that adults with mTBI, who are in the chronic stage of recovery, displayed reduced processing speed, but intact sustained attention. Contrary to our hypotheses, individuals with mTBI who are in the acute stage of recovery did not exhibit deficits in processing speed or sustained attention, responding similar to healthy controls. One possible explanation for the observed discrepancy between acute and chronic mTBI groups is that adults who are in the chronic phase of recovery may be more likely to participate in research studies if they continue to experience mTBI-related symptoms, while those in the acute mTBI group may be more likely to participate regardless of symptomology. Another interpretation of the current findings is that recovery from mTBI may represent a dynamic process in which symptoms present during the acute phase may not be present in the chronic phase and vice versa. Ongoing research is necessary to identify potential underlying neural mechanisms associated with the onset and duration of injury-related deficits. Furthermore, the manifestation of cognitive deficits at different times post-injury suggests that individuals may benefit from clinical support and/or intervention at different times following an mTBI.

Impact of mTBI on Lexical-Semantic Retrieval

The aforementioned preliminary findings, in conjunction with previous studies, provide convergent evidence that individuals with mTBI suffer a range of cognitive deficits. However,

the extent to which mTBI-related deficits impact lexical-semantic retrieval has yet to be fully explored. Therefore, we aimed to (1) identify verbal fluency skills in mTBI compared to healthy controls and (2) determine lexical-semantic and/or executive function factors that best predict verbal fluency in those with mTBI.

Verbal Fluency: The Delis-Kaplan Executive Functions System (D-KEFS) was used to measure verbal fluency in a subset of the current data, including 20 healthy controls and 33 individuals with mTBI (16 in the acute phase and 17 in the chronic phase). Participants were required to provide as many words as possible in 60 seconds, when given a letter (e.g. F, A, and S). Primary measures included clustering (the use of semantic categories to generate words) and switching (changing from one semantic category to another). In our preliminary results, we found a significantly reduced number of unique clusters in the chronic mTBI group compared to healthy controls.

Learning and Memory following mTBI

Cognitive function is frequently impaired after a mTBI. However, little is known about neurocognitive performance throughout various stages of the recovery process. The cross-sectional design of the study enables us to compare performance in initial and later stages of recovery from mTBI. Our current preliminary analyses focused on structural integrity of lexico-semantic pathways associated with self-initiated recall strategies during verbal learning.

This analysis involved a subsample of 57 participants, including 20 healthy controls. We collapsed across initial and later stages of time since injury. Therefore, the acute mTBI group included individuals with documented injuries between 2 and 12 weeks (n= 22) and the chronic mTBI group included individuals with documented injuries between 6 and 12 months (n=15). The California Verbal Learning Test was used to measure two different self-initiated recall strategies. Serial clustering results when words are recalled based on presentation order. Whereas, semantic clustering results when words are recalled based on semantic grouping (i.e. furniture, animals, modes of transportation, and vegetables).

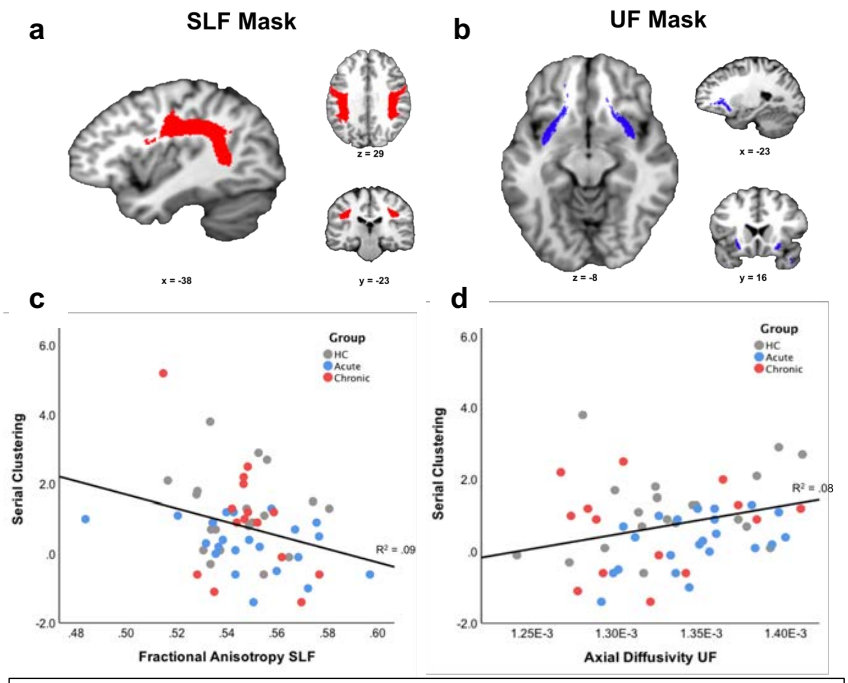


Figure S79. White matter integrity was assessed in the superior longitudinal fasciculus (SLF) and the uncinate fasciculus (UF) for the entire sample. White matter integrity predicted serial clustering scores.

Serial clustering differed significantly between the groups ($F = 3.28$, $p < .05$). Post-hoc analysis revealed significantly greater serial clustering in the HC, compared to the acute mTBI group.

We examined white matter integrity of the superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF) by creating masks of the targeted pathways (see **Figure S79a, b**). Diffusion tensor imaging data were analyzed using Tract Based Spatial Statistics in FSL. Output measures included fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity.

Serial clustering was predicted by fractional anisotropy in the left SLF ($\beta = -.28$, $p < .05$) and axial diffusivity in the right UF ($\beta = .25$, $p < .05$), accounting for 16% of the total variance (see **Figure S79c, d**).

Our preliminary findings suggest that the utilization of self-initiated strategies differ between healthy controls and those who have recently suffered a mTBI. Furthermore, we have provided preliminary support for the association between lexico-semantic pathways and serial clustering, although these did not appear to differ between groups.

Semantic, but not Serial Clustering Aids Verbal Recall in Sub-Acute mTBI

Injury to the brain can impede learning and memory due to impairments in attention and memory. Although neuropsychological impairments are common in mTBI, few studies have examined learning and memory performance at various stages in the recovery process. Semantic and serial clustering, two different self-initiated recall strategies that can improve verbal recall on the California Verbal Learning Test (CVLT), were assessed in sub-acute and chronic stages of mTBI-recovery, relative to healthy controls. We expanded upon our previous analyses with roughly ***double the sample size***, as more data were acquired over this past year. These preliminary findings are based on 108 participants (29 HCs, 40 sub-acute mTBI, and 39 chronic mTBI).

Recall Strategy: Consistent with our prior analyses on the smaller sample, we found that the groups differed significantly in the use of semantic (χ^2 (2) = 8.54, $p = .01$) and serial ($\chi^2(2) = 9.07$, $p = .01$) clusters. The sub-acute mTBI group produced significantly more semantic clusters and significantly fewer serial cluster compared to the HC and chronic mTBI groups ($p < 0.05$; corrected for multiple comparisons). These findings are summarized in **Figure S80.**

Total Verbal Recall: Verbal recall, as measured by total words recalled on the CVLT did not differ significantly between the three groups (F (2, 105) = 1.55, $p = .22$, $\eta^2 = .03$). However, the groups differed on the association between the recall strategy used and total words recalled. While all groups showed significant positive correlations between semantic clustering and total words (HC, $r = 0.56$, $p < 0.01$; sub-acute, $r = 0.56$, $p < 0.01$; chronic, $r = 0.74$, $p < 0.001$), the sub-acute mTBI group was the only group to exhibit a significant negative correlation between serial clustering and total words ($r = -0.35$, $p = 0.02$).

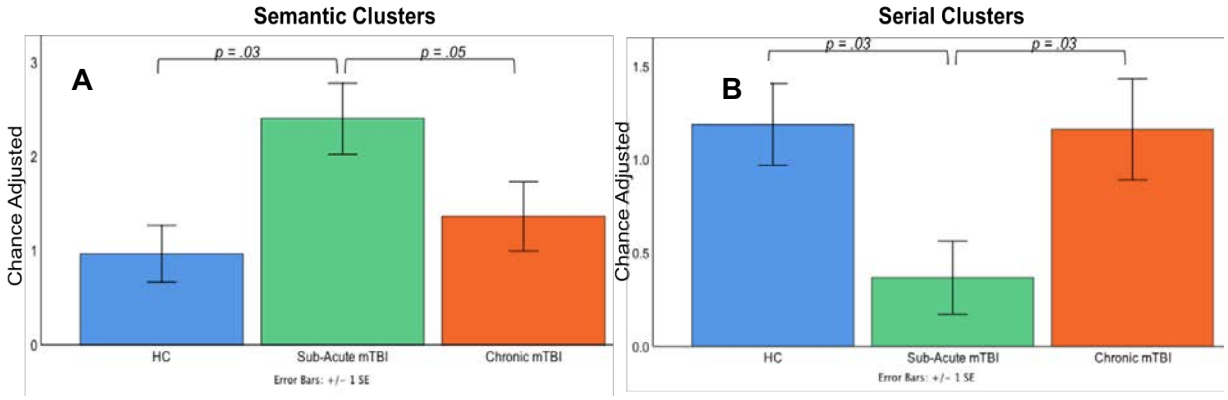


Figure S80. Comparison of semantic (A) and serial (B) cluster production between healthy controls (HCs), participants 2-12 weeks post-injury (Sub-Acute mTBI), and participants 6-12 months post-injury (Chronic mTBI).

Summary: Overall, our findings identify the differential use of recall strategies at various stages of mTBI recovery. Adults in the sub-acute stage (2 to 12 weeks post-injury) relied more heavily on semantic clustering, a beneficial strategy for verbal learning, whereas serial clustering was found to be a detrimental strategy – possibly due to high working memory demands. These findings were presented at the 47th annual meeting of the International Neuropsychological Society, in New York, NY.

Lexical-Semantic Retrieval Across Time Since Injury

Although our aforementioned preliminary data, as well as others', suggest differences in the cognitive processes used during lexical retrieval, there remains considerable disagreement regarding the extent to which such functions are impacted following mTBI. Few studies have directly linked brain structure to language performance at different time-points post injury. The goal of this preliminary analysis was to compare verbal fluency at sub-acute and chronic stages of injury, to healthy controls (HCs), and identify the underling brain mechanisms.

A subset of the completed sample was included in the analysis. Groups consisted of 19 HCs, 22 adults in the sub-acute recovery phase, and 17 adults in the chronic recovery phase. Responses on the Delis-Kaplan Executive Functions System (D-KEFS) semantic verbal fluency task were coded for (a) clusters, the production of words belonging to the same semantic subcategory, and (b) switches, shifts between subcategories.

Verbal Fluency: The groups differed significantly in the number of clusters *(F* (2, 54) = 3.42, p = .04, η^2 = .11), but not switches (*F* (2, 54) = 2.32, p = .12, η^2 = .08) produced. The sub-acute mTBI group produced significantly more clusters when compared to the chronic mTBI group. These findings are summarized in **Figure S81.**

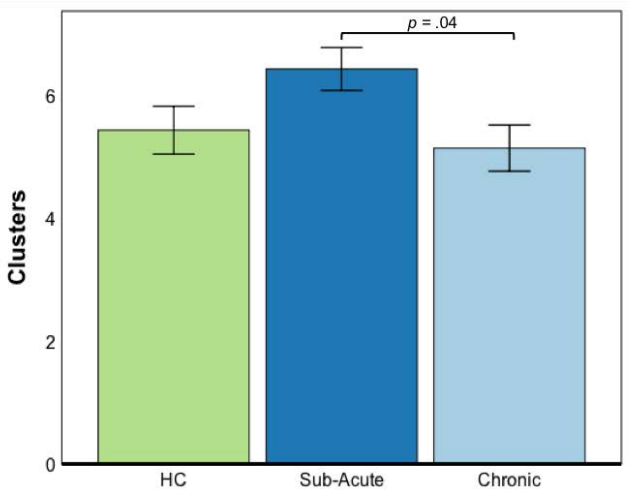


Figure S81. Comparison of semantic clusters produced by healthy controls, sub-acute mTBI, and chronic mTBI groups.

Cortical Surface Area (CSA): The production of clusters was associated with CSA of the parahippocampus (r = -0.52, p = 0.03) in HCs, and CSA of the medial orbitofrontal gyrus (r = 0.53; p = 0.03) in the chronic mTBI group (see **Figure S82A, B**). In contrast, switches were significantly associated with CSA of the caudal middle

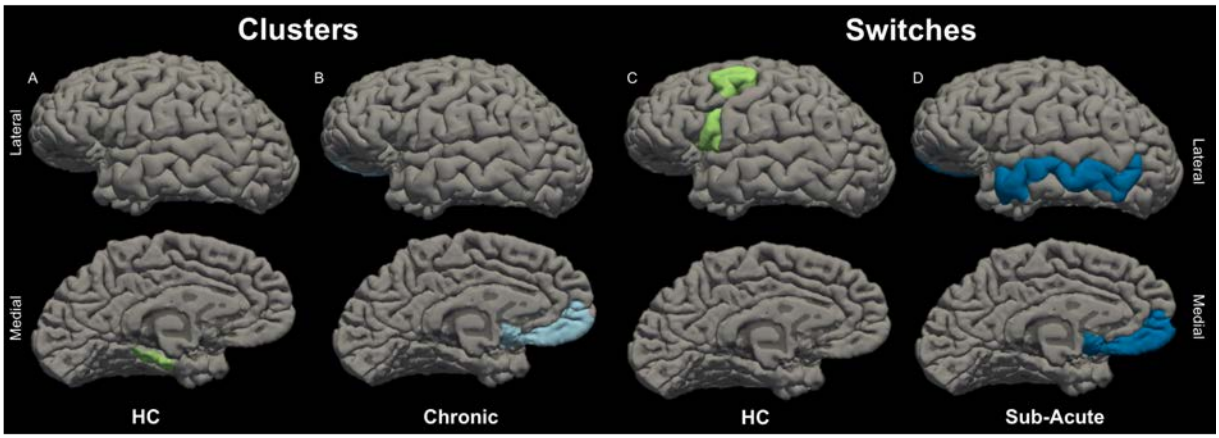


Figure S82. Left hemisphere regions where cortical surface area (CSA) is significantly associated with cluster production in healthy control (A) and chronic mTBI (B) groups and regions where CAS is significantly associated with switches in healthy control (C) and sub-acute mTBI (D) groups.

frontal region (r = 0.60; p < 0.01) and the pars opercularis (r = -0.60; p < 0.01) in HCs (see **Figure S82C**). In the sub-acute mTBI group, switches were associated with CSA of the medial orbitofrontal gyrus (r = -0.44; p < 0.05) and the middle temporal gyrus (r = -0.49; p < 0.02) (see **Figure S82D**).

<u>Daytime Sleepiness and Functional Connectivity following mTBI</u>

Changes in sleep are commonly reported by upwards of 70% of individuals who have experienced a mild traumatic brain injury (mTBI). Previous research demonstrates changes to thalamocortical connectivity associated with daytime sleepiness in healthy populations. Therefore, our current preliminary analyses focused on identifying the association between

thalamocortical connectivity and sleepiness following a mTBI. A subsample of 64 participants, including 23 healthy controls and 41 individuals with mTBI, were included in these analyses. We collapsed across time since injury, resulting in one mTBI group with documented injuries within the past 12 months. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and functional connectivity was measured using resting-state functional magnetic resonance imaging (rs-fMRI). Data were analyzed using the CONN Toolbox.

Figure S83 shows significantly greater daytime sleepiness in those with mTBI, compared to healthy controls ($t = -4.57$, $p < .001$). On average, those with an mTBI scored in the clinically significant range of daytime sleepiness (i.e., a score >10 on the ESS).

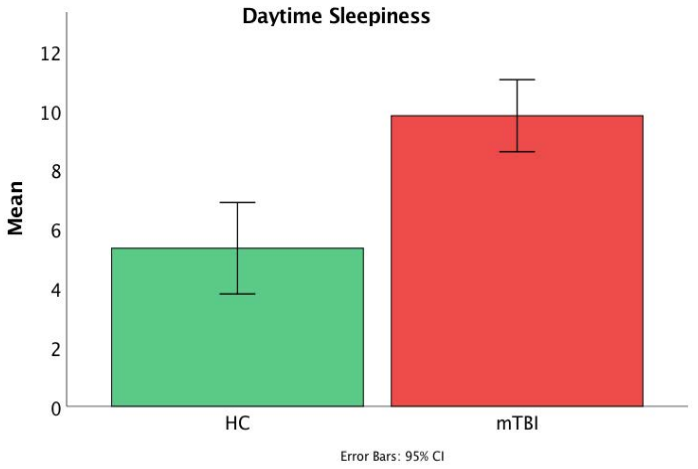


Figure 83. Significant differences in daytime sleepiness was found between the healthy control (HC) and mild traumatic brain injury (mTBI) groups.

We examined resting state functional connectivity within the brain by setting a seed region within the bilateral thalamus and examining whole brain correlations with thalamic activity, with ESS as a covariate of interest. Significant anticorrelations between thalamocortical connectivity and ESS were found in the HC group, compared to limited associations in the mTBI group (whole-brain height threshold $p<.001$ uncorrected, two-sided; cluster threshold $p<.05$ FWE-corrected). Specifically, lower ESS scores were associated with greater functional connectivity between the thalamus and bilateral premotor cortices (BA6; R, $p<.001$; L, $p<.05$), left primary somatosensory cortex (BA1; $p<.001$), left primary motor cortex (BA4; $p<.01$), and the right hippocampus ($p<.05$), an association that was weaker in mTBI (see Figure S84).

We have previously published findings on this same network and daytime sleepiness in healthy individuals (Killgore et al., 2013, *NeuroReport, 26*, 779-784) and now replicate this same association here. Moreover, our preliminary findings suggest the well-established thalamocortical associations with sleepiness are disrupted following mTBI. These findings may reflect a neurobiological underpinning for sleep and/or arousal disturbances in mTBI.

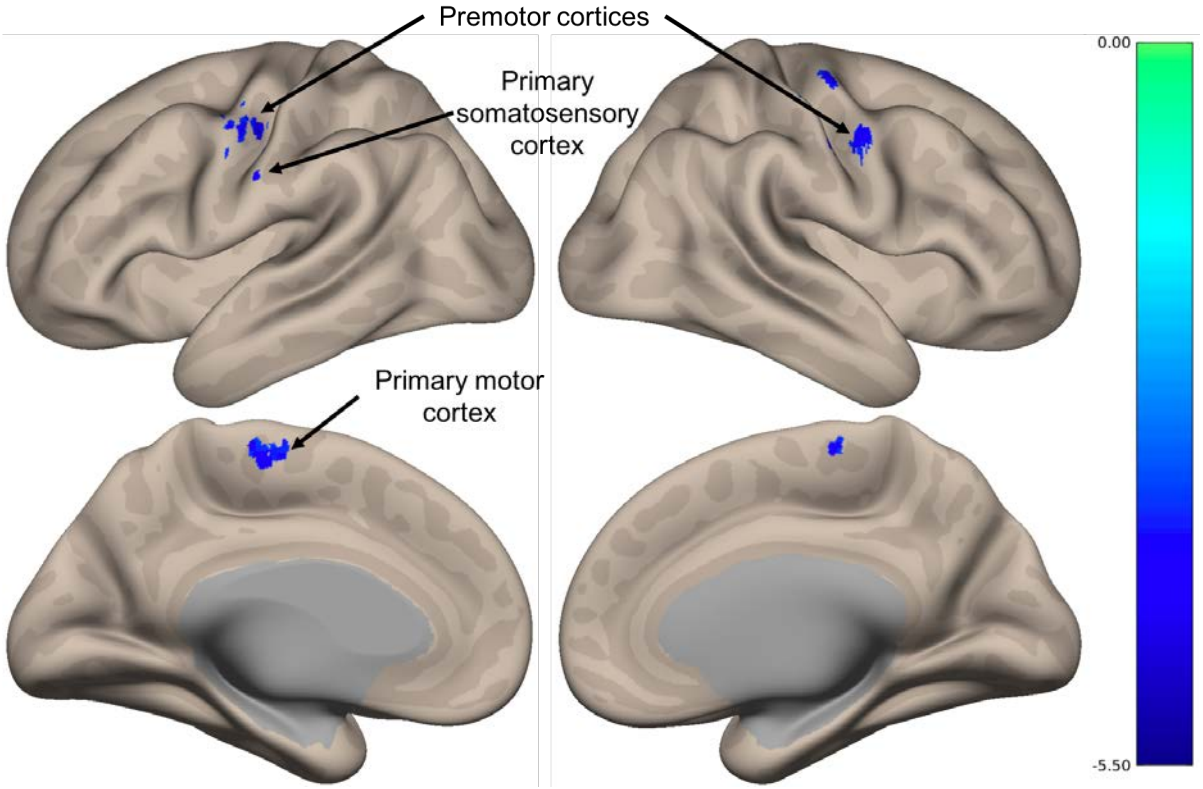


Figure S84. Significant anticorrelations between thalamocortical connectivity and daytime sleepiness in the healthy control group, compared to those with mild traumatic brain injury.

Daytime Sleepiness and Cognitive Function

Sleep disruptions and cognitive deficits are common symptoms reported by individuals who experience a mild traumatic brain injury (mTBI). However, the extent to which cognitive deficits are compounded by sleep disruptions in those with mTBI has yet to be fully explored. Our preliminary analyses, therefore, focused on daytime sleepiness and psychomotor vigilance in adults with and without mTBI. We hypothesized the combination of excessive daytime sleepiness in conjunction with an mTBI would result in significantly worse performance on a psychomotor vigilance task relative to those without a head injury.

A subsample of 57 participants (19 healthy controls; 38 mTBI) were included in these analyses. We collapsed across time since injury, which resulted in a single mTBI group with a documented mTBI within the past 12 months. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and cognitive function was measured using the Psychomotor Vigilance Task (PVT).

An independent samples t-test was calculated with group (HC and mTBI) as the independent variable and ESS as the dependent variable. ESS was significantly higher in the mTBI compared to HC group ($t(55) = -5.06$, $p < 0.001$) (Figure S85a). The Mann-Whitney U-test was calculated, due to non-normality, with group (HC and mTBI) as the independent variable and PVT lapses as

the dependent variable. The mTBI group exhibited significantly more PVT lapses, compared to the HC group ($U = 133.5$, $p = 0.001$) (Figure S85b).

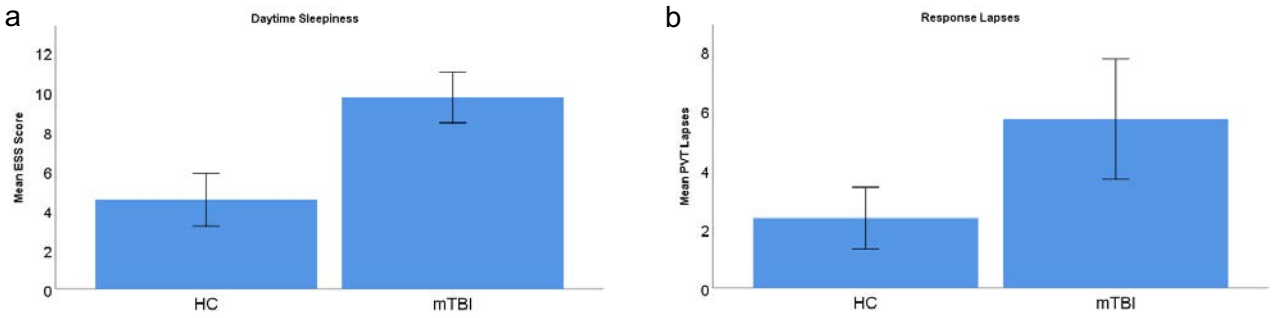


Figure S85. Reports of daytime sleepiness (a) and cognitive performance (b) between healthy controls (HC) and individuals with mild traumatic brain injury (mTBI).

Based on the previously described finding of increased sleepiness in those with mTBI, we wanted to determine whether those with mTBI *and* excess daytime sleepiness would exhibit greater lapses compared to HCs, and individuals *without* excessive daytime sleepiness. Individuals with mTBI were therefore divided into two groups, those with excessive daytime sleepiness (ESS ≥ 10) and those without excessive daytime sleepiness (ESS score < 10). The three groups differed significantly differed on the number of lapses ($H = 10.7$, $p <$ 0.01). Post-hoc analyses revealed the HC had significantly fewer lapses compared to the mTBI low ESS group ($U = 78.5$, $p < 0.01$) and mTBI high ESS group $U = 55.0$, $p < 0.01$) (Figure S86). No difference in lapses was found between the two mTBI groups.

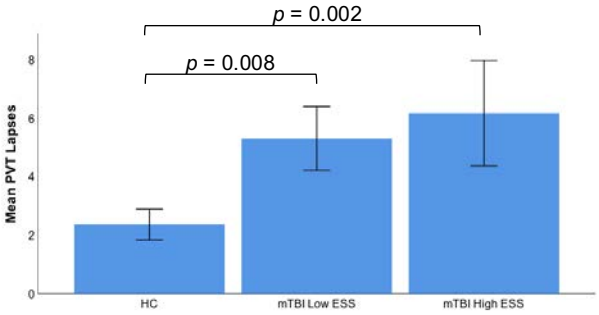


Figure S86. Cognitive performance between healthy controls (HC), individuals with mild traumatic brain injury with low (mTBI Low ESS) or high (mTBI High ESS) daytime sleepiness.

Our preliminary findings suggest disrupted sleep and neurobehavioral deficits (i.e., increased lapses) are present in adults who sustained an mTBI within the past 12 months. Although neurobehavioral performance was worse in those with mTBI, contrary to our hypothesis, those with mTBI and *excessive* daytime sleepiness performed similarly to those with mTBI and no excessive daytime sleepiness. This raises the possibility that lapses of attention that are observed among individuals with mTBI may be independent from the experience of daytime sleepiness and may represent a non-sleep-related deficit of the injury.

Disrupted Thalamocortical Connectivity After mTBI

Individuals who sustain a mild traumatic brain injury (mTBI) report sleep disruptions, including increased daytime sleepiness. Moreover, prior research from our lab indicates daytime sleepiness is associated with thalamocortical connectivity in healthy adults (Killgore et al., 2013). Despite prior work, the functioning of large-scale neural networks after a mTBI

remains poorly understood. The aim of this preliminary analysis was to identify brain regions associated with daytime sleepiness in adults who sustained a mTBI within 12 months. A subset of the larger study sample was used, which included 23 healthy controls (HCs) and 41 adults with mTBI.

Daytime Sleepiness: The Epworth Sleepiness Scale (ESS) was completed by all participants. Daytime sleepiness was significantly greater in adults with mTBI compared to HCs ($t = -4.57$, $p < 0.001$). More importantly, the majority of mTBI participants reported daytime sleepiness in clinical range (i.e. ESS score $\geq$ 10).

Functional Connectivity: We identified several brain areas which showed significantly stronger anticorrelations in HCs compared to individuals with mTBI. Lower ESS scores were associated with greater functional connectivity between the thalamus and the bilateral precentral gyrus (R.PreCG, $p < 0.001$; L.PreCG, $p < 0.05$), left post central gyrus (L.PostCG, $p < 0.001$), right hippocampus ($p < 0.05$) (see **Figure S87.**).

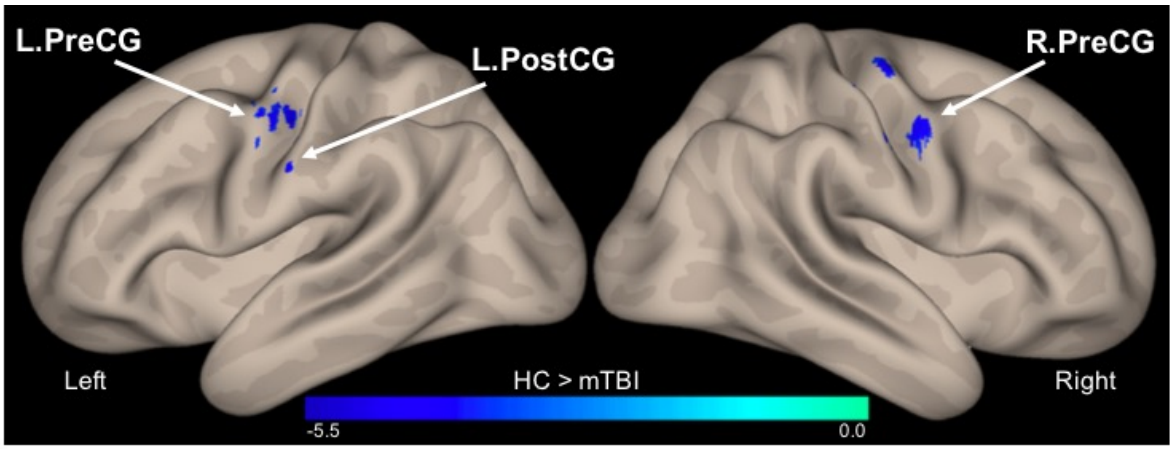


Figure S87. Comparison of resting state thalamocortical connectivity between healthy controls (HCs) and adults with mild traumatic brain injury (mTBI).

Summary: Our preliminary findings indicate disruption to well established networks between the thalamus and frontal regions implicated in arousal, while also replicating the same functional network associated with daytime sleepiness in healthy controls (Killgore et al., 2013, *NeuroReport, 26,* 779-784). These findings were recently presented at the annual *SLEEP* 2019 conference in San Antonio, TX.

Cognitive Performance and Excessive Daytime Sleepiness

As indicated in our above preliminary findings, excessive daytime sleepiness is a common complaint among patients who sustained a mTBI. It has yet to be determined, however, if sustaining a mTBI alone, or the combination of excessive daytime sleepiness and brain injury more greatly impact cognitive and motor function. The goal of this preliminary analysis was to determine whether individuals with mTBI and excessive daytime sleepiness (ESS scores $\geq$ 10) exhibit slower reaction times (RT) and increased response lapses on a vigilance task, when compared to healthy controls, and an mTBI group without excessive daytime

sleepiness (ESS scores < 10). This subsample contained 32 HCs and 90 participants with mTBI.

Psychomotor Vigilance Task (PVT): To assess the effect of mTBI and daytime sleepiness on vigilance, we fit a Poisson regression to the number of lapses occurring during the PVT (see **Figure S88.**). The model included both group (healthy control vs. mTBI) and Epworth Sleepiness Scale scores. This model demonstrated that the rate of lapses increased by 6.9% for every 1-point increase in ESS score. Additionally, PVT lapse rate was 1.87x higher (p < 0.001) for individuals with a history of mTBI.

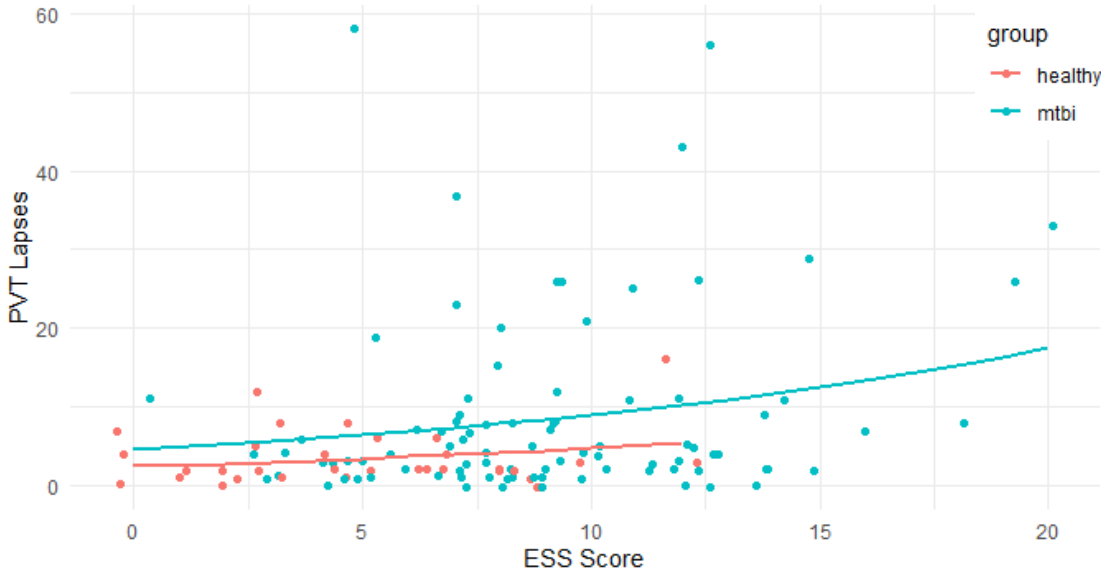


Figure S88. Regression model depicting the rate of lapses on the psychomotor vigilance task (PVT) as a function of daytime sleepiness (ESS) and history of

Summary: These findings provide evidence of a potentially devastating compounding effect of daytime sleepiness and brain injury. Although vigilance is reduced roughly 7% as daytime sleepiness increases even in healthy controls, this rate of reduced vigilance is doubled in those with mTBI. As recruitment continues, we plan to re-run these analyses considering time-since injury, to determine whether these compounding effects are more pronounced in certain recovery stages.

<u>Compounding Impact of Daytime Sleepiness and Brain Injury</u>

As previously reported, daytime sleepiness is among the most frequent self-reported sleep complaint following a mTBI. It has yet to be determined, however, if sustaining a mTBI alone, or the combination of daytime sleepiness and brain injury more greatly impacts cognitive function. The goal of this preliminary analysis was to determine the association between vigilance, daytime sleepiness, and the presence or absence of mTBI. A sub-set of 135 participants (M_{age} = 24.89±7.2; 83 females) were entered into the analysis, including 34 healthy controls and 101 individuals with mTBI. Participants with a history of mTBI were further divided based on time-since-injury to include acute (n=29; 2-weeks and 1-month post-injury), 3-

months (n=23), 6-months (n=20), and chronic (n=29; 1-year post-injury). To assess the effect of mTBI and daytime sleepiness on vigilance, a Poisson regression was fit to the number of lapses on the Psychomotor Vigilance Task (PVT), with group and Epworth Sleepiness Scale (ESS) as predictors.

ESS scores were significantly higher (p<.001) and there were significantly more PVT lapses (p=.03) among those with a recent mTBI, compared to HCs. For those with mTBI, the rate of lapses increased by 7.5% for every 1-point increase in ESS score (p< .001; see **Figure S89**). Furthermore, when compared to HCs, the PVT lapse rate was 1.5x higher for the acute group (p = .001), 1.7x higher for the 3-month group (p< .001), 1.8x higher for the 6-month group (p< .001), and 1.4x higher for the chronic group (p = 0.002), after controlling for ESS scores. These findings provide evidence of a significant compounding effect of daytime sleepiness and brain injury on sustained vigilant attention. Clinical evaluation of mTBI would benefit from routine assessment of daytime sleepiness.

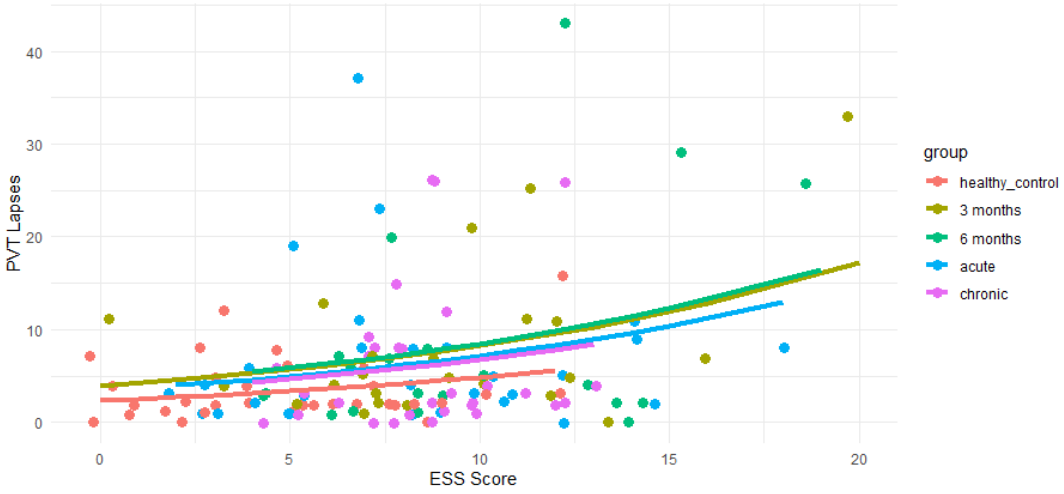


Figure S89. The association between daytime sleepiness (ESS) and vigilance (PVT).

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

Although not a primary research goal of the study, this project provided training and professional development for students, staff, and researchers involved in the project. Training and professional development opportunities associated with this project are listed below in reverse chronological order.

5 members of our lab presented research findings at the remote International Neuropsychological Society, February 2-5, 2021.

6 members of our lab presented research findings at the remote Annual Meeting of The Associated Professional Sleep Societies, August 27-30, 2020.

5 members of our lab presented findings at the virtual International Neuropsychological Society conference, July, 1-2, 2020.

6 members of our lab presented research findings and lectures at the International Neuropsychological Society, Denver, CO, February 5-8, 2020.

4 members of our lab presented research findings and lectures at the American Speech-Language Hearing Association Convention, Orlando, FL, November 21-23, 2019.

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

4 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 Tucson, AZ, August 2016.

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 Fitness/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, Boston, MA, April 2016.

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, Albuquerque, NM, January 2016.

15 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.

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

1 graduate student was supervised for his doctoral dissertation 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 25 members of our lab have undergone basic training modules in ethical conduct, statistical analysis, and neuroanatomy. All lab members have been certified in CPR and basic life support and first aid.

d. **How were the results disseminated to communities of interest?**

Throughout the duration of the study, findings were disseminated to academic and clinical communities of interest through conference presentations including at the International Neuropsychological Society, Military Health Systems Research

Symposium, SLEEP, and American Speech-Language Hearing Association. Senior research personnel presented study findings through invited university talks including at Harvard, the University of Arizona, and the University of Minnesota. In addition to conferences and invited talks, study results were disseminated through meetings with members of local military instillations including Davis Monthan Air Force Base and Fort Huachuca, and with local clinical organizations specializing in mTBI recovery and rehabilitation. Finally, subsets of preliminary findings are published in peer-reviewed scientific journals (see section 6. Products)

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

Nothing to report.

4. IMPACT

a. **Effect on the development of the principal discipline(s) of the project.**

We have continued to present our findings at scientific and military conferences. These findings have advanced our understanding of the effects of mTBI on various outcomes, including daytime sleepiness and vigilance, language processing, reading fluency, and memory capacity, and how these are associated with concussion-related changes in brain organization. Thus, the field of concussion research, in and out of the military, has been advanced by the preliminary knowledge that has been disseminated throughout this study.

b. **Effect on other disciplines.**

While the findings have been primarily disseminated within the concussion and neuropsychology community, we have also presented this work at conferences focused on sleep and on speech-language-hearing. Thus, the findings are having widespread reach beyond the primary discipline of neuropsychology.

c. **Effect on technology transfer.**

Nothing to report.

d. **Effect on society beyond science and technology.**

Our team has given small tabletop presentations in the local Tucson community to expand awareness of concussions to the non-professional and lay audiences. This has helped to communicated concussion awareness to athletes and the general student population. We have also given presentations at local Veteran's groups over the duration of the study, which has further enhanced awareness of the impact of concussions on mood, sleep, and cognitive function.

5. CHANGES/PROBLEMS:

a. **Changes in approach and reasons for change**

Study related amendments are listed below in chronological order. Approval data for each amendment is provided, along with a brief description of the reason for changes made to the study.

***Amendments*:**

- Amendment #1 (Approved by local IRB: 04 AUG 2014):
  - The amendment updated the VOTF to include recently hired personnel.
- Amendment #2 (Approved by local IRB: 09 OCT 2014):
  - The amendment proposed the inclusion of urine pregnancy tests, updated assessments to remove possible PHI, improved recruitment materials, phone scripts for screening purposes, and additional assessments that measure different aspects of memory.
- Amendment #3 (Approved by the local IRB: 03 NOV 2014):
  - The amendment updated the informed consent form and F200 to remove requests for medical records to confirm a mTBI/concussion diagnosis.
- Amendment #4 (Approved by local IRB: 19 NOV 2014):
  - The amendment proposed the inclusion of a MRI Metal checklist, improved recruitment methods (website), a NHLBI certificate of confidentiality (relevant language was added to all applicable forms), heart rate measurement throughout the research visit, and voice recording during an assessment to improve scoring accuracy.
- Amendment #5 (Approved by local IRB: 14 JAN 2015):
  - The amendment proposed the inclusion of the ImPACT test, a marijuana questionnaire, language pertaining to collaboration with Dr.Dagher's lab, and improved recruitment methods (social media). It also proposed the modification of the inclusion/exclusion criteria to update the age range to 18-45 from 20-45 as well as remove marijuana use and contact sports from the list of exclusionary criteria.
- Amendment #6 (Approved by local IRB: 13 MAR 2015):
  - The amendment removed the language pertaining to collaboration with Dr. Dagher's lab from all relevant documents.
- Amendment #7 (Approved by local IRB: 15 APR 2015):
  - The amendment proposed the addition of language that allowed the removal of subjects at the discretion of the PI to protect subjects, data and resources. It also proposed the addition of language stating that subjects would be formed if psychiatric or heart abnormalities were found during the duration of the study.
- Amendment #8 (Approved by local IRB: 12 MAY 2015):
  - The amendment proposed the inclusion of an additional assessment, improved recruitment methods, voice recording during additional assessments to improve scoring accuracy, the removal of the ImPACT test, updated forms such as the informed consent and updated participant correspondence scripts.

- Amendment #9 (Approved by local IRB: 17 JUL 2015):
    - The amendment proposed the addition of a new MRI scan sequence, updated forms such as the F200, and improved recruitment materials. It also proposed further refining the exclusion criteria surrounding alcohol or substance dependence/abuse.
- Amendment #10 (Approved by local IRB: 22 DEC 2015):
    - The amendment updated the list of key personnel.
- Amendment #11 (Approved by local IRB: 23 MAR 2016):
    - The amendment proposed the removal of heart rate monitoring during visits and improved recruitment methods.
- Amendment #12 (Approved by local IRB: 16 MAY 2016):
    - The amendment proposed updated language on the Informed Consent form.
- Amendment #13 (Approved by local IRB: 25 JUL 2016):
    - The amendment updated the list of key personnel.
- Amendment #14 (Approved by local IRB: 01 SEP 2016):
    - The amendment proposed improved recruitment methods and the addition of a new MRI sequence.
- Amendment #15 (Approved by local IRB: 15 NOV 2016):
    - The amendment proposed the addition of a medical database as a source of recruitment and improved recruitment materials.
- Amendment #16 (Approved by local IRB: 07 FEB 2017):
    - The amendment included new and updated participant correspondence scripts and improved recruitment methods.
- Amendment #17 (Approved by local IRB: 05 APR 2017):
    - The amendment updated the list of key personnel.
- Amendment #18 (Approved by local IRB: 02 JUNE 2017):
    - The amendment updated the list of key personnel.
- Amendment #19 (Approved by local IRB: 01 SEP 2017):
    - The amendment proposed the addition of a new online recruitment survey and improved recruitment materials.
- Amendment #20 (Approved by local IRB: 29 SEP 2017):
    - The amendment updated the list of key personnel.
- Amendment #21 (Approved by local IRB: 13 OCT 2017):
    - The amendment proposed a new video advertisement for recruitment purposes.
- Amendment #22 (Approved by local IRB: 07 JUNE 2018):
    - The amendment included the addition of the UA Research Associate Program and Twilio as sources for recruitment, increased number of healthy controls from 30 to 40, modified inclusionary criteria and improved recruitment materials.
- Amendment #23 (Approved by local IRB: 12 JUL 2018):
    - The amendment proposed the removal of left-handedness from the list of exclusionary criteria, improved recruitment materials and updated participant correspondence scripts.

- Amendment #24 (Approved by local IRB: 17 AUG 2018):
    - The amendment proposed the addition of the UA psychology research pool as a recruitment source.
- Amendment #25 (Approved by local IRB: 08 NOV 2018):
    - The amendment included updated participant correspondence scripts and improved recruitment materials.
- Amendment #26 (Approved by local IRB: 04 DEC 2018):
    - The amendment proposed an increase in subject pay (from $200 to $300), improved recruitment materials and updated participant correspondence scripts.
- Amendment #27 (Approved by local IRB: 23 JAN 2019):
    - The amendment proposed an additional payment for individuals that travel from outside of Tucson to participate, improved recruitment materials and updated participant correspondence.
- Amendment #28 (Approved by local IRB: 12 MAR 2019):
    - The amendment proposed a modified pay structure for subjects that are excluded or removed from the study (change from $25 per hour for all subjects, to $25 per hour for subjects who provide head injury documentation (HID) and $11 per hour for subjects with no HID. It also included improved recruitment materials, updated participant correspondence and relevant to reflect the change in pay structure.
- Amendment #29 (Approved by local IRB: 26 JUL 2019):
    - The amendment proposed the removal of colorblindness, alcoholism/substance abuse or dependence, excess current alcohol use, history of marijuana use, and marijuana use prior to age 16 from the list of exclusionary criteria. It also included updated participant correspondence to reflect the changes to the exclusion criteria.
- Amendment #30 (Approved by local IRB: 20 SEP 2019):
    - The amendment proposed the addition of language stating that roughly 30 subjects will be included in each of the five mTBI groups, improved recruitment materials and updated participant correspondence.
- Amendment #31 (Approved by local IRB: 23 JAN 2020):
    - The amendment proposed the removal of reference to affiliate hospital as possible research site, the addition of a new MRI sequence and updated participant correspondence.

b. **Actual or anticipated problems or delays and actions or plans to resolve them.**

Nothing to report.

c. **Changes that had a significant impact on expenditures**

Nothing to report.

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.**

Nothing to report.

6. PRODUCTS

a. **Publications/Presentations:**

We have had 6 peer reviewed papers published and 41 conference abstract/talk/poster presentations submitted or completed that were supported in part by this project:

Manuscripts (reverse chronological order):

1. Bajaj, S., Dailey, N.S., Rosso, I., Rauch, S., & Killgore, W.D.S. (2018). *Time-dependent differences in cortical measures and their associations with behavioral measures following mild traumatic brain injury*. Human Brain Mapping. PMID:29359498
2. Dailey, N.S., Smith, R., Vanuk, J.R., Raikes, A.C. & Killgore, W.D.S. (in press, 2018). *Resting-State Functional Connectivity as a Biomarker of Aggression in Mild Traumatic Brain Injury*. NeuroReport, DOI: 10.1097/WNR.0000000000001127
3. Dailey, N.S., Smith, R., Bajaj, S., Alkozei, A., Gottschlich, M.K., Raikes, A.C., Satterfield, B.C., & Killgore, W. D. S. (2018). *Elevated Aggression and Reduced White Matter Integrity in Mild Traumatic Brain Injury: A DTI Study*. Frontiers in Behavioral Neuroscience, 12, DOI: 10.3389/fnbeh.2018.00118
4. Raikes, A.C., Bajaj, S., Dailey, N.S., Smith, R., 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*. Frontiers in Neurotrauma, 9, DOI: 10.3389/fneur.2018.00468
5. Killgore, WDS, 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.
6. Singh, P, & Killgore WDS. Time dependent differences in gray matter volume post mild traumatic brain injury. Neural Regeneration Research, 11, 920-921, 2016.

Books or other non-periodical, one-time publications:

1. Klimova, A, Singh, P, & Killgore WDS. *White matter abnormalities in MS: Advances in diffusion tensor imaging/tractography*. Nutrition and Lifestyle in Neurological Autoimmune Diseases,21-28, 2017.

Abstracts/Talks/Posters (reverse chronological order):

2020

Dailey, N.S., Raikes, A., Bajaj, S., Alkozei, Sanasac, S., & Killgore, W.D.S. (2020, July). *Frontal and Temporal Cortical Surface Area is Associated with Lexical-Semantic Knowledge in Adults with Mild Traumatic Brain Injury*. Talk presented at the virtual 48th meeting of the International Neuropsychological Society 2020.

Esbit, S., Raygoza, D., Meinhausen, C., Dailey, N.S., & Killgore, W.D.S. (2020, July). *Discrepancies Between Working Memory and Clustering Strategies in Total Recall Performance for Mild Traumatic Brain Injury*. Poster presented at the virtual 48th annual meeting of the International Neuropsychological Society 2020.

Meinhausen, C., Esbit, S., Dailey, N.S., & Killgore, W.D.S. (2020, July). *Self-Initiated Verbal Recall Strategies Following Mild Traumatic Brain Injury*. Poster presented at the virtual 48th annual meeting of the International Neuropsychological Society 2020.

Dailey, N.S., Raikes, A.C., Wager, M.E., Grandner, M.A., Alkozei, A., & Killgore, W.D.S. (2020, August*). The Compounding Impact of Daytime Sleepiness and Brain Injury on Sustained Vigilance*. Poster presented at the virtual 34th Annual Meeting of the Associated Professional Sleep Societies.

Dailey, N.S., Raikes, A.C., Alkozei, A., Grandner, M.A., & Killgore, W.D.S. (2020, August). *Reduced Cortical Thickness as a Biomarker of Daytime Sleepiness in Mild Traumatic Brain Injury*. Poster presented at the virtual 34th Annual Meeting of the Associated Professional Sleep Societies.

2019

Dailey, N.S. & Killgore, W.D.S. (2019, November). *Disrupted Thalamocortical Connectivity following Mild Traumatic Brain Injury: Associations with Daytime Sleepiness*. Oral presentation at the American Speech-Language Hearing Association Conference, Orlando, FL.

Dailey, N.S. & Killgore, W.D.S. (2019, November*). Reading Fluency in Mild Traumatic Brain Injury*. Poster presented at the American Speech-Language Hearing Association Conference, Orlando FL.

Dailey, N.S., Meinhausen, C., & Killgore, W.D.S. (2019, February). *Self-Initiated Recall Strategies in Mild Traumatic Brain Injury: Identifying the Neural Correlates*. Poster presented at the 47th annual meeting of the International Neuropsychological Society, New York, NY.

Esbit, S., Dailey, N.S., & Killgore, W.D.S. (2019, February). *Making a List and Checking It Twice: Episodic Verbal Recall in Mild Traumatic Brain Injury*. Poster presented at the 47th annual meeting of the International Neuropsychological Society, New York, NY.

Meinhausen, C., Dailey, N.S., & Killgore, W.D.S. (2019, February). *Identifying Memory Retrieval Strategies during the Acute and Chronic Stages following a Mild Traumatic Brain Injury, using the CVLT-II*. Poster presented at the 47th annual meeting of the International Neuropsychological Society, New York, NY.

Dailey, N.S., Satterfield, S.C., Raikes, A.C., Strong, M.J., Forbeck, B., Grandner, M.A., & Killgore, W.D.S. (2019, June). *Disrupted Thalamocortical Connectivity following Mild Traumatic Brain Injury: Associations with Daytime Sleepiness*. Oral Platform Presentation at the 33rd Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas.

Wager, M.E., Dailey, N.S., & Killgore, W.D.S. (2019, April). *Excessive Daytime Sleepiness and mTBI: Determining Factors Leading to Decreased Cognitive Function*. Poster presented at the Spring 2019 Physiology Poster Session, Tucson, Arizona.

2018

Dailey, N.S., Bajaj, S., Alkozei, A., Smith, R., Knight, S.A., & Killgore, W.D.S. (2018, February). *Neural Correlates of Aggression in the Chronic and Post-acute States of Recovery from Mild Traumatic Brain Injury: A DTI Study*. Poster presented at International Neuropsychological Society, Washington, DC.

Dailey, N.S., Raikes, A.C., Smith, R., Alkozei, A., & Killgore, W.D.S. (2018, February). *The Executive Control Network after mild traumatic brain injury: Associations between functional connectivity and aggression*. Abstract presented at Big Sky Athletic Training Sports Medicine Conference, Big Sky, MT.

Dailey, N.S., Smith, R., Raikes, A.C., Alkozei, A., & Killgore, W.D.S. (2018, May). *Reduced Functional Connectivity in the Executive Control Network Following Mild Traumatic Brain Injury: Implications for Emotional Regulation*. Poster presented at the Society for Biological Psychiatry, New York, NY.

Dailey, N.S., Bajaj, S., Smith, R., Raikes, A. C., Alkozei, A., & Killgore, W. D. S. (2018, June*). Functional Connectivity in the Executive Control Network following Mild Traumatic Brain Injury*. Poster presented at the Organization for Human Brain Mapping Annual Meeting, Singapore, Malaysia.

Raikes, A. C., Bajaj, S., Dailey, N. S., Smith, R., Alkozei, A., Satterfield, B. C., & Killgore, W. D. S. (2018, February). *White Matter Correlates of Self-Reported Sleep Quality after a Mild Traumatic Brain Injury: A DTI Study*. Poster presented at the Big Sky Athletic Training and Sports Medicine Conference, Big Sky, MT.

Raikes, A. C., Satterfield, B. C., Dailey, N. S., Bajaj, S., & Killgore, W. D. S. (2018, February). *Self-Reported Sleep Quality is Related to Cerebellar Grey Matter*

Volume After Mild Traumatic Brain Injury. Poster presented at the Big Sky Athletic Training and Sports Medicine Conference, Big Sky, MT.

Raikes, A.C., Satterfield, B.S., Knight, S.A., & Killgore, W.D.S. (2018, February). *Grey Matter Volumetric Differences with Increasing Numbers of Previous Mild Traumatic Brain Injuries: A Voxel-Based Morphometric Study*. Poster presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, DC.

Raikes, A. C., Bajaj, S., Dailey, N. S., Smith, R., Alkozei, A., Satterfield, B. C., & Killgore, W. D. S. (2018, May). *Self-Reported Sleep Quality is Associated with Reductions in White-Matter Integrity Following Recent Mild Traumatic Brain Injury*. Poster presented at the 32nd Annual Meeting of the Associated Professional Sleep Societies, Baltimore, MD.

Raikes, A. C., Satterfield, B. C., Dailey, N. S., Bajaj, S., & Killgore, W. D. S. (2018, May). *Subjectively Poor Sleep Quality is Associated with Increased Cerebellar Grey Matter Volume Following Mild Traumatic Brain Injury*. Poster presented at the 32nd Annual Meeting of the Associated Professional Sleep Societies, Baltimore, MD.

Raikes, A. C., Bajaj, S., Dailey, N. S., Smith, R., Alkozei, A., Satterfield, B. C., & Killgore, W. D. S. (2018, June). *Post-mTBI White Matter Correlates of Self-Reported Sleep Quality: A DTI Study*. Poster presented at the Organization for Human Brain Mapping 2018 Annual Meeting, Singapore.

Dailey, N.S., Smith, R., Satterfield, B.C., Raikes, A.C., & Killgore, W.D.S. (2018, November). *Verbal Fluency following Mild Traumatic Brain Injury: The Strength of Switching*. Talk presented at the American Speech-Language Hearing Association Conference, Boston, MA.

Forbeck, B., Dailey, N.S., Esbit, S., & Killgore, W.D.S. (2018, November). *Reduced Information Processing Speed: A Dynamic Deficit in Mild Traumatic Brain Injury*. Poster presented at the American Speech-Language Hearing Association Conference, Boston, MA.

Meinhausen, C., Dailey, N.S., Miller, M. A., & Killgore, W.D.S., (2018, November). *Identifying Memory Retrieval Strategies Following a Mild Traumatic Brain Injury Using the CVLT-II*. Oral presentation at the Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN.

Raikes, A. C., Dailey, N. S., Bajaj, S., & Killgore, W. D. S. (2018, April). *White Matter Structure Changes Associated with Depressive Symptoms Following Recent Mild Traumatic Brain Injury*. Poster presented at the Anxiety and Depression Association of America, Washington, D.C.

Singh, A., Thurston, M.D., Gottschlich, M.K., Miller, M.A., & Killgore, W.D.S. (2018, February). *Trait Anxiety Predicts Hostile Tendencies in Post-Traumatic Brain Injury*. Poster presented at the Anxiety and Depression Association of America, Washington, D.C.

Raikes, A.C., & Killgore, W.D.S. (February, 2018). *Increased cerebellar grey matter in the presence of decreased subjective sleep quality following mild traumatic brain injury*. Poster presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, D.C.

2017

Dailey, N.S., Bajaj, S., Alkozei, A., & Killgore, W.D.S. (2017, November). *Neural Correlates of Aggression during Chronic and Post-Acute Stages of Recover from Mild Traumatic Brain Injury*. Poster presentation at Junior Investigator Poster Forum, College of Medicine, University of Arizona.

Bajaj, S. Alkozei, A., & Killgore, W. D. S. (2017, June). *Dynamics of brain's cortical measures following a mild traumatic brain injury*. Abstract presented at the Organization for Human Brain Mapping, Vancouver, CA.

Bajaj, S., Alkozei, A., & Killgore, W. D. S. (2017, May). *Automatic brain recovery following a mild traumatic brain injury*. Abstract presented at the Society for Biological Psychiatry, San Diego, CA.

Gottschlich MK, Hyman S, Millan M, Pisner D, Singh A, Knight SA, Grandner MA, Killgore WDS. (2017, June) *Post-Concussion Severity is associated with Sleep Problems and Neuropsychological Status*. Poster presented at the 31st Annual Meeting of the Associated Professional Sleep Societies, Boston, MA.

Dailey, N.S., Bajaj, S., Smith, R., Alkozei, A., & Killgore, W. D. S. (2017, August). *Neural Correlates of Aggression during Chronic and Post-Acute Stages of Recover from Mild Traumatic Brain Injury*. Poster presented at the Military Health Systems Research Symposium, Kissimmee, FL.

2016

Singh, P, Pisner, D, Fridman, A, Singh A, Millan, M, & Killgore, WD. (2016, May). *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.

Bernstein, AS, Pisner, D, Klimova, A, Umapathy, L, Do, L, Squire, S, Killgore, WD, & Trouard, T. (2016, May). *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.

Pisner, D, Singh, P, Fridman, A, & Killgore, WD. (2016, February.) *Resilience following mild traumatic brain injury is associated with gray matter volume in the left precentrual gyrus*. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Singh, P, Fridman, A, Pisner, D, & Killgore, WD. (2016, February). *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.

Fridman, A, Pisner, D, Singh, P, & Killgore, WD. (2016, February). *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.

Singh, P, Pisner, D, Fridman, A, Roberts, S, & Killgore, WD. (2016, February). *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.

Singh, P, Fridman, A, Pisner, D, Singh, A, & Killgore, WD. (2016, February). *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 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Klimova, A, Pisner, D & Killgore, WD. (2016, February). *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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **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: Natalie Dailey, Ph.D., CCC-SLP
Project Role: Research Scientist
Nearest person month worked: 2
Contribution to Project: Dr. Dailey oversees neuroimaging acquisition, performs data analysis and processing for the project, in addition to providing scientific support.
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 regulatory support.
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: Ted Trouard
Project Role: Co-Primary Investigator
Nearest person month worked: 0.000
Contribution to Project: Dr. Trouard provides support on brain imaging aspects of the study, including scanner parameters and data analysis.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Cameron Barnes
Project Role: Research Technician
Nearest person month worked: 0.150
Contribution to Project: Ms. Barnes provides support with data collection, data entry, 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: Brittany Forbeck
Project Role: Research Technician

Nearest person month worked: 1.200
Contribution to Project: Ms. Forbeck provides organizational oversight, support with data collection, and assists with participant recruitment activities 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: Anna Alkozei, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 4
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Ryan Smith, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 4
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Sahil Bajaj, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 3
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: Sara Knight
Project Role: Lab Manager
Nearest person month worked: 3
Contribution to Project: Ms. Knight oversees 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-16-1-0062

Name: Matthew Allbright
Project Role: Research Technician
Nearest person month worked: 2
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Garrett Baker
Project Role: Research Assistant
Nearest person month worked: 1
Contribution to Project: Mr. Baker assisted on the technical aspects of the project and assisted in database export, storage, and management.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Sarah (Markowski) Berryhill
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mrs. Berryhill 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: Skye Challenger
Project Role: Research Technician
Nearest person month worked: 1
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Melissa Gottschlich
Project Role: ResearchTechnician
Nearest person month worked: 3
Contribution to Project: Ms. Gottschlich oversaw project needs and managed day-to-day aspects of project operations.
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: 1
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
Nearest person month worked: 2
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: 1
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: Michael Strong
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Strong provides support with data collection recruitment activities and manages the day-to-day needs of 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: Matthew Thurston
Project Role: Research Technician

Nearest person month worked: 1
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: 1
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: Miriam Chinkers
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Chinkers assists in database storage and management.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Simon Esbit
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Mr. Esbit provides support with 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: Yinya Huang
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Huang assists in database storage and management.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Michael Lazar
Project Role: Research Technician
Nearest person month worked: 1
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Meltem Ozcan
Project Role: Research Technician
Nearest person month worked: 1
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-16-1-0062
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Jeffrey Skalamera
Project Role: Research Technician
Nearest person month worked: 1
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-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Molly Richards
Project Role: Research Technician
Nearest person month worked: 2
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-16-1-0062
USAMRAA W81XWH-12-1-0386

b. **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

c. **What other organizations were involved as partners?**

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Please see updated Quad Chart attached in Appendix.

REFERENCES CITED

Arenth, P.M., Russell, K.C., Scanlon, J.M., Kessler, L.J., & Ricker, J.H. (2013). Corpus Callosum Integrity and Neuropsychological Performance After Traumatic Brain Injury: A Diffusion Tensor Imaging Study. *The Journal of head trauma rehabilitation*.

Belanger, H.G., Curtiss, G., Demery, J.A., Lebowitz, B.K., & Vanderploeg, R.D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *J Int Neuropsychol Soc, 11*(3), 215-227.

Bogdanova, Y., & Verfaellie, M. (2012). Cognitive sequelae of blast-induced traumatic brain injury: recovery and rehabilitation. *Neuropsychology review, 22*(1), 4-20.

Eyres, S., Carey, A., Gilworth, G., Neumann, V., & Tennant, A. (2016). Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire. *Clinical Rehabilitation, 19*(8), 878-887.

Greicius, M.D., Krasnow, B., Reiss, A.L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 100*(1), 253-258.

Humphreys, I., Wood, R.L., Phillips, C.J., & Macey, S. (2013). The costs of traumatic brain injury: a literature review. *ClinicoEconomics and outcomes research : CEOR, 5*, 281-287.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., & Slobounov, S. (2012). Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. *Neuroimage, 59*(1), 511-518.

Jorge, R.E., Acion, L., White, T., Tordesillas-Gutierrez, D., Pierson, R., Crespo-Facorro, B., & Magnotta, V.A. (2012). White matter abnormalities in veterans with mild traumatic brain injury. *The American journal of psychiatry, 169*(12), 1284-1291.

Lange, R.T., Brickell, T.A., French, L.M., Merritt, V.C., Bhagwat, A., Pancholi, S., & Iverson, G.L. (2012). Neuropsychological outcome from uncomplicated mild, complicated mild, and moderate traumatic brain injury in US military personnel. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 27*(5), 480-494.

Lange, R.T., Brickell, T.A., Ivins, B., Vanderploeg, R.D., & French, L.M. (2013). Variable, not always persistent, postconcussion symptoms after mild TBI in U.S. military service members: a five-year cross-sectional outcome study. *J Neurotrauma, 30*(11), 958-969.

Lee, M.H., Hacker, C.D., Snyder, A.Z., Corbetta, M., Zhang, D., Leuthardt, E.C., & Shimony, J.S. (2012). Clustering of Resting State Networks. *Plos One, 7*(7).

Leong, B.K., Mazlan, M., Abd Rahim, R.B., & Ganesan, D. (2013). Concomitant injuries and its influence on functional outcome after traumatic brain injury. *Disability and rehabilitation, 35*(18), 1546-1551.

Mayer, A.R., Mannell, M.V., Ling, J., Gasparovic, C., & Yeo, R.A. (2011). Functional connectivity in mild traumatic brain injury. *Human brain mapping, 32*(11), 1825-1835.

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*(19), 2556-2563.

Morey, R.A., Haswell, C.C., Selgrade, E.S., Massoglia, D., Liu, C., Weiner, J., . . . McCarthy, G. (2012). Effects of chronic mild traumatic brain injury on white matter integrity in Iraq and Afghanistan war veterans. *Human brain mapping*.

Petrides, M., Collins, D.L., Chakravarty, M.M., & Germann, J. (2020). Tight Coupling between Morphological Features of the Central Sulcus and Somatomotor Body Representations: A Combined Anatomical and Functional MRI Study. *Cerebral Cortex, 30*(3), 1843-1854.

Potter, S., Leigh, E., Wade, D., & Fleminger, S. (2006). The Rivermead Post Concussion Symptoms Questionnaire. *Journal of Neurology, 253*(12), 1603-1614.

Raichle, M.E. (2011). The Restless Brain. *Brain Connectivity, 1*(1).

Spitz, G., Maller, J.J., O'Sullivan, R., & Ponsford, J.L. (2013). White matter integrity following traumatic brain injury: the association with severity of injury and cognitive functioning. *Brain topography, 26*(4), 648-660.

Vanderploeg, R.D., Curtiss, G., & Belanger, H.G. (2005). Long-term neuropsychological outcomes following mild traumatic brain injury. *J Int Neuropsychol Soc, 11*(3), 228-236.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141.

Yeh, P.H., Wang, B., Oakes, T.R., French, L.M., Pan, H., Graner, J., . . . Riedy, G. (2013). Postconcussional disorder and PTSD symptoms of military-related traumatic brain injury associated with compromised neurocircuitry. *Human brain mapping*.

APPENDICES
Table of Contents **Page**

References…… 189

List of Assessments…… 192

Copies of Questionnaires & Examples of Computer-Administered Tasks…….. 193

Publications…… 377

William D. “Scott” Killgore, Ph.D. Curriculum Vitae…… 492

Quad Chart…… 601

A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry Following Traumatic Brain Injury

Study Tasks and Assessments

Day of Scan Questionnaire

Epworth Sleepiness Scale (ESS)

OSU TBI Interview

Glasgow Outcome Scale – Extended (GOS-E)

MINI International Psychiatric Interview (MINI)

California Verbal Learning Test (CVLT)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Delis-Kaplan Executive Function System (D-KEFS)

Go/No Go

Brief Visual Memory Test-Revised (BVMT-R)

Buss Perry Aggression Questionnaire (BPAQ)

Psychomotor Vigilance Test (PVT)

Pittsburgh Sleep Quality Index (PSQI)

State Trait Anxiety Inventory (STAI)

Automated Neuropsychological Assessment Metrics (ANAM)

Beck Depression Inventory (BDI-II)

Wechsler Abbreviated Scale of Intelligence (WASI II)

Connor- Davidson Resilience Scale (CD-RISC)

Craig Handicap Assessment and Reporting Technique Short Form (CHART-SF)

Personality Assessment Inventory (PAI)

Alcohol Use Disorder Identification Test (AUDIT)

Rivermead Post Concussion Symptoms Questionnaire (RPCSQ)

Snaith Hamilton Pleasure Scale (SHAPS)

Satisfaction With Life Scale (SWLS)

Edinburgh Handedness Survey (EHS)

Marijuana Use Questionnaire (MUSE)

Woodcock Johnson Sentence Reading Fluency (WJ IV)

Injury Report

AGE _____ years

HEIGHT _____ ft/inches

WEIGHT _____ lbs

SEX ☐ **MALE** ☐ **FEMALE**

For females only:

When was the start of your last menstrual period?

Be as precise as possible.

Date of period:_____

or about _____days ago.

RIGHT or LEFT-HANDED?

☐ **RIGHT**

☐ **LEFT**

☐ **BOTH/NEITHER**

Do you have any problems with reading? ☐ **NO** ☐ **YES**

EDUCATION: What is the highest grade or level of school you have completed or the highest degree you have obtained? *Please choose one:*

☐ 9th Grade
☐ 10th Grade
☐ 11th Grade
☐ 12th Grade, no diploma
☐ High school graduate
☐ GED or equivalent
☐ Some college, no degree
☐ Associate degree: occupational, technical, or vocational program
☐ Associate degree: academic program
☐ Bachelor's degree (e.g., BA, AB, BS, BBA)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MBA)
☐ Professional school degree (e.g., MD, DDS, DVM, JD)
☐ Doctoral degree (e.g., PhD, EdD)
☐ Unknown

RACE: With what ethnicity do you identify?

☐ White
☐ Hispanic/Latino
☐ Black/African American
☐ Native American/ American Indian
☐ Asian/Pacific Islander
☐ Other

Are you currently doing shift work (e.g., working early morning, evening, or night shifts?

☐ **NO** ☐ **YES**

Do you engage in regular exercise?

☐ **NO** ☐ **YES**

Which sport? _____

How many days per week? _____

How many minutes per exercise session (on average)? _____

CAFFEINE USE

Did you have any caffeine containing products today?

☐ **NO** ☐ **YES** How much? _____

On average, how many cups (=8oz) of caffeinated coffee do you drink per day? _____

On average, how many cups (=8oz) 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? _____ (brand)

Do you use any other caffeinated products (e.g. Vivarin)?

☐ **NO** ☐ **YES** Brand? _____

How much? _____

How often? _____

NICOTINE AND OTHER SUBSTANCE USE

Do you currently smoke cigarettes?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked cigarettes in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke large cigars?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked large cigars in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke small cigars?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked small cigars in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke cigarillos?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked cigarillos in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently use smokeless tobacco, such as dip or chew?

☐ **NO** ☐ **YES**

About how much/ many? _____daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever used smokeless tobacco in the past?

☐ **NO** ☐ **YES**

About how much/ many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently use any other nicotine-containing products?

☐ **NO** ☐ **YES**

Which kind? _____

For how long? _____ years _____ months

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever used any other kind of nicotine containing products?

☐ **NO** ☐ **YES**

Which kind? _____

For how long? _____ years _____ months

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Are you currently taking diet pills?

☐ **NO** ☐ **YES**

What brand? _____

For how long? _____ years _____ months _____ days

How much? _____

How often? _____ daily / weekly / monthly / yearly (*circle one*)

Are you currently taking any medications, vitamins, or supplements?

☐ **NO** ☐ **YES**

Please list:

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Have you ever used any street drugs?

☐ **NO** ☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

In the past year, did you use any other street drugs?

☐ **NO**☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Do you currently use any other street drugs?

☐ **NO** ☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Do you drink alcohol?

☐ **NO** ☐ **YES**

How many times per month? _____

Using the below chart, what is the average number of drinks you consume on these occasions? _____

Using the chart, what is the largest number of drinks you consume? _____

One drink equals:

12 fl oz of **regular beer**	=	8-9 fl oz of **malt liquor** (shown in a 12-oz glass)	=	5 fl oz of **table wine**	=	3-4 oz of **fortified wine** (such as sherry or port, 3.5 oz shown)	=	2-3 oz of **cordial, liqueur, or aperitif** (2.5 oz shown)	=	1.5 oz of **brandy** (a single jigger or shot)	=	1.5 fl oz shot of **80-proof spirits** ("hard liquor")
												
about 5% alcohol		about 7% alcohol		about 12% alcohol		about 17% alcohol		about 24% alcohol		about 40% alcohol		about 40% alcohol

INFORMATION ON THE MOST RECENT DOCUMENTED INJURY

Injury date and time: __ __ _ /__ __/ __ __ __ __**:** __ __(24 hour clock)
(day /month/ year)

What happened? _____

_____

_____

Did you experience any symptoms or changes after the injury?

☐ **NO** ☐ **YES, IMMEDIATELY AFTER THE INJURY**

☐ **YES, NOT IMMEDIATELY AFTER THE INJURY**

Which symptoms or changes did you experience?

_____

_____

_____

At the time of the injury, were you under the influence of alcohol, medication or drugs at that time?

☐ **NO** ☐ **YES, ALCOHOL**

☐ **YES, MEDICATION** (which?) _____

☐ **YES, DRUGS** (which?) _____

Were medical services received after injury?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Did you “see stars” during your last concussion?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Did you experience loss of consciousness?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Duration of loss of consciousness:

- ☐ <1 minute
- ☐ 1-29 minutes
- ☐ 30-59 minutes
- ☐ 1-24 hours
- ☐ 1-7 days
- ☐ > 7 days
- ☐ Unknown

How was the loss of consciousness verified?

☐ **Self-report** ☐ **Witness** ☐ **Medical chart**

Do you have a PERSONAL memory of the event/ incident itself?

☐ **YES, I FULLY REMEMBER** ☐ **YES, BUT THERE ARE GAPS IN MY MEMORY**

☐ **NO, I DO NOT REMEMBER AT ALL**

How much do you NOT remember after the injury?

- ☐ <1 minute
- ☐ 1-29 minutes
- ☐ 30-59 minutes
- ☐ 1-24 hours
- ☐ 1-7 days
- ☐ > 7 days
- ☐ Unknown

How was the memory loss verified?

☐ **Self-report** ☐ **Witness** ☐ **Medical chart**

After the injury, when did you feel back to yourself or 100%? Please state the approximate number of days. _____

How many separate injuries do you think have you sustained in total? _____

How many of these were documented by a health professional, athletic trainer, coach, etc.? _____

SLEEP HABITS

How much sleep did you get last night? _____ HRS

Before your injury, what time did you typically awaken on:

Weekdays (Mon-Fri)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Sat-Sun)? _____ AM PM

Before your injury, how long did it typically take you to fall asleep at night?

Week nights (Sun-Thur) _____ MIN HRS (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat) _____ MIN HRS

Before your injury, at what time did you normally go to bed at night on:

Week nights (Sun-Thur)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat)? _____ AM PM

Before the injury, did you experience sleep problems?

☐ **NO** ☐ **YES, I had trouble falling asleep.**

How often? _____ times per WEEK MONTH YEAR

☐ **YES, I had trouble staying asleep.**

How often? _____ times per WEEK MONTH YEAR

Since the injury, did you notice that your sleep became worse?

☐ **NO** ☐ **YES**

What sleep problems became more noticeable to you? (*check all that apply*)

☐ 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.

How often? _____ times per WEEK MONTH YEAR *(circle one)*

☐ 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 have trouble staying asleep.

How often? _____ times per WEEK MONTH YEAR (circle one)

☐ 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.

Since your injury, how much do you typically sleep on weeknights (Sun-Thur)? _____ HRS

Since your injury, how much do you typically sleep on weekend nights (Fri-Sat)? _____ HRS

Since your injury, at what time do you normally go to bed at night on:

Week nights (Sun-Thur)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat)? _____ AM PM

Since your injury, what time do you typically awaken on:

Weekdays (Mon-Fri)? _____ AM PM

Weekends (Sat-Sun)? _____ AM PM

Since your Injury, how long does it typically take you to fall asleep at night?

Week nights (Sun-Thur)? _____ MIN HRS

Weekends (Fri-Sat)? _____ MIN HRS

Since your injury,

at what time of day do you feel sleepiest? _____ AM PM

at what time of day do you feel most alert? _____ AM PM

how many hours do you need to sleep to feel your best? _____

if you get less than _____ hours of sleep, you notice impairment in your ability to function at work.

if you get more than _____ hours of sleep, you notice impairment in your ability to function at work.

Since your injury, do you take more than two daytime naps per month?

☐ **NO** ☐ **YES**

How many times per week do you nap? _____

At what time? ____:____ AM/PM to ____:____AM/PM

Do you consider yourself a light, normal, or heavy sleeper?

☐ **LIGHT** ☐ **NORMAL** ☐ **HEAVY**

Have you been told or do you think that you snore excessively?

☐ **NO** ☐ **YES**

Have you ever been diagnosed or treated for sleep apnea or sleep disordered breathing?

☐ **NO** ☐ **YES**

Is daytime sleepiness currently a problem for you?

☐ **NO** ☐ **YES**

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your **usual way of life in recent times**. 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

SITUATION	CHANCE OF DOZING			
Sitting and reading	**0**	**1**	**2**	**3**
Watching TV	**0**	**1**	**2**	**3**
Sitting, inactive in a public place (e.g. a theater or meeting)	**0**	**1**	**2**	**3**
As a passenger in a car for an hour without a break	**0**	**1**	**2**	**3**
Lying down to rest in the afternoon when circumstances permit	**0**	**1**	**2**	**3**
Sitting and talking to someone	**0**	**1**	**2**	**3**
Sitting quietly after a lunch without alcohol	**0**	**1**	**2**	**3**
In a car, while stopped for a few minutes in the traffic	**0**	**1**	**2**	**3**

Ohio State University TBI Identification Method Short Form*

I would like to ask you about injuries to your head or neck that you may have had at anytime in your life.
Interviewer instruction: Record cause and any details provided spontaneously in the box at the bottom of the page. DO NOT query further about LOC or other details at this stage.

1. Have you ever been hospitalized or treated in an emergency room following an injury to your head or neck? Think about any childhood injuries you remember or were told about.
   - ❑ Yes—Record cause(s) in table below
   - ❑ No
2. Have you ever injured your head or neck in a car accident or from some other moving vehicle accident (e.g. motorcycle, ATV)?
   - ❑ Yes—Record cause(s) in table below
   - ❑ No
3. Have you ever injured your head or neck in a fall or from being hit by something (e.g. falling from a bike, horse, or rollerblades, falling on ice, being hit by a rock)? Have you ever injured your head or neck playing sports or on the playground?
   - ❑ Yes—Record cause(s) in table below
   - ❑ No
4. Have you ever injured your head or neck in a fight, from being hit by someone, or from being shaken violently? Have you ever been shot in the head?
   - ❑ Yes—Record cause(s) in table below
   - ❑ No
5. Have you ever been nearby when an explosion or a blast occurred? If you served in the military, think about any combat- or training-related incidents.
   - ❑ Yes—Record cause(s) in table below
   - ❑ No
6. If all above are "no" then proceed to question 7. If answered "yes" to *any* of the questions above, ask the following for each injury: **Were you knocked or did you lose consciousness (LOC)? If yes, how long? If no, were you dazed or did you have a gap in your memory from the injury? How old were you? (*age is only needed if there was LOC)***

Cause	Loss of consciousness (LOC)/knocked out				Dazed/Memory Gap		Age
	No LOC	< 30 min	30 min-24 hrs	> 24 hrs.	Yes	No	

* adapted with permission from the Ohio State University TBI Identification Method (Corrigan, J.D., Bogner, J.A. (2007). Initial reliability and validity of the OSU TBI Identification Method. *J Head Trauma Rehabil, 22*(6):318-329,

© reserved 2007, The Ohio Valley Center for Brain Injury Prevention and Rehabilitation

If more injuries with LOC: How many more?___ Longest knocked out?___ How many ≥ 30 mins.?___ Youngest age? ___

7. Have you ever lost consciousness from a drug overdose or being choked? ____# overdose ____# choked

SCORING

_____ **# TBI-LOC** (number of TBI's with loss of consciousness from #6a)
_____ **# TBI-LOC ≥ 30 (**number of TBI's with loss of consciousness ≥ 30 minutes from #6a)
_____ **age at first TBI-LOC** (youngest age from #6a)
_____ **TBI-LOC before age 15** (if youngest age from #7B < 15 then =1, if ≥ 15 then = 0)
_____ **Worst Injury** (1-5):
If responses to #1-5 are "no" classify as 1 "improbable TBI".
If in response to #6a and 6b reports never having LOC, being dazed or having memory lapses classify as 1 "improbable TBI".
If in response to #6b reports being dazed or having a memory lapse classify as 2 "possible TBI".
If in response to #6a loss of consciousness (LOC) does not exceed 30 minutes for any injury classify as 3 "mild TBI".
If in response to #6a LOC for any one injury is between 30 minutes and 24 hours classify as 4 "moderate TBI".
If in response to #6a LOC for any one injury exceeds 24 hours classify as 5 "severe TBI".
_____ **# anoxic injuries** (sum of incidents reported in #7)

© reserved 2007, The Ohio Valley Center for Brain Injury Prevention and Rehabilitation

Subject ID: _____ Date: _____

Glasgow Outcome Scale – Extended

CONSCIOUSNESS			
1.	Is the subject able to obey simple commands, or say words?	NO	YES
INDEPENDENCE IN THE HOME			
2.a	Is assistance of another person at home essential every day for some activities of daily living?	NO	YES
	Notes.		
2.b	Do you need frequent help or someone to be around at home most of the time?	NO *(UPPER SD)*	YES *(LOWER SD)*
2.c	Was assistance at home essential before the injury?	NO	YES
	Notes.		
INDEPENDENCE OUTSIDE OF HOME			
3.a	Do you shop without assistance?	NO *(UPPER SD)*	YES
3.b	Did you need assistance before the injury?	NO	YES
	Notes.		
4.a	Do you travel without assistance?	NO *(UPPER SD)*	YES
4.b	Did you need assistance before the injury?	NO	YES
	Notes.		

Subject ID: _____ Date: _____

WORK				
5.a	Are you currently working to your previous capacity?	NO		YES
5.b	How restricted are you?	Reduced work capacity. (UPPER MD)		Able to work in sheltered workshop or non-competitive job, or unable to work (LOWER MD)
5.c	Have you been working or seeking employment before the injury?	NO		YES
	Notes.			
SOCIAL & LEISURE ACTIVITIES				
6.a	Are you able to resume regular social and leisure activities outside home?	NO		YES
6.b	What is the extent of the restriction?	Participate a bit less: at least half as often as before injury (LOWER GR)	Participate much less: less than half as often (UPPER MD)	Unable to participate: rarely, if ever (LOWER MD)
6.c	Did you engage in regular social and leisure activities before the injury?	NO		YES
	Notes.			
FAMILY & FRIENDSHIPS				
7.a	Have there been any psychological problems which have resulted in ongoing family disruption or disruption of friendship?	NO		YES

Subject ID: _____ Date: _____

7.b	What is the extent of disruption or strain?	Occasional: less than weekly	Frequent: once a week or more, but tolerable	Constant: daily and intolerable
7.c	Were there problems with family or friends before the injury?	NO	YES	
	Notes.			
RETURN TO NORMAL LIFE				
8.a	Are there any other current problems relating to the injury which affect daily life?	NO (UPPER GR)	YES (LOWER GR)	
8.b	Were similar problems present before injury?	NO	YES	
	Notes.			

SCORING		
1	Dead	
2	Vegetative State	VS
3	Lower Severe Disability	Lower SD
4	Upper Severe Disability	Upper SD
5	Lower Moderate Disability	Lower MD
6	Upper Moderate Disability	Upper MD
7	Lower Good Recovery	Lower GR
8	Upper Good Recovery	Upper GR

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

USA: **D. Sheehan[1], J. Janavs, K. Harnett-Sheehan, M. Sheehan, C. Gray.**
[1]University of South Florida College of Medicine- Tampa, USA

EU: **Y. Lecrubier[2], E. Weiller, T. Hergueta, C. Allgulander, N. Kadri, D. Baldwin, C. Even.**
[2]Centre Hospitalier Sainte-Anne – Paris, France

© Copyright 1992-2009 Sheehan DV & Lecrubier Y

All rights reserved. No part of this document may be reproduced or transmitted in any form, or by any means, electronic or mechanical, including photocopying, or by any information storage or retrieval system, without permission in writing from Dr. Sheehan or Dr. Lecrubier. Researchers and clinicians working in nonprofit or publicly owned settings (including universities, nonprofit hospitals, and government institutions) may make paper copies of a M.I.N.I. instrument for their own clinical and research use.

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:

David V Sheehan, M.D., M.B.A.
University of South Florida College of Medicine
3515 East Fletcher Ave, Tampa, FL USA 33613-4706
tel : +1 813 974 4544; fax : +1 813 974 4575
e-mail : dsheehan@health.usf.edu

Yves Lecrubier, M.D. / Christian Even, M.D.
Centre Hospitalier Sainte-Anne
Clinique des Maladies Mentales de l'Encéphale
100 rue de la Santé, 75674 Paris Cedex 14, France
tel : +33 (0) 1 53 80 49 41; fax : +33 (0) 1 45 65 88 54
e-mail: ylecrubier@noos.fr or even-sainteanne@orange.fr

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.

		Current Episode	Past Episode
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? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
	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.

Scientific committee for the MINI 6.0.0:

A. Carlo Altamura, Milano, Italy
Cyril Hoschl, Praha, Czech Republic
George Papadimitriou, Athens, Greece
Hans Ågren, Göteborg, Sweden
Hans-Jürgen Möller, München, Germany
Hans-Ulrich Wittchen, Dresden, Germany
István Bitter, Budapest, Hungary
Jean-Pierre Lépine, Paris, France
Jules Angst, Zurich, Switzerland
Julio Bobes, Oviedo, Spain
Luciano Conti, Pisa, Italy
Marelli Colon-Soto MD, Puerto Rico, United States
Michael Van Ameringen MD, Toronto, Canada
Rosario Hidalgo MD, Tampa, United States
Siegfried Kasper, Vienna, Austria
Thomas Schlaepfer, Bonn, Germany

Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:**
Afrikaans	R. Emsley, W. Maartens	
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Braille (English)		
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Czech		P. Svlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis, GN Papidimitriou, T Matsoukas CR Soldatos
Gujarati		M. Patel, B. Patel, Organon
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir, Organon
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima

Kannada		Organon
Korean		K.S. Oh and Korean Academy of Anxiety Disorders
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Luganda		WW. Muhweziosal, H. Agren
Malayalam		Organon
Marathi		Organon
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak, M. Klisinska.
Serbian	I. Timotijevic	I. Timotijevic
Setswana	K. Ketlogetswe	
Slovenian	M. Kocmur	
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze, C. Santana, R. Hidalgo
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, H. Agren M. Waern, A. Brimse, M. Humble.
Tamil		Organon
Telugu		Organon
Thai		P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat, P. Silpakit,, M. Khamwongpin, S. Srikosai.
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner, A.Engeler
Urdu		S. Gambhir
Yiddish		J. Goldman, Chana Pollack, Myrna Mniewski

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

CVLT-II
California Verbal Learning Test®
Second Edition • Adult Version

California Verbal Learning Test–Second Edition

Dean C. Delis Joel H. Kramer Edith Kaplan Beth A. Ober

Standard Form

ID#: _____ Examiner: _____

	Year	Month	Day
Date Tested			
Age at Testing			

Sex: ☐ F ☐ M Race/Ethnicity: _____ Education (years): _____

Handedness: ☐ R ☐ L ☐ Ambidextrous Hearing adequate? ☐ Y ☐ N Hearing aid? ☐ Y ☐ N

First language: _____ Preferred language: _____ Effort appear adequate? ☐ Y ☐ ? ☐ N

Affect and mood: _____ Physical appearance: _____

Other behaviors: _____

Major complaints: _____

Diagnostic history: _____

_____

Current medications: _____

	Raw Score	Standard Score		Raw Score	Standard Score
Trial 1 Free Recall **Correct**			Long-Delay Free Recall **Correct**		
Trial 2 Free Recall **Correct**			Long-Delay Cued Recall **Correct**		
Trial 3 Free Recall **Correct**			Free-Recall **Intrusions** (Immediate & Delayed, All Types)		
Trial 4 Free Recall **Correct**			Cued-Recall **Intrusions** (All Types)		
Trial 5 Free Recall **Correct**			Total **Intrusions** (All Recall Trials, All Types)		
Trials 1–5 Free Recall Total **Correct**		(*T* score)	Total **Repetitions** (All Recall Trials)		
List B Free Recall **Correct**			Long-Delay Yes/No Recognition **Hits**		
Short-Delay Free Recall **Correct**			Long-Delay Yes/No Recognition **False-Positives**		
Short-Delay Cued Recall **Correct**			Long-Delay Forced-Choice Recognition **Accuracy** (# hits _____ /16) × 100	%	

PEARSON

Copyright © 2000 NCS Pearson, Inc. All rights reserved.

PsychCorp

Product Number 0154035742

List A Immediate Free Recall Trial 1

I'm going to read a list of words to you. Listen carefully, because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can. Are you ready?

Read List A at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say: **Go ahead.**

Trial 2

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order. Be sure to also say words from the list that you told me the first time.

Trials 3 and 4

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

Trial 5

I'm going to read the same list one more time. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

Record all responses verbatim, in the order recalled. Prompt only once (e.g., Anything else?) at the end of each free and cued recall trial (i.e., after 15 seconds with no response or when the examinee says he/she cannot remember more words).

List A

truck
spinach
giraffe
bookcase
onion
motorcycle
cabinet
zebra
subway
lamp
celery
cow
desk
boat
squirrel
cabbage

	Trial 1	Resp Type	Trial 2	Resp Type	Trial 3	Resp Type	Trial 4	Resp Type	Trial 5	Resp Type
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
Total Correct	C		C		C		C		C	
Total Repetitions	R		R		R		R		R	
Total Intrusions	I		I		I		I		I	

List B Immediate Free Recall

Now I'm going to read a second list of words to you. When I'm through, I want you to tell me as many words from this second list as you can, in any order. Don't tell me words from the first list, just this second list.

Read List B at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say: **Go ahead.**

List A Short-Delay Free Recall

Now I want you to tell me all the words you can from the *first* list, the one I read to you several times. Don't tell me words from the second list, just the first list. Go ahead.

List A Short-Delay Cued Recall

Tell me all the words from the first list that are furniture.
Tell me all the words from the first list that are vegetables.
Tell me all the words from the first list that are ways of traveling.
Tell me all the words from the first list that are animals.

Record all responses verbatim, in the order recalled. Prompt only once (e.g., Anything else?) at the end of each free and cued recall trial (i.e., after 15 seconds with no response or when the examinee says he/she cannot remember more words).

List B

violin
cucumber
elephant
closet
turnip
guitar
basement
sheep
clarinet
garage
corn
rabbit
patio
saxophone
tiger
radishes

Trial B

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		

Total Correct C ☐
Total Repetitions R ☐
Total Intrusions I ☐

List A

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		

Total Correct C ☐
Total Repetitions R ☐
Total Intrusions I ☐

Furniture

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		

Vegetables

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		

Ways of Traveling

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		

Animals

		Resp Type
1		
2		
3		
4		
5		
6		
7		
8		

Total Correct C ☐
Total Repetitions R ☐
Total Intrusions I ☐

*There should be approximately a **20-minute delay** between the completion of Short-Delay Cued Recall and the start of Long-Delay Free Recall. Do not inform the examinee that there will be later CVLT–II trials.*

List A Long-Delay Free Recall

I read two different lists of words to you earlier: a first list that I read to you several times, and a second list that I read to you once. Tell me all the words you can that were from the *first* list. Don't tell me words from the second list, just the first list. Go ahead.

List A	Resp Type
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

List A Long-Delay Cued Recall

Tell me all the words from the first list that are furniture.
Tell me all the words from the first list that are vegetables.
Tell me all the words from the first list that are ways of traveling.
Tell me all the words from the first list that are animals.

Furniture	Resp Type	Vegetables	Resp Type	Ways of Traveling	Resp Type	Animals	Resp Type
1		1		1		1	
2		2		2		2	
3		3		3		3	
4		4		4		4	
5		5		5		5	
6		6		6		6	
7		7		7		7	
8		8		8		8	

Total Correct C ☐ Total Repetitions R ☐ Total Intrusions I ☐

List A Long-Delay Yes/No Recognition

Now I'm going to read more words to you. After I read each one, say "Yes" if that word was from the first list, or say "No" if it was not from the first list.

If the examinee responds "I don't know" during Yes/No Recognition, say, "Tell me whether you think _____ was on the first list."

	Response	Item Type		Response	Item Type		Response	Item Type		Response	Item Type
wallet	Y N	UN	violin	Y N	BN	dog	Y N	PR	turnip	Y N	BS
boat	**Y** N	T	**cow**	**Y** N	T	**bookcase**	**Y** N	T	**cabinet**	**Y** N	T
saxophone	Y N	BN	fork	Y N	UN	matches	Y N	UN	**onion**	**Y** N	T
cucumber	Y N	BS	bus	Y N	PR	**spinach**	**Y** N	T	lion	Y N	PR
giraffe	**Y** N	T	**celery**	**Y** N	T	clarinet	Y N	BN	camera	Y N	UN
carrot	Y N	PR	**lamp**	**Y** N	T	**truck**	**Y** N	T	guitar	Y N	BN
patio	Y N	BN	radishes	Y N	BS	rabbit	Y N	BS	**subway**	**Y** N	T
cabbage	**Y** N	T	table	Y N	PR	chair	Y N	PR	tiger	Y N	BS
desk	**Y** N	T	rose	Y N	UN	corn	Y N	BS	coffee	Y N	UN
bracelet	Y N	UN	**motorcycle**	**Y** N	T	seashell	Y N	UN	**zebra**	**Y** N	T
car	Y N	PR	sheep	Y N	BS	garage	Y N	BN	lettuce	Y N	PR
elephant	Y N	BS	basement	Y N	BN	**squirrel**	**Y** N	T	closet	Y N	BN

T = Target
Distractor Types: BS = List B Shared; BN = List B Non-Shared; PR = Prototypical; UN = Unrelated

Total Hits ☐

Total False-Positives ☐

*There should be approximately a **10-minute delay** between the completion of Yes/No Recognition and the start of Forced-Choice Recognition. Do not inform the examinee that there will be a later CVLT–II trial.*

List A Long-Delay Forced-Choice Recognition (Optional)

Earlier, I read some lists of words to you, remember? Now I am going to read some words two at a time. After I read both words, say which of the words was from the *first* list, the one I read to you several times. It may be difficult to remember which one to pick, but even if it's hard for you, just try your best. Ready?

Was *boat* or *flag* on the first list?

Was ____ or ____ on the first list?

Circle the examinee's responses.

If the examinee says "I don't know," say, "I know it may be difficult, but just take your best guess."

			Score (1 or 0)	Dist. type
boat	or	flag		C
cake	or	**desk**		C
majority	or	**cow**		A
celery	or	aspirin		C
bookcase	or	silence		A
blender	or	**truck**		C
onion	or	logic		A
baseball	or	**zebra**		C
instruction	or	**cabinet**		A
squirrel	or	direction		A
blanket	or	**cabbage**		C
subway	or	technique		A
height	or	**spinach**		A
giraffe	or	towel		C
subject	or	**motorcycle**		A
lamp	or	sprinkler		C

Distractor types: C = concrete; A = abstract Total Hits ____

Total Accuracy: (_____ /16) × 100 = _____ %

Notes: _____

PEARSON

Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437
800.627.7271 www.PsychCorp.com

Copyright © 2000 NCS Pearson, Inc. All rights reserved.

Warning: No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the copyright owner.

Pearson, **PsychCorp**, the **PSI logo**, **California Verbal Learning Test**, and **CVLT** are trademarks in the U.S. and/or other countries of Pearson Education, Inc., or its affiliate(s).

Portions of this work were published in previous editions.

Printed in the United States of America.

24 A B C D E

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

9 780154 166036

27 28 29 30 CDE

PEARSON

Copyright © 1998 NCS Pearson, Inc. All rights reserved. **Warning:** No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the copyright owner. **Pearson, PsychCorp,** the **PSI logo,** and **RBANS** are trademarks, in the U.S. and/or other countries, of Pearson Education, Inc. or its affiliate(s). The Line Orientation portion of the RBANS is adapted from the "Judgment of Line Orientation" by Dr. Arthur Benton, under license from and reprinted with permission of Psychological Assessment Resources, Inc. Printed in the United States of America.

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.

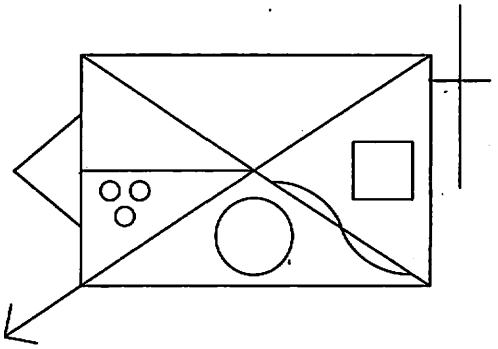


Figure Copy Criteria

(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.

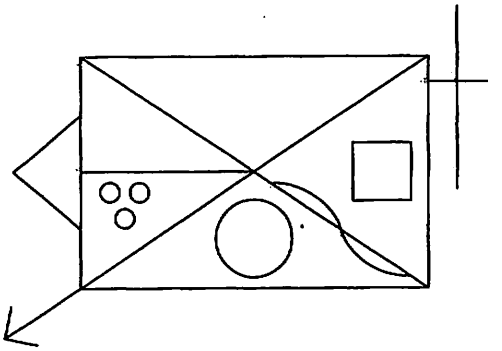


Figure Recall Criteria

(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.)

DELIS • KAPLAN
D-KEFS™
Executive Function System™

Delis–Kaplan Executive Function System

Dean C. Delis Edith Kaplan Joel H. Kramer

Standard Record Form

ID: _____ Examiner: _____

Sex: ❑ F ❑ M Handedness: ❑ R ❑ L ❑ Ambidextrous

Highest Level of Education (years): _____

Current Grade (if applicable): _____

School (if applicable): _____

	Year	Month	Day
Date Tested			
Age at Testing			

Referral Source/Reason for Referral/Presenting Complaints: _____

Attitude Toward Testing: _____

Affect and Mood: _____

Unusual Behaviors and Comments: _____

Physical Appearance: _____

Visual/Auditory/Motor Problems: _____

Language Background: _____

Diagnostic History: _____

Current Medications: _____

PEARSON

Copyright © 2001 NCS Pearson, Inc. All rights reserved.

PsychCorp

Product Number 0154091154

D-KEFS Trail Making Test: Summary of Scores

Primary Measures: Completion Times

Condition 1: Visual Scanning	Condition 2: Number Sequencing	Condition 3: Letter Sequencing	Condition 4: Number–Letter Switching	Condition 5: Motor Speed
Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score

Primary Combined Measure: Completion Times

Combined Number Sequencing + Letter Sequencing

Number Sequencing Scaled Score + Letter Sequencing Scaled Score = Sum of Scaled Scores → **Composite Scaled Score**

Primary Contrast Measures: Completion Times

	Switching: Scaled Score		Scaled Score		Scaled Score Difference		Contrast Scaled Score*
			Visual Scanning				
Number–Letter Switching vs. Visual Scanning*		–		=		→	
			Number Sequencing				
Number–Letter Switching vs. Number Sequencing*		–		=		→	
			Letter Sequencing				
Number–Letter Switching vs. Letter Sequencing*		–		=		→	
			Number Sequencing + Letter Sequencing				
Number–Letter Switching vs. Combined Number Sequencing + Letter Sequencing*		–	Composite	=		→	
			Motor Speed				
Number–Letter Switching vs. Motor Speed*		–		=		→	

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Measures: Error Analysis

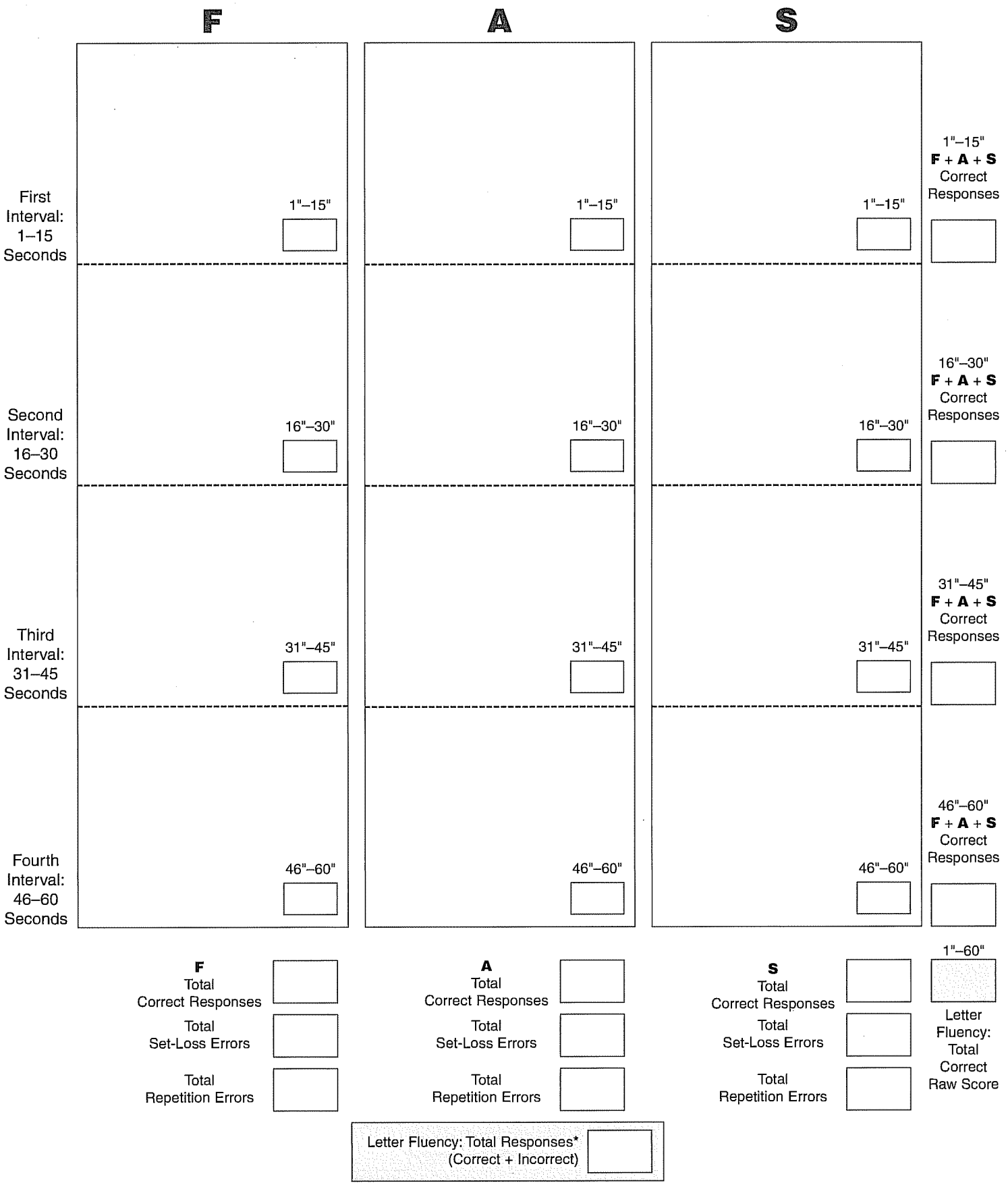
	Condition 1: Visual Scanning	Condition 2: Number Sequencing	Condition 3: Letter Sequencing	Condition 4: Number–Letter Switching	Condition 5: Motor Speed
Omission Errors	Raw Score; Cumulative Percentile Rank				
Sequencing Errors		Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	
Commission Errors	Raw Score; Cumulative Percentile Rank				
Set-Loss Errors		Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	
Time-Discontinue Errors		Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank	Raw Score; Cumulative Percentile Rank

Condition 4: All Error Types — Total Raw Score; **Scaled Score**

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

D-KEFS Verbal Fluency Test

Condition 1: Letter Fluency



* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

D-KEFS Verbal Fluency Test *(continued)*

Condition 2: Category Fluency

	Animals	Boys' Names	1"–15" **Animals** + **Boys' Names** Correct Responses
First Interval: 1–15 Seconds	1"–15" ☐	1"–15" ☐	☐
Second Interval: 16–30 Seconds	16"–30" ☐	16"–30" ☐	16"–30" **Animals** + **Boys' Names** Correct Responses ☐
Third Interval: 31–45 Seconds	31"–45" ☐	31"–45" ☐	31"–45" **Animals** + **Boys' Names** Correct Responses ☐
Fourth Interval: 46–60 Seconds	46"–60" ☐	46"–60" ☐	46"–60" **Animals** + **Boys' Names** Correct Responses ☐

Animals Total Correct Responses	☐	**Boys' Names** Total Correct Responses	☐	1"–60" ☐ Category Fluency: Total Correct Raw Score
Total Set-Loss Errors	☐	Total Set-Loss Errors	☐	
Total Repetition Errors	☐	Total Repetition Errors	☐	

Category Fluency: Total Responses (Correct + Incorrect)* ☐

* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

D-KEFS Verbal Fluency Test *(continued)*

Condition 3: Category Switching

Fruits / Furniture

First Interval: 1–15 Seconds		1"–15" **Fruits** + **Furniture** Correct Responses* ☐
Second Interval: 16–30 Seconds		16"–30" **Fruits** + **Furniture** Correct Responses* ☐
Third Interval: 31–45 Seconds		31"–45" **Fruits** + **Furniture** Correct Responses* ☐
Fourth Interval: 46–60 Seconds		46"–60" **Fruits** + **Furniture** Correct Responses* ☐

☐ Category Switching: Total Switching Accuracy

☐ **Fruits** Total Correct Responses* + ☐ **Furniture** Total Correct Responses* = ☐ 1"–60" Raw Score — Category Switching: Total Correct Responses*

* Correct responses are summed independent of switching accuracy.

☐ Total Set-Loss Errors

☐ Total Repetition Errors

Category Switching: Total Responses (Correct + Incorrect)** ☐

** *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

D-KEFS Verbal Fluency Test: Summary of Scores

Primary Measures

Condition 1: Letter Fluency Total Correct	Condition 2: Category Fluency Total Correct	Condition 3: Category Switching Total Correct Responses	Condition 3: Category Switching Total Switching Accuracy
Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score

Primary Contrast Measures

Letter Fluency vs. Category Fluency*

Letter Fluency: Total Correct (Scaled Score) − Category Fluency: Total Correct (Scaled Score) = Scaled-Score Difference → Contrast Scaled Score*

Category Switching vs. Category Fluency*

Category Switching: Total Correct Responses (Scaled Score) − Category Fluency: Total Correct (Scaled Score) = Scaled-Score Difference → Contrast Scaled Score*

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Measures: Conditions 1–3 Combined

	Condition 1: Letter Fluency Raw Score		Condition 2: Category Fluency Raw Score		Condition 3: Category Switching Raw Score		Total Raw Score	Scaled Score
First Interval (1"–15"): Total Correct		+		+		=		
Second Interval (16"–30"): Total Correct		+		+		=		
Third Interval (31"–45"): Total Correct		+		+		=		
Fourth Interval (46"–60"): Total Correct		+		+		=		
Set-Loss Errors		+		+		=		
Repetition Errors		+		+		=		
Total Responses (Correct + Incorrect)*		+		+		=		

* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

Percent Set-Loss Errors

Total Set-Loss Errors (Raw Score) ÷ Total Responses* (Raw Score) × 100 → Percent Raw Score → Scaled Score

Percent Repetition Errors

Total Repetition Errors (Raw Score) ÷ Total Responses* (Raw Score) × 100 = Percent Raw Score → Scaled Score

Category Switching: Percent Switching Accuracy (Condition 3 Only)

[Total Switching Accuracy (Raw Score) + 1] ÷ [Total Responses Condition 3 Only* (Raw Score)] × 100 = Percent Raw Score → Scaled Score

* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total responses measure.

D-KEFS Design Fluency Test: Summary of Scores

Primary Measures

Condition 1 Filled Dots: Total Correct		Condition 2 Empty Dots Only: Total Correct		Condition 3 Switching: Total Correct		Design Fluency Total Correct
Raw Score	+	Raw Score	+	Raw Score	=	Raw Score
↓		↓		↓		
Scaled Score	+	Scaled Score	+	Scaled Score	=	Sum of Scaled Scores → Composite Scaled Score

Design Fluency: Total Correct

Primary Combined Measure: Filled Dots + Empty Dots

Combined Filled Dots + Empty Dots: Total Correct

Condition 1 Filled Dots		Condition 2 Empty Dots Only		Sum of Scaled Scores	Composite Scaled Score
Scaled Score	+	Scaled Score	=		→

Primary Contrast Measure

Switching vs. Combined Filled Dots + Empty Dots*

Condition 3 Switching: Total Correct		Conditions 1 + 2 Combined		Scaled Score Difference	Contrast Scaled Score*
Scaled Score	−	Composite Scaled Score	=		→

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Measures

	Condition 1 Filled Dots		Condition 2 Empty Dots Only		Condition 3 Switching			
	Set-Loss Designs		Set-Loss Designs		Set-Loss Designs		Total Set-Loss Designs	**Total Set-Loss Designs**
Total Set-Loss Designs	Raw Score	+	Raw Score	+	Raw Score	=	Raw Score →	Scaled Score
	Repeated Designs		Repeated Designs		Repeated Designs		Total Repeated Designs	**Total Repeated Designs**
Total Repeated Designs	Raw Score	+	Raw Score	+	Raw Score	=	Raw Score →	Scaled Score
	Attempted Designs		Attempted Designs		Attempted Designs		Total Attempted Designs	**Total Attempted Designs***
Total Attempted Designs*	Raw Score	+	Raw Score	+	Raw Score	=	Raw Score →	Scaled Score

* *Note*: Some repetition errors are coded also as set-loss errors; each double-coded error counts as only one response for the total attempted designs measure.

Percent Design Accuracy

[**Design Fluency: Total Correct** Raw Score ÷ **Total Attempted Designs*** Raw Score] × 100 = **Percent Raw Score** → **Scaled Score**

D-KEFS Color-Word Interference Test

Ages 8–89
Materials: Record Form, Stimulus Booklet (Flat Position), Stopwatch

Condition 1: Color Naming

Discontinue

Discontinue if the examinee has marked difficulty or makes four uncorrected errors on the practice lines. Otherwise, discontinue the scored task after 90 seconds.

Administration and Recording

Place the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee so that the two practice lines of Condition 1 are positioned at the top of the page from the examinee's perspective. Say,

> **This page has patches of color on it. I'd like you to say the colors as quickly as you can without skipping any or making mistakes. When you finish this line** (sweep across the first practice line of five squares with your finger), **go on to this one** (point to the first square of the second row). **Now try these first two lines for practice.**

If the examinee is able to complete the two practice lines, say, **Good. Now, when I say begin, I want you to say the rest of the colors. Begin here** (point to the first square on the first line of 10 squares below the practice lines) **and say each color, one after the other, without skipping any. When you finish this line** (sweep across the first row with your finger), **go on to this one** (point to the first square of the second row). **Keep saying the colors until you reach the end of the last line** (point). **Say the colors as quickly as you can without making mistakes. Ready? Begin.**

Start timing. Follow the examinee's progress item by item. Record errors by writing the first letter of the incorrect color name beneath the correct response and record any nonsense words (e.g., "bleen") verbatim. Indicate self-corrections by drawing a slash mark through the letter or word. Record total completion time in seconds.

Allow the examinee to use a finger to maintain his or her place on the stimulus page. If the examinee skips a line accidentally, point out the error immediately and redirect the examinee to the correct line. Keep the stopwatch running while pointing out line-skipping errors.

If the examinee does not complete the task at the end of 90 seconds, say, **Stop.** Indicate the last item attempted and record 90 seconds as the total completion time. Items to which the examinee did not respond because the time limit was reached are not counted as errors. Turn the page in the stimulus booklet to Condition 2: Word Reading.

green red blue green blue

red blue green blue green

red blue red green red blue green blue red green

blue green red green red green blue red blue green

red green blue red green red green blue green red

blue red green blue red green blue red blue green

red blue red green blue green blue red blue green

Condition 1: Color Naming

Total Uncorrected Errors	Total Self-Corrected Errors	Total Time To Complete

D-KEFS Color-Word Interference Test *(continued)*

Condition 2: Word Reading

Discontinue

Discontinue if the examinee has marked difficulty or makes four uncorrected errors on the two practice lines. Otherwise, discontinue the scored task after 90 seconds.

Administration and Recording

Place the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee, with the rows of words printed in black ink facing the examinee. Say,

> **Now look at this page with words printed on it. I'd like you to read the words aloud as quickly as you can without skipping any or making mistakes. When you finish this line** (sweep across the first practice line of five words with your finger), **go on to this one** (point to the first word of the second row). **Now try reading these first two lines for practice.**

If the examinee is able to complete the two practice lines, say,

> **Good. Now, when I say begin, I want you to read the rest of the words. Begin here** (point to the first word on the first line of 10 words below the practice lines) **and read each word, one after the other, without skipping any. Keep reading the words until you reach the end** (point to the last word on the last line). **Read the words as quickly as you can without making mistakes. Ready? Begin.**

Start timing. Follow the examinee's progress item by item. Record errors by writing the first letter of the incorrect word beneath the correct response and record any nonsense words (e.g., "bleen") verbatim. Indicate self-corrections by drawing a slash mark through the letter or word. Record total completion time in seconds.

Allow the examinee to use a finger to maintain his or her place on the stimulus page. If the examinee skips a line accidentally, point out the error immediately and redirect the examinee to the correct line. Keep the stopwatch running while pointing out line-skipping errors.

If the examinee does not complete the task at the end of 90 seconds, say, **Stop.** Indicate the last item attempted and record 90 seconds as the total completion time. Items to which the examinee did not respond because the time limit was reached are not counted as errors. Turn the page in the stimulus booklet to Condition 3: Inhibition.

red blue green red blue

green blue green red green

green red blue green blue red blue green blue green

red green blue green blue green red blue red green

red green blue green red blue green red blue red

blue green red blue green red blue green blue red

green red blue red blue green red blue red green

Condition 2: Word Reading

Total Uncorrected Errors	Total Self-Corrected Errors	Total Time To Complete

Condition 3: Inhibition

Discontinue

Discontinue if the examinee has marked difficulty or requires four corrections on the two practice lines. Otherwise, discontinue the scored task after 180 seconds.

Administration and Recording

Place the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee, with the rows of words printed in dissonant ink colors facing the examinee. Say,

> **Now look at this page. It's going to be a little harder than the other pages because the color names are printed in a different-colored ink. For example** (point to the first word on the first practice line of five words)**, do you see how the word *red* is printed in *green* ink here? This time, you are to name *the color of the ink* that the letters are printed in and *not read the word*. So, what would you say for this one?** (Point again to the first word on the first practice line and allow the examinee to respond. Correct any errors.) **Good. And this one?** (Point to the next two practice items. Correct any errors.) **Good. Now try these first two lines for practice.**

If the examinee has difficulty understanding the task, you may demonstrate it by naming the ink colors on the first practice line, then inviting the examinee to respond to the second line. If the examinee requires four corrections on the two practice lines, discontinue this condition and do not administer Condition 4: Inhibition/Switching.

If the examinee is able to complete the two practice lines, say,

> **Good. Now, when I say begin, I want you to do the same thing for the rest of them. Say the color of the ink the letters are printed in; do not read the words. Begin here** (point to the first word on the first line of 10 words below the practice lines) **and say each ink color, one after the other, without skipping any. Keep saying the ink colors until you reach the end** (point to the last word of the last line)**. Say the ink colors as quickly as you can without making mistakes. Ready? Begin.**

Start timing. Follow the examinee's progress item by item. The single letter (*r* for red, *b* for blue, *g* for green) printed in parentheses next to each correct response represents the error response if the examinee reads the word rather than naming the ink color. Record errors by circling the letter or by writing the initial letter of other incorrect colors beneath the correct response. Also record any nonsense words (e.g., "bleen") verbatim. Indicate self-corrections by drawing a slash through the letter or word. Record total completion time in seconds.

Allow the examinee to use a finger to maintain his or her place on the stimulus page. If the examinee skips a line accidentally, point out the error immediately and redirect the examinee to the correct line. Keep the stopwatch running while pointing out line-skipping errors.

If the examinee makes three consecutive errors of reading the words, prompt him or her to name the ink color. Provide this prompt only once during this condition and keep the stopwatch running.

If the examinee does not complete the task at the end of 180 seconds, say, **Stop.** Indicate the last item attempted and record 180 seconds as the total completion time. Items to which the examinee did not respond because the time limit was reached are not counted as errors. Turn the page in the stimulus booklet to Condition 4: Inhibition/Switching.

green(r) red(b) blue(g) green(b) red(g)

blue(r) red(b) green(r) red(g) green(r)

red(b) blue(g) red(b) green(r) red(b) blue(r) green(b) blue(r) red(b) green(r)

red(b) blue(g) green(b) blue(g) green(r) blue(g) red(b) green(r) red(b) blue(g)

green(r) blue(g) green(r) red(b) blue(g) green(r) red(g) blue(r) green(b) red(g)

green(b) blue(g) red(b) green(r) blue(g) red(b) green(r) blue(g) green(r) red(g)

blue(g) green(b) blue(r) red(b) blue(g) green(r) red(b) blue(g) green(r) red(b)

Condition 3: Inhibition

Total Uncorrected Errors	Total Self-Corrected Errors	Total Time To Complete

D-KEFS Color-Word Interference Test *(continued)*

Condition 4: Inhibition/Switching

Discontinue

Do not administer Condition 4 if the examinee had marked difficulty or did not finish before the time limit was reached on Condition 3: Inhibition. Discontinue if the examinee has marked difficulty or requires four corrections on the practice lines of Condiditon 4. Otherwise, discontinue the scored task after 180 seconds.

Administration and Recording

Place the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee, with the rows of words printed in dissonant ink colors, half of which are contained in rectangles, facing the examinee. Say,

> **This is the fourth and last page. This time, for many of the words, you are to do the same thing you just did: Name the color of the ink and do not read the words. But if a word is inside a little box, you should read the word and not name the ink color.** (Point to the first three items in the first practice line of five words.) **For example, what would you say for these first three words?** (Allow the examinee to respond and provide corrections if necessary.) **Good. Now try these first two lines for practice.**

If the examinee has difficulty understanding the task, you may demonstrate it by responding to the items on the first practice line, then inviting the examinee to respond to the second line. If the examinee requires four corrections on the two practice lines, discontinue this condition. If the examinee is able to complete the practice lines, say,

> **Very good. Now, when I say begin, I want you to do the same thing for the rest of them. Say the color of the ink the letters are printed in or read the word if it is in a box. Begin here** (point to the first word on the first line of 10 words below the practice lines) **and keep going until you reach the end** (point to the last word of the last line). **Say the ink colors or words as quickly as you can without making mistakes. Ready? Begin.**

Start timing. Follow the examinee's progress item by item. The single letter (*r* for red, *b* for blue, *g* for green) printed in parentheses next to each correct response represents the error response if the examinee either (a) reads the word rather than naming the ink color for an item not contained in a rectangle or (b) names the ink color rather than reading the word for an item contained in a rectangle. Record errors by circling the letter or by writing the initial letter of other incorrect colors beneath the correct response. Also record any nonsense words (e.g., "bleen") verbatim. Indicate self-corrections by drawing a slash through the letter or word. Record total completion time in seconds.

Allow the examinee to use a finger to maintain his or her place on the stimulus page. If the examinee skips a line accidentally, point out the error immediately and redirect the examinee to the correct line. Keep the stopwatch running while pointing out line-skipping errors.

If the examinee makes three consecutive errors, prompt him or her either to name the ink color or to read the word in the rectangle. Provide this prompt only once during this condition and keep the stopwatch running.

If the examinee does not complete the task at the end of 180 seconds, say, **Stop.** Indicate the last item attempted and record 180 seconds as the total completion time. Items to which the examinee did not respond because the time limit was reached are not counted as errors.

			red(b)	blue(r)	green(r)	blue(r)	green(b)		
			blue(g)	red(g)	blue(g)	green(r)	blue(r)		
red(g)	blue(g)	red(g)	green(b)	red(b)	green(r)	blue(r)	green(r)	green(r)	blue(r)
red(b)	blue(r)	green(r)	red(g)	blue(g)	red(g)	green(b)	red(b)	green(r)	blue(r)
green(b)	blue(r)	green(r)	red(g)	blue(r)	green(r)	green(b)	red(b)	green(b)	red(b)
red(b)	green(b)	red(b)	green(b)	red(g)	blue(r)	green(r)	blue(r)	blue(g)	red(g)
green(r)	red(g)	blue(r)	red(b)	green(b)	red(b)	blue(r)	green(r)	blue(g)	red(g)

Condition 4: Inhibition/Switching

Total Uncorrected Errors	Total Self-Corrected Errors	Total Time To Complete

Color

D-KEFS Color-Word Interference Test: Summary of Scores

Primary Measures: Completion Times

Condition 1: Color Naming	Condition 2: Word Reading	Condition 3: Inhibition	Condition 4: Inhibition/Switching
Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score	Raw Score → Scaled Score

Primary Combined Measure: Completion Times

	Condition 1: Color Naming		Condition 2: Word Reading		Sum of Scaled Scores		Composite Scaled Score
Combined Naming + Reading	Scaled Score	+	Scaled Score	=		→	

Primary Contrast Measures: Completion Times

	Scaled Score		Scaled Score		Scaled-Score Difference		Contrast Scaled Score*
	Inhibition		Color Naming				
Inhibition vs. Color Naming*		–		=		→	
	Inhibition/Switching		Combined Naming + Reading				
Inhibition/Switching vs. Combined Naming + Reading*		–	Composite	=		→	
	Inhibition/Switching		Inhibition				
Inhibition/Switching vs. Inhibition*		–		=		→	

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Contrast Measures: Completion Times

	Inhibition/Switching: Scaled Score		Scaled Score		Scaled-Score Difference		Contrast Scaled Score*
			Color Naming				
Inhibition/Switching vs. Color Naming*		–		=		→	
			Word Reading				
Inhibition/Switching vs. Word Reading*		–		=		→	

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Measures: Error Analysis

	Condition 1: Color Naming	Condition 2: Word Reading	Condition 3: Inhibition	Condition 4: Inhibition/Switching
Corrected Errors	Raw Score	Raw Score	Raw Score, Cumulative Percentile Rank	Raw Score, Cumulative Percentile Rank
+	+	+	+	+
Uncorrected Errors	Raw Score	Raw Score	Raw Score, Cumulative Percentile Rank	Raw Score, Cumulative Percentile Rank
↓	↓	↓	↓	↓
Total Errors	Raw Score, Cumulative Percentile Rank	Raw Score, Cumulative Percentile Rank	Raw Score, Scaled Score	Raw Score, Scaled Score

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

D-KEFS Sorting Test

Screening Pretest

Words Incorrectly Read: _____ Raw Score: _____

Words Not Understood: _____ Raw Score: _____

Condition 1–Free Sorting: Card Set 1

Discontinue administration of Card Set 1 after either (a) the examinee indicates that he or she cannot identify any more sorts, even after receiving the single prompt to keep trying; (b) 240 seconds (4 minutes) of cumulative ***sorting*** time have elapsed; or (c) the examinee has completed 10 attempted sorts.

First Sort

Description:

Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Animals Transportation	Air Land	1 Syllable 2 Syllables

Verbal Sorts

Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Second Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Animals Transportation	Air Land	1 Syllable 2 Syllables

Verbal Sorts

Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Third Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Animals Transportation	Air Land	1 Syllable 2 Syllables

Verbal Sorts

Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

Perceptual Sorts

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Fourth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals Transportation	Air Land	1 Syllable 2 Syllables	Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Fifth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals Transportation	Air Land	1 Syllable 2 Syllables	Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Sixth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals Transportation	Air Land	1 Syllable 2 Syllables	Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Seventh Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Animals Transportation	Air Land	1 Syllable 2 Syllables	Large Small	Curved Straight	Uppercase Lowercase	Blue Yellow	White Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Eighth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Ninth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Tenth Sort

Description:

Cumulative Sorting Time (Seconds) ☐

Sort:

Verbal Sorts			Perceptual Sorts				
Animals / Transportation	Air / Land	1 Syllable / 2 Syllables	Large / Small	Curved / Straight	Uppercase / Lowercase	Blue / Yellow	White / Red

For an ***incorrect*** sort, mark the cards of one group: Airplane Bus Car Duck Eagle Tiger

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 1

Raw Score

Total Description Score ☐

Number of Confirmed Correct Sorts ☐

Condition 1–Free Sorting: Card Set 2

Discontinue administration of Card Set 2 after either (a) the examinee indicates that he or she cannot identify any more sorts, even after receiving the single prompt to keep trying; (b) 240 seconds (4 minutes) of cumulative ***sorting*** time have elapsed; or (c) the examinee has completed 10 attempted sorts.

First Sort

Description:

Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Second Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Third Sort

Description:

Cumulative Sorting Time (Seconds) ☐

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 2 *(continued)*

Fourth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Fifth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Sixth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Seventh Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Verbal Sorts			Perceptual Sorts				
Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Eighth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Ninth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Tenth Sort

Description:

Cumulative Sorting Time (Seconds)

Sort:

Clothing Body Parts	Head Feet	Plural Singular	Filled Triangles Empty Triangles	Cursive Printed	Slope Up Slope Down	Triangles Above Triangles Below	Diagonals Close Diagonals Apart
Verbal Sorts			**Perceptual Sorts**				

For an ***incorrect*** sort, mark the cards of one group: Ears Hat Mouth Shoe Socks Toes

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

PRIMARY SORTING MEASURE	
Confirmed Correct Sort	Y
OPTIONAL SORTING MEASURES	
Repeated Sort	Y
Unconfirmed Target Sort	Y
Set-Loss Sort	Y
Nontarget Even Sort	Y
Sort Type	V P

Free Sorting: Card Set 2

Raw Score

Total Description Score

Number of Confirmed Correct Sorts

Condition 2–Sort Recognition: Card Set 1

Administer all eight target sorts to the examinee. Discontinue administration of ***each sort*** after either (a) the examinee provides a correct or incorrect description, (b) the examinee indicates that he or she cannot identify the sorting rules, or (c) 45 seconds have elapsed after the examiner made the sort and the examinee failed to initiate a description response.

First Sort — Perceptual Sort

RULE

Small Cards	Large Cards
(Bus Car Eagle)	*(Airplane Duck Tiger)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Second Sort — Verbal Sort

RULE

Animals	Transportation
(Duck Eagle Tiger)	*(Airplane Bus Car)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Third Sort — Perceptual Sort

RULE

Straight Outer Edges	Curved Outer Edges
(Airplane Bus Tiger)	*(Car Duck Eagle)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Fourth Sort — Verbal Sort

RULE

One-Syllable Words	Two-Syllable Words
(Bus Car Duck)	*(Airplane Eagle Tiger)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Fifth Sort — Perceptual Sort

RULE

Blue Cards	Yellow Cards
(Bus Duck Tiger)	*(Airplane Car Eagle)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sixth Sort — Verbal Sort

RULE

Air *(Airplane Duck Eagle)* | Land *(Bus Car Tiger)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Seventh Sort — Perceptual Sort

RULE

Red Label *(Airplane Bus Duck)* | White Label *(Car Eagle Tiger)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Eighth Sort — Perceptual Sort

RULE

Uppercase Letters *(Bus Duck Eagle)* | Lowercase Letters *(Airplane Car Tiger)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort Recognition: Card Set 1

Raw Score

Total Description Score ☐

Condition 2–Sort Recognition: Card Set 2

Administer all eight target sorts to the examinee. Discontinue administration of ***each sort*** after either (a) the examinee provides a correct or incorrect description, (b) the examinee indicates that he or she cannot identify the sorting rules, or (c) 45 seconds have elapsed after the examiner made the sort and the examinee failed to initiate a description response.

First Sort — Perceptual Sort

RULE

Diagonals Close *(Ears Shoe Socks)* | Diagonals Apart *(Hat Mouth Toes)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Second Sort — Verbal Sort

RULE

Body Parts *(Ears Mouth Toes)* | Clothing *(Hat Shoe Socks)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Third Sort — Perceptual Sort

RULE

Triangles Above Word *(Ears Mouth Socks)* | Triangles Below Word *(Hat Shoe Toes)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Fourth Sort — Perceptual Sort

RULE

Cursive Letters *(Ears Hat Toes)* | Printed Letters *(Mouth Shoe Socks)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Fifth Sort — Verbal Sort

RULE

Plural Words *(Ears Socks Toes)* | Singular Words *(Mouth Shoe Hat)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort Recognition: Card Set 2 *(continued)*

Sixth Sort — Perceptual Sort

RULE

Diagonals Slope Up	Diagonals Slope Down
(Ears Hat Shoe)	*(Mouth Socks Toes)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Seventh Sort — Verbal Sort

RULE

Related to Head	Related to Feet
(Ears Hat Mouth)	*(Shoe Socks Toes)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Eighth Sort — Perceptual Sort

RULE

Filled Triangles	Empty Triangles
(Ears Mouth Shoe)	*(Hat Socks Toes)*

Description:

PRIMARY DESCRIPTION MEASURES	
1st Group Description Score	0 1 2
2nd Group Description Score	0 1 2
OPTIONAL DESCRIPTION MEASURES	
Incorrect Description	Y
Repeated Description	Y
No/Don't Know Response	Y
Noncredit Description	Y
Overly Abstract Description	Y
Description Type	V P

Sort Recognition: Card Set 2

Raw Score

Total Description Score ☐

276624-3 / 10 / 10 /

D-KEFS Sorting Test: Summary of Scores

Primary Measures

	Card Set 1	+	Card Set 2	=	Raw Score	Scaled Score
Condition 1: Free Sorting						
Confirmed Correct Sorts	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐
Free Sorting Description Score	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐
Condition 2: Sort Recognition						
Sort Recognition Description Score	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐

Combined Conditions 1 + 2

	Condition 1: Free Sorting Description Score	+	Condition 2: Sort Recognition Description Score	=	Sum of Scaled Scores	Composite Scaled Score
Combined Description Score	☐ Scaled Score	+	☐ Scaled Score	=	☐ →	☐

Contrast Measure: Sort Recognition Versus Free Sorting Description Score

	Condition 2: Sort Recognition Description Score	−	Condition 1: Free Sorting Description Score	=	Scaled-Score Difference	Contrast Scaled Score*
	☐ Scaled Score	−	☐ Scaled Score	=	☐ →	☐

* A low or high contrast scaled score may reflect different cognitive problems; see examiner's manual.

Optional Measures

Screening Pretest

	Raw Score	Cumulative Percentile Rank
Word Reading Errors	☐ →	☐
Word Comprehension Errors	☐ →	☐

Optional Measures *(continued)*

Condition 1: Free Sorting Sorting Measures (Optional)

Confirmed Correct Sorts: Card Set 1 — Raw Score ☐ → ☐ **Scaled Score**

Confirmed Correct Sorts: Card Set 2 — Raw Score ☐ → ☐ **Scaled Score**

	Card Set 1	+	Card Set 2	=	Total Raw Score	Scaled Score
Confirmed Correct Verbal Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐
Confirmed Correct Perceptual Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐
Confirmed/Unconfirmed Target Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐
Repeated Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐
Set-Loss Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐ **Cumulative Percentile Rank**
Nontarget Even Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐ **Cumulative Percentile Rank**
Attempted Sorts	____ Raw Score	+	____ Raw Score	=	☐	→ ☐

Percent Sorting Accuracy

$$\left[\frac{\text{Confirmed Correct Sorts (Total Raw Score)}}{\text{Attempted Sorts (Total Raw Score)}}\right] \times 100 = \text{Percent Raw Score} \rightarrow$$

Time-Per-Sort Ratio**

$$\frac{\text{Cumulative Sorting Time Cards Sets 1 + 2 (Total Raw Score)}}{\text{Attempted Sorts (Total Raw Score)}} = \text{Ratio Raw Score} \rightarrow$$

Condition 1: Free Sorting Description Measures (Optional)

	Raw Score	Scaled Score
Free Sorting Description Score: Card Set 1	☐	→ ☐
Free Sorting Description Score: Card Set 2	☐	→ ☐

	Card Set 1	+	Card Set 2	=	Total Raw Score	
Free Sorting Incorrect Descriptions*	____ Raw Score	+	____ Raw Score	=	☐	→ ☐
Free Sorting Repeated Descriptions*	____ Raw Score	+	____ Raw Score	=	☐	→ ☐ **Cumulative Percentile Rank**

Percent Description Accuracy

$$\left[\frac{\text{Free Sorting Description Score}}{\text{Total Raw Score}} \div \left[\text{Attempted Sorts (Total Raw Score)} \times 4\right]\right] \times 100 = \text{Percent Raw Score} \rightarrow$$

* No/Don't Know responses are not included in these measures.

** A low or high ratio scaled score may reflect different cognitive problems; see examiner's manual.

276624-3 / 9 / 10 /

Optional Measures *(continued)*

Condition 2: Sort Recognition Description Measures (Optional)

	Raw Score		Scaled Score
Sort Recognition Description Score: Card Set 1	☐	→	☐
Sort Recognition Description Score: Card Set 2	☐	→	☐

	Card Set 1	+	Card Set 2	=	Total Raw Score
Sort Recognition Incorrect Descriptions*	_____ Raw Score	+	_____ Raw Score	=	☐ → ☐
Sort Recognition Repeated Descriptions*	_____ Raw Score	+	_____ Raw Score	=	☐ → ☐ Cumulative Percentile Rank

Combined Conditions 1 + 2: Description Measures (Optional)

	Condition 1: Free Sorting Total	+	Condition 2: Sort Recognition Total	=	Combined Raw Score	Scaled Score
Combined Description Score: Verbal Rules	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐
Combined Description Score: Perceptual Rules	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐
Combined No/Don't Know Responses	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐
Combined Noncredit Descriptions	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐ Cumulative Percentile Rank
Combined Overly Abstract Descriptions	_____ Raw Score	+	_____ Raw Score	=	☐ →	☐ Cumulative Percentile Rank

	Condition 1: Free Sorting Incorrect Descriptions	+	Condition 2: Sort Recognition Incorrect Descriptions	=	Sum of Scaled Scores	Composite Scaled Score
Combined Incorrect Descriptions*	☐ Scaled Score	+	☐ Scaled Score	=	☐ →	☐
	Repeated Descriptions		**Repeated Descriptions**		**Total Raw Score**	
Combined Repeated Descriptions*	☐ Raw Score	+	☐ Raw Score	=	☐ →	☐ Cumulative Percentile Rank

* No/Don't Know responses are not included in these measures

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

D-KEFS Twenty Questions Test

Ages 8–89

Materials

Record Form

Stimulus Booklet (Flat Position)

Discontinue

Do not discontinue. Administer all four items to examinees in the order in which they appear here. Discontinue each item after the examinee either has identified the target object or has asked 20 yes/no questions without identifying the target object. Do not reveal the target object if the examinee has failed to identify it after asking 20 questions.

Administration and Recording

Position the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee's midline, with the pictures facing the examinee.

Say,

> **Now we are going to do something where you ask *me* questions. I have picked *one* of these pictures, and I want you to figure out which one it is by asking me questions. You can only ask questions that I can answer yes or no. You can ask any question at all, as long as I can answer it yes or no. Try to guess the picture that I have picked with the fewest number of questions you can. I'm going to write down your questions so I can remember them. Go ahead and ask me the fewest number of yes/no questions you can to figure out which picture I have selected.**

Record verbatim each of the examinee's questions in the order that they are asked. Answer **Yes** if the examinee's question encompasses or identifies the target item or **No** if it does not. Circle *Y* (for yes) or *N* (for no) to indicate your answer to each of the examinee's questions.

Whether or not the examinee correctly identifies the target object for Item 1 after asking 20 yes/no questions or fewer, say,

> **Good. Let's try the next one. I've picked a new picture, and I want you to ask me the fewest number of yes/no questions you can to figure out which one it is. Go ahead.**

Repeat these administration and recording procedures for each of Items 2–4.

COMMON PROMPTS

- If an examinee's first question for an item refers only to one object (e.g.,"Is it the elephant?"), record and answer the question. Then say, **Remember, try to ask the fewest number of questions you can.** Provide this prompt only once for each item.
- When answering questions, respond only with yes or no as much as possible. In deciding how to answer, base your response on how most people would respond to the same question. If the question could possibly be answered either way, you may say, **Most people would say yes** or **Most people would say no.** If an answer is true or untrue for an item most of the time, you may say, **Usually yes** or **Usually no.**
- If you do not know the answer to an examinee's question, say, **That's an excellent question. I'm not sure I know the answer. Try another question.** Do not count this question as one of the 20 questions.
- If an examinee asks a compound question (e.g., "Is it red and a plant?"), record the response and say, **I can answer only one of those questions. Which one do you want me to answer?** If the examinee asks an either/or question (e.g., "Is it an animal or a fruit?"), ask him or her to rephrase it as a yes/no question. After these prompts, if the examinee provides a yes/no question that clarifies the compound or either/or question, consider both responses as representing one yes/no question.
- If you are unsure of how to answer a spatial question, say, **Show me the ones you mean.** Pointing to the target object is an acceptable correct response.
- Some common types of questions ("Is it living?" or "Is it dead?") can be difficult to answer yes or no for some target items. If the object is organic or natural, say, **Yes, it is or once was living.** If the object is inorganic or human-made, say, **No, it never was alive.**
- If the examinee's question is vague (e.g., "Is it big?"), say, **Could you make your question more specific?** Consider both the vague question and any additional specific question as representing only one question.
- If an examinee fails to identify the target object after 20 questions but wants to know which one it is, say, **I can't tell you, but try to guess the next one.**

SPECIAL CONSIDERATIONS

- If an examinee has difficulty perceiving an object on the stimulus page because of visual problems and asks for clarification (e.g., "Is that a fork?"), record and answer the question; however, do not score or count it as one of the 20 questions allowed for that item.
- An examinee may have difficulty remembering previously asked questions, your yes/no answers to those questions, or both, and request that the information be repeated. You may provide such information as often as it is requested.
- If an examinee points to the correct target object but misnames it, the response is still considered correct.

276624-3 / 8 / 10 /

D-KEFS Twenty Questions Test

Discontinue each item after the examinee asks 20 questions without identifying the target object.

Total Questions Asked (Circle One)	Item 1 (banana)	Examiner's Answer	Weighted Achievement Score (Circle One)
1		Y N	1
2		Y N	1
3		Y N	2
4		Y N	5
5		Y N	5
6		Y N	4
7		Y N	4
8		Y N	3
9		Y N	3
10		Y N	3
11		Y N	2
12		Y N	2
13		Y N	2
14		Y N	2
15		Y N	1
16		Y N	1
17		Y N	1
18		Y N	1
19		Y N	1
20		Y N	1
21	← Failed to guess in 20 questions →		0

Total Questions Asked (Circle One)	Item 2 (spoon)	Examiner's Answer	Weighted Achievement Score (Circle One)
1		Y N	1
2		Y N	1
3		Y N	2
4		Y N	5
5		Y N	5
6		Y N	4
7		Y N	4
8		Y N	3
9		Y N	3
10		Y N	3
11		Y N	2
12		Y N	2
13		Y N	2
14		Y N	2
15		Y N	1
16		Y N	1
17		Y N	1
18		Y N	1
19		Y N	1
20		Y N	1
21	← Failed to guess in 20 questions →		0

	Raw Score
Initial Abstraction Score*	
Optional Scores:	
# Spatial Questions	
# Repeated Questions	
# Set-Loss Questions	

Item 1: Total Questions Asked Max. = 21

Item 1: Weighted Achievement Score Max. = 5

Item 2: Total Questions Asked Max. = 21

	Raw Score
Initial Abstraction Score*	
Optional Scores:	
# Spatial Questions	
# Repeated Questions	
# Set-Loss Questions	

Item 2: Weighted Achievement Score Max. = 5

* Minimum number of objects eliminated by the first question asked regardless of the yes or no answer.

D-KEFS Twenty Questions Test *(continued)*

Discontinue each item after the examinee asks 20 questions without identifying the target object.

Total Questions Asked (Circle One)	Item 3 (owl)	Examiner's Answer	Weighted Achievement Score (Circle One)
1		Y N	1
2		Y N	1
3		Y N	2
4		Y N	5
5		Y N	5
6		Y N	4
7		Y N	4
8		Y N	3
9		Y N	3
10		Y N	3
11		Y N	2
12		Y N	2
13		Y N	2
14		Y N	2
15		Y N	1
16		Y N	1
17		Y N	1
18		Y N	1
19		Y N	1
20		Y N	1
21	← Failed to guess in 20 questions →		0

Total Questions Asked (Circle One)	Item 4 (helicopter)	Examiner's Answer	Weighted Achievement Score (Circle One)
1		Y N	1
2		Y N	1
3		Y N	2
4		Y N	5
5		Y N	5
6		Y N	4
7		Y N	4
8		Y N	3
9		Y N	3
10		Y N	3
11		Y N	2
12		Y N	2
13		Y N	2
14		Y N	2
15		Y N	1
16		Y N	1
17		Y N	1
18		Y N	1
19		Y N	1
20		Y N	1
21	← Failed to guess in 20 questions →		0

	Raw Score
Initial Abstraction Score*	
Optional Scores:	
# Spatial Questions	
# Repeated Questions	
# Set-Loss Questions	

Item 3: Total Questions Asked Max. = 21

Item 3: Weighted Achievement Score Max. = 5

Item 4: Total Questions Asked Max. = 21

	Raw Score
Initial Abstraction Score*	
Optional Scores:	
# Spatial Questions	
# Repeated Questions	
# Set-Loss Questions	

Item 4: Weighted Achievement Score Max. = 5

* Minimum number of objects eliminated by the first question asked regardless of the yes or no answer.

276624-3/7/10/

D-KEFS Twenty Questions Test: Summary of Scores

Primary Measures

	Item 1 Raw Score		Item 2 Raw Score		Item 3 Raw Score		Item 4 Raw Score		Total Raw Score	Scaled Score
Initial Abstraction Score*		+		+		+		=		
Total Questions Asked		+		+		+		=		
Total Weighted Achievement Score		+		+		+		=		

* Minimum number of objects eliminated by the first question asked regardless of the yes or no answer.

Optional Measures

	Item 1 Raw Score		Item 2 Raw Score		Item 3 Raw Score		Item 4 Raw Score		Total Raw Score	Cumulative Percentile Rank
Spatial Questions		+		+		+		=		
Repeated Questions		+		+		+		=		
Set-Loss Questions		+		+		+		=		

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

D-KEFS Word Context Test

Do not discontinue. Administer all items in the order presented here and in the stimulus booklet.

Practice Item: sev (apple)

Examinee's Responses:

1. _____
2. _____
3. _____
4. _____
5. _____

1. prifa (eat)

Examinee's Responses:

1. _____
2. _____
3. _____
4. _____
5. _____

Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
Y N	5	5
Y N	4	4
Y N	3	3
Y N	2	2
Y N	1	1

Optional:
Repeated Incorrect
Raw Score
No/DK Responses
Raw Score
Correct-To-Incorrect
Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

2. enton (dance)

Examinee's Responses:

1. _____
2. _____
3. _____
4. _____
5. _____

Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
Y N	5	5
Y N	4	4
Y N	3	3
Y N	2	2
Y N	1	1

Optional:
Repeated Incorrect
Raw Score
No/DK Responses
Raw Score
Correct-To-Incorrect
Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

2700247 / 0 / 10 /

D-KEFS Word Context Test *(continued)*

3. delz (voice)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
1. _____	Y N	5	5
2. _____	Y N	4	4
3. _____	Y N	3	3
4. _____	Y N	2	2
5. _____	Y N	1	1

Optional:
Repeated Incorrect: ____ Raw Score
No/DK Responses: ____ Raw Score
Correct-To-Incorrect: ____ Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

4. vern (horse)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
1. _____	Y N	5	5
2. _____	Y N	4	4
3. _____	Y N	3	3
4. _____	Y N	2	2
5. _____	Y N	1	1

Optional:
Repeated Incorrect: ____ Raw Score
No/DK Responses: ____ Raw Score
Correct-To-Incorrect: ____ Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

5. nelzen (make)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
1. _____	Y N	5	5
2. _____	Y N	4	4
3. _____	Y N	3	3
4. _____	Y N	2	2
5. _____	Y N	1	1

Optional:
Repeated Incorrect: ____ Raw Score
No/DK Responses: ____ Raw Score
Correct-To-Incorrect: ____ Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

6. gesh (fill)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)	Optional: # Repeated Incorrect
1. _____	Y N	5	5	Raw Score
2. _____	Y N	4	4	# No/DK Responses
3. _____	Y N	3	3	Raw Score
4. _____	Y N	2	2	# Correct-To-Incorrect
5. _____	Y N	1	1	Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

7. luri (motor, engine)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Cricle One)	1st Sentence Consecutively Correct (Circle One)	Optional: # Repeated Incorrect
1. _____	Y N	5	5	Raw Score
2. _____	Y N	4	4	# No/DK Responses
3. _____	Y N	3	3	Raw Score
4. _____	Y N	2	2	# Correct-To-Incorrect
5. _____	Y N	1	1	Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

8. krame (tooth, teeth)

Examinee's Responses:

	Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)	Optional: # Repeated Incorrect
1. _____	Y N	5	5	Raw Score
2. _____	Y N	4	4	# No/DK Responses
3. _____	Y N	3	3	Raw Score
4. _____	Y N	2	2	# Correct-To-Incorrect
5. _____	Y N	1	1	Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

276624-3 / 5 / 10 /

9. kapla (word)

Examinee's Responses:

1. _____
2. _____
3. _____
4. _____
5. _____

Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
Y N	5	5
Y N	4	4
Y N	3	3
Y N	2	2
Y N	1	1

Optional:
Repeated Incorrect ____ Raw Score
No/DK Responses ____ Raw Score
Correct-To-Incorrect ____ Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

10. grot (curtain)

Examinee's Responses:

1. _____
2. _____
3. _____
4. _____
5. _____

Response Correct	1st Sentence Correct (Circle One)	1st Sentence Consecutively Correct (Circle One)
Y N	5	5
Y N	4	4
Y N	3	3
Y N	2	2
Y N	1	1

Optional:
Repeated Incorrect ____ Raw Score
No/DK Responses ____ Raw Score
Correct-To-Incorrect ____ Raw Score

Incorrect responses on all sentences: 0

Incorrect response on Sentence 5: 0

D–KEFS Word Context Test: Summary of Scores

Primary Measure

Total Consecutively Correct

[ ] Raw Score → [ ] **Scaled Score**

Optional Measures

Consistently Correct Ratio

[Total Consecutively Correct Score [ ] Raw Score ÷ Total First Sentence Correct Score [ ] Raw Score] × 100 = Percent Raw Score [ ] → **Scaled Score** [ ]

Repeated Incorrect Responses

[ ] Total Raw Score → [ ] **Scaled Score**

No/Don't Know Responses

[ ] Total Raw Score → [ ] **Cumulative Percentile Rank**

Total Correct-To-Incorrect Errors

[ ] Total Raw → [ ] **Cumulative Percentile Rank**

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

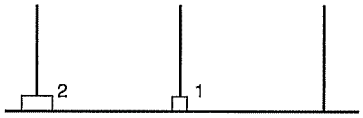
D-KEFS Tower Test

Discontinue after three consecutive item failures. Disk Labels: 1 = Smallest to 5 = Largest.

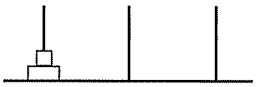
Item 1: Two Disks

Time Limit: 30"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 1)	# Rule Violations	Item Completion Time
			Correct Tower Y N

Demonstrate 1-move solution if examinee fails to solve item in 1 move.

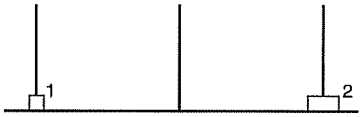
Achievement Score

	Correct Within Time Limit	
	>1 Moves	1 Move
Failed		
0	**1**	**2**

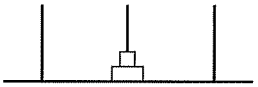
Item 2: Two Disks

Time Limit: 30"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 2)	# Rule Violations	Item Completion Time
			Correct Tower Y N

Demonstrate 2-move solution if examinee fails to solve item in 2 moves.

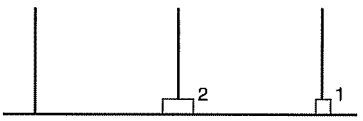
Achievement Score

	Correct Within Time Limit	
	>2 Moves	2 Moves
Failed		
0	**1**	**2**

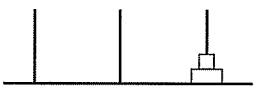
Item 3: Two Disks

Time Limit: 30"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 3)	# Rule Violations	Item Completion Time
			Correct Tower Y N

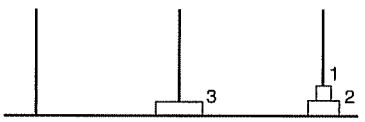
Achievement Score

	Correct Within Time Limit		
	>4 Moves	4 Moves	3 Moves
Failed			
0	**1**	**2**	**3**

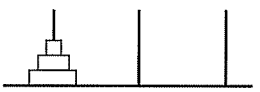
Item 4: Three Disks

Time Limit: 60"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 4)	# Rule Violations	Item Completion Time
			Correct Tower Y N

Achievement Score

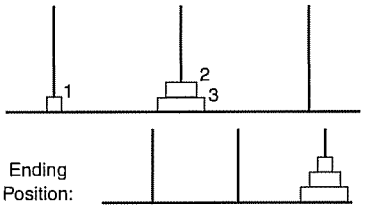
	Correct Within Time Limit		
	>5 Moves	5 Moves	4 Moves
Failed			
0	**1**	**2**	**3**

276624-3 / 4 / 10 /

Item 5: Three Disks

Time Limit: 120"

Starting Position (Examiner's View)



Ending Position:

1st Move Time	Total # Moves (Min. = 7)	# Rule Violations	Item Completion Time
			Correct Tower Y N

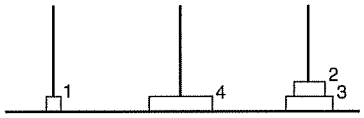
Achievement Score

Correct Within Time Limit				
Failed	>9 Moves	9 Moves	8 Moves	7 Moves
0	1	2	3	4

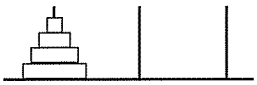
Item 6: Four Disks

Time Limit: 120"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 9)	# Rule Violations	Item Completion Time
			Correct Tower Y N

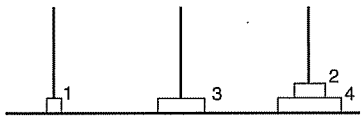
Achievement Score

Correct Within Time Limit				
Failed	>11 Moves	11 Moves	10 Moves	9 Moves
0	1	2	3	4

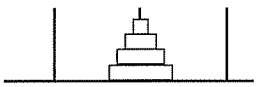
Item 7: Four Disks

Time Limit: 180"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 13)	# Rule Violations	Item Completion Time
			Correct Tower Y N

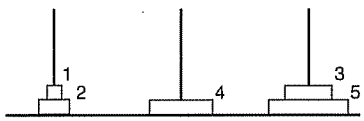
Achievement Score

Correct Within Time Limit				
Failed	>15 Moves	15 Moves	14 Moves	13 Moves
0	1	2	3	4

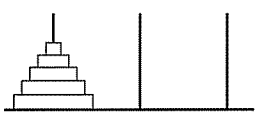
Item 8: Five Disks

Time Limit: 240"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 20)	# Rule Violations	Item Completion Time
			Correct Tower Y N

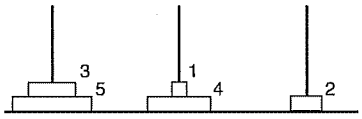
Achievement Score

Correct Within Time Limit				
Failed	>24 Moves	23–24 Moves	21–22 Moves	20 Moves
0	1	2	3	4

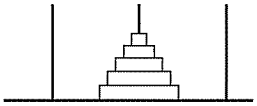
Item 9: Five Disks

Time Limit: 240"

Starting Position (Examiner's View)



Ending Position:



1st Move Time	Total # Moves (Min. = 26)	# Rule Violations	Item Completion Time
			Correct Tower Y N

Achievement Score

Correct Within Time Limit				
Failed	>32 Moves	30–32 Moves	27–29 Moves	26 Moves
0	1	2	3	4

D–KEFS Tower Test: Summary of Scores

Totals for Items Administered

Total # Items Administered	Total 1st-Move Time	Total # Moves	Total # Rule Violations	Total Item Completion Times	Total Achievement Score
☐	☐	☐	☐	☐	☐

Primary Measure

Total Achievement Score	☐ →	☐	
	Total Raw Score	**Scaled Score**	

Optional Measures

Mean First-Move Time*	Total 1st-Move Times ☐	÷	Total # Items Administered ☐	=	**Ratio Score** ☐ →	**Scaled Score** ☐
Time-Per-Move Ratio*	Total Item-Completion Times ☐	÷	Total # Moves ☐	=	**Ratio Score** ☐ →	**Scaled Score** ☐
Move Accuracy Ratio*	Total # Moves ☐	÷	Total # Minimum Moves ☐	=	**Ratio Score** ☐ →	**Scaled Score** ☐
Total Rule Violations	☐			→		☐
	Total Raw Score					**Cumulative Percentile Rank**
Rule-Violations-Per-Item Ratio	Total # Rule Violations ☐	÷	Total # Items Administered ☐	=	**Ratio Score** ☐ →	**Scaled Score** ☐

Total Cumulative Minimum Moves Possible

Number of Items Administered	Cumulative Minimum Moves Possible
1	1
2	3
3	6
4	10
5	17
6	26
7	39
8	59
9	85

Circle the cumulative minimum number of moves possible for the number of items administered to determine the total number of minimum moves.

* A low or high ratio scaled score on these measures may reflect different cognitive problems; see examiner's manual.

276824-3 / 3 / 10 /

D-KEFS Proverb Test

Do not discontinue.

		Condition 1: Free Inquiry (Circle Score)			Condition 2: Multiple Choice (Circle Letter Choice/Score)		
		Accuracy Score	+ Abstraction Score	Total Achievement Score (Score 0 if Accuracy = 0)	0 Points (Phon / Unrel)	2 Points	4 Points
Common Proverbs (Items 1–5)	1. You can't judge a book by its cover.	0 1 2	0 2		b a 0	d 2	***c*** *4*
	2. Don't count your chickens before they are hatched.	0 1 2	0 2		c b 0	d 2	***a*** *4*
	3. Rome wasn't built in a day.	0 1 2	0 2		a d 0	c 2	***b*** *4*
	4. Too many cooks spoil the soup.	0 1 2	0 2		d a 0	b 2	***c*** *4*
	5. People who live in glass houses shouldn't throw stones.	0 1 2	0 2		a c 0	b 2	***d*** *4*
Uncommon Proverbs (Items 6–8)	6. An old ox plows a straight row.	0 1 2	0 2		d c 0	a 2	***b*** *4*
	7. A small leak will sink a large ship.	0 1 2	0 2		b d 0	a 2	***c*** *4*
	8. No bread is without a crust.	0 1 2	0 2		d c 0	a 2	***b*** *4*
		Total Accuracy Score ▽	Total Abstraction Score ▽	Total Achievement Score ▽			Total Achievement Score ▽
		☐	☐	☐			☐
		Free Inquiry					**Multiple Choice**

D-KEFS Proverb Test: Summary of Scores

Primary Measures

	Total Raw Score		Scaled Score / Cumulative Percentile Rank
Total Achievement Score: Free Inquiry	☐	→	☐ Scaled Score
Total Achievement Score: Multiple Choice	☐	→	☐ Cumulative Percentile Rank

Optional Measures: Free Inquiry

	Total Raw Score		Scaled Score / Cumulative Percentile Rank
Common Proverb Achievement Score: Free Inquiry Items 1–5	☐	→	☐ Scaled Score
Uncommon Proverb Achievement Score: Free Inquiry Items 6–8	☐	→	☐ Scaled Score
Accuracy Only Score	☐	→	☐ Scaled Score
Abstraction Only Score	☐	→	☐ Scaled Score
No/Don't Know Responses	☐	→	☐ Cumulative Percentile Rank
Repeated Responses	☐	→	☐ Cumulative Percentile Rank

Optional Measures: Multiple Choice

	Total Raw Score		Cumulative Percentile Rank
Common Proverb Achievement Score: Multiple Choice Items 1–5	☐	→	☐ Cumulative Percentile Rank
Uncommon Proverb Achievement Score: Multiple Choice Items 6–8	☐	→	☐ Cumulative Percentile Rank
Total Correct Abstract Choices	☐	→	☐ Cumulative Percentile Rank
Total Correct Concrete Choices	☐	→	☐ Cumulative Percentile Rank
Total Incorrect Phonemic Choices	☐	→	☐ Cumulative Percentile Rank
Total Incorrect Unrelated Choices	☐	→	☐ Cumulative Percentile Rank
Total Incorrect Phonemic + Unrelated Choices	☐	→	☐ Cumulative Percentile Rank

Note: Cumulative percentile ranks for the D–KEFS were scaled to reflect the percentage of the normative sample that obtained raw scores equal to or worse than the raw score obtained by the examinee.

276624-3 / 2 / 10 /

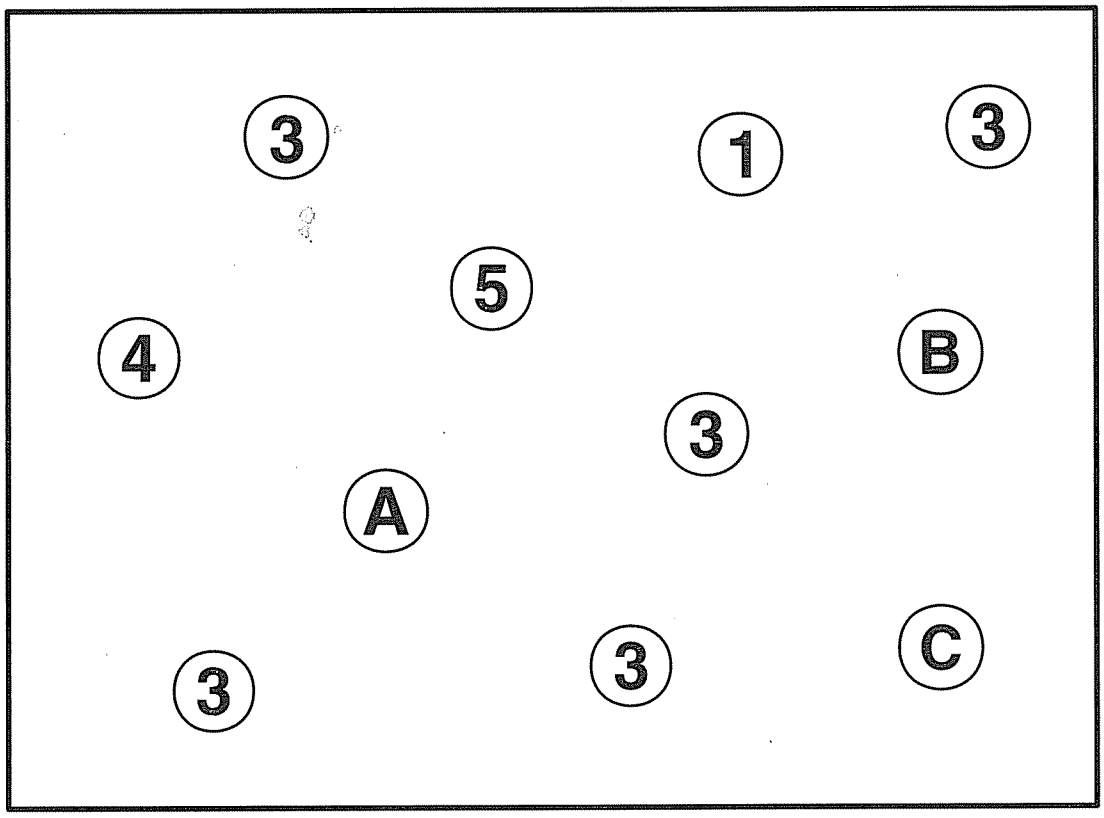
DELIS • KAPLAN
D-KEFS™
Executive Function System™

Name _____ Age _____
ID _____ Date _____
Examiner _____
Notes _____

Trail-Making Test

Condition 1
Visual Scanning

Practice

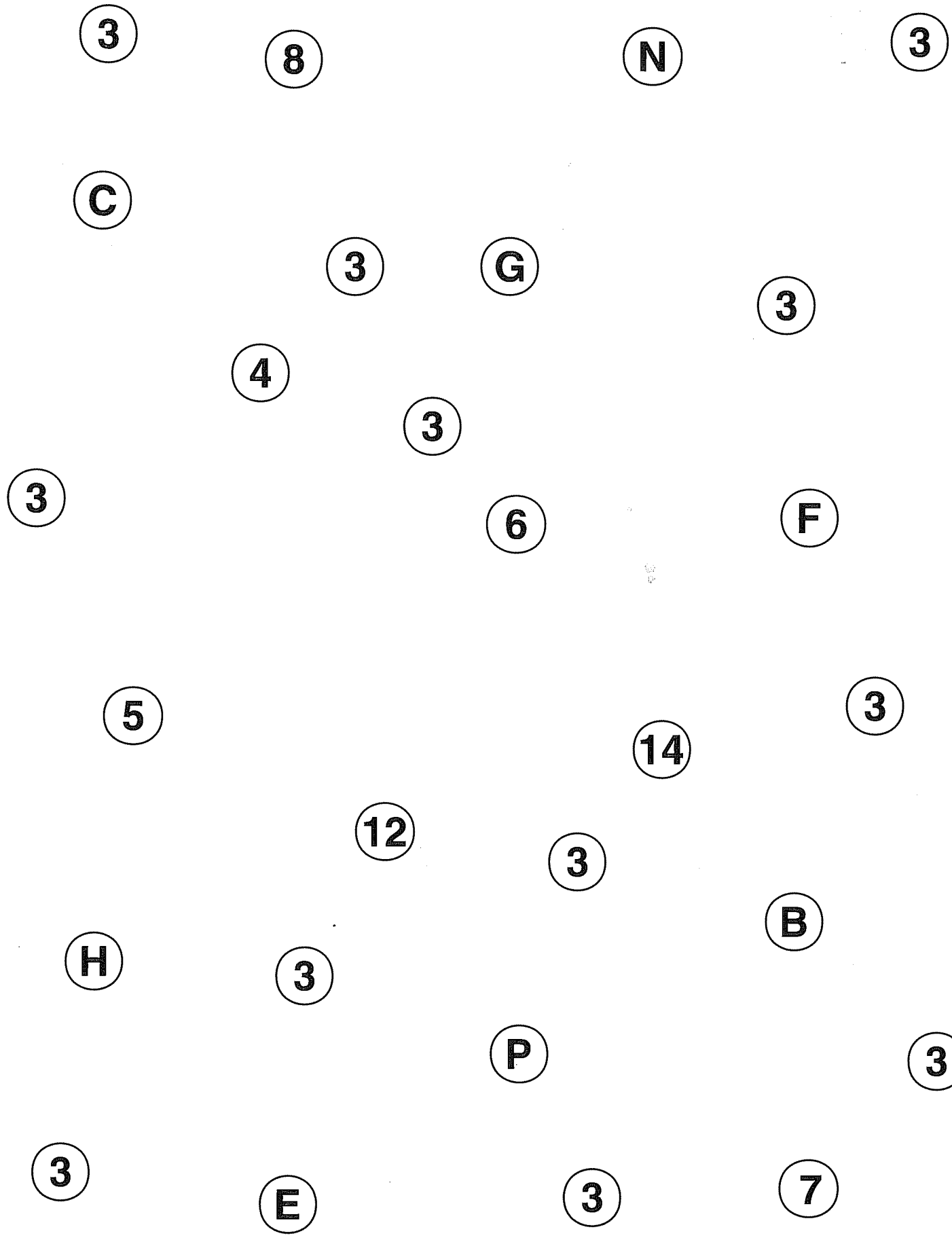


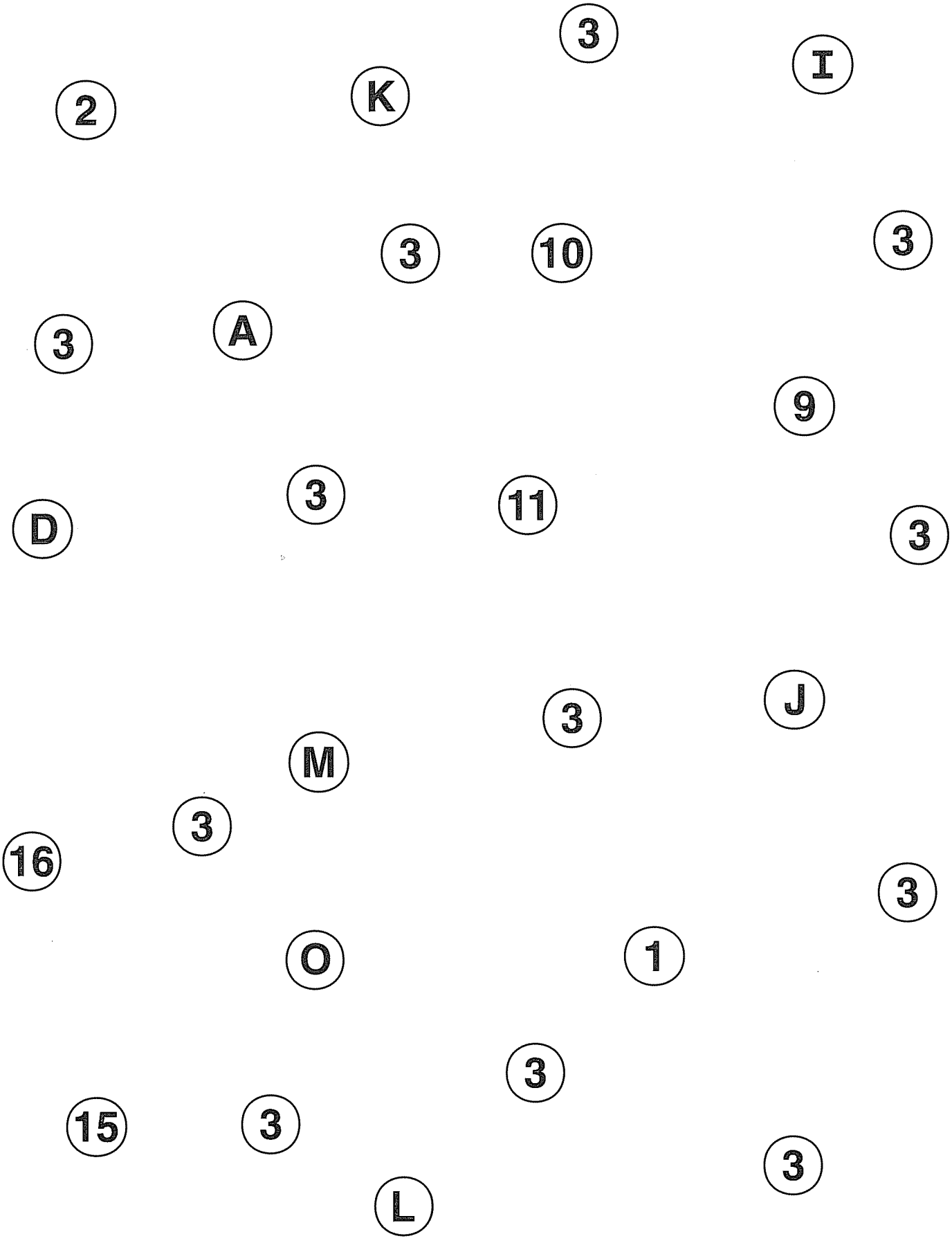
29 30 A B C D E

PEARSON

Copyright © 2001 by NCS Pearson, Inc. All rights reserved. Printed in the United States of America.

PsychCorp™


3
8
N
3
C
3
G
3
4
3
3
6
F
5
3
14
12
3
B
H
3
P
3
3
E
3
7


3
I
2
K
3
10
3
3
A
9
3
11
D
3
3
J
3
M
3
16
3
O
1
3
15
3
3
L

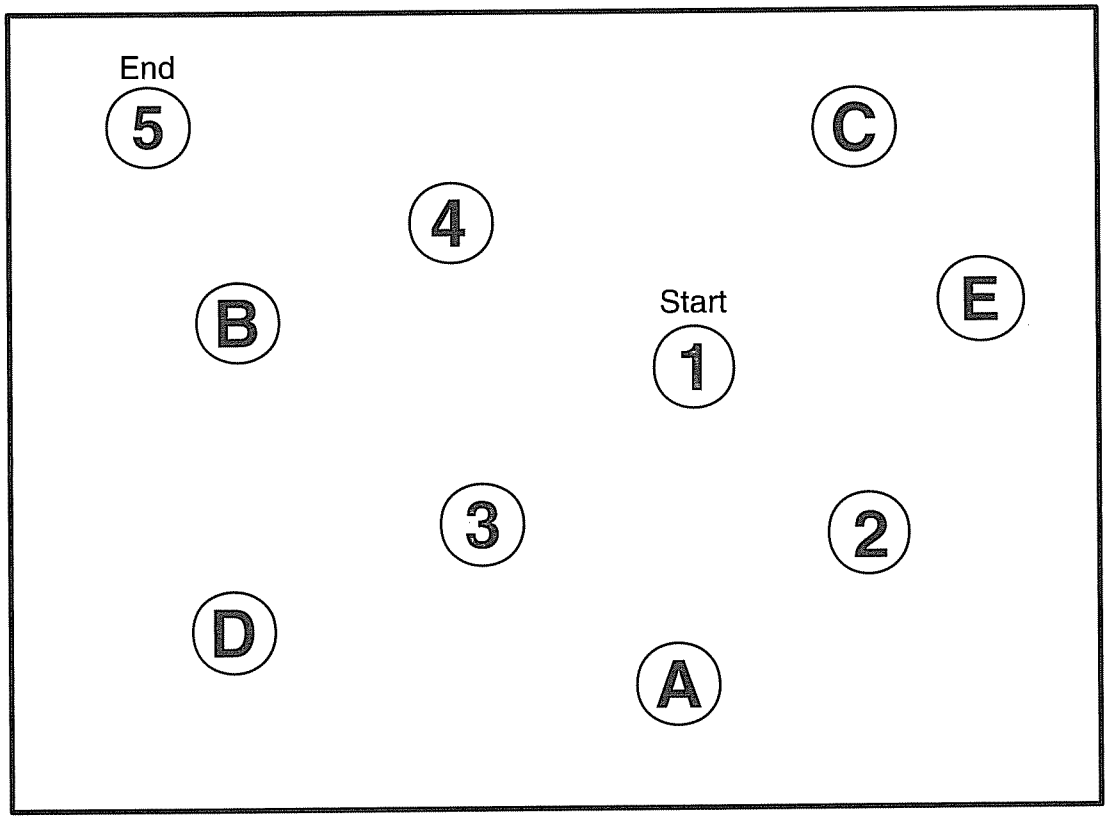
DELIS • KAPLAN
D-KEFS
Executive Function System™

Name _____ Age _____
ID _____ Date _____
Examiner _____
Notes _____

Trail Making Test

Condition 2
Number Sequencing

Practice

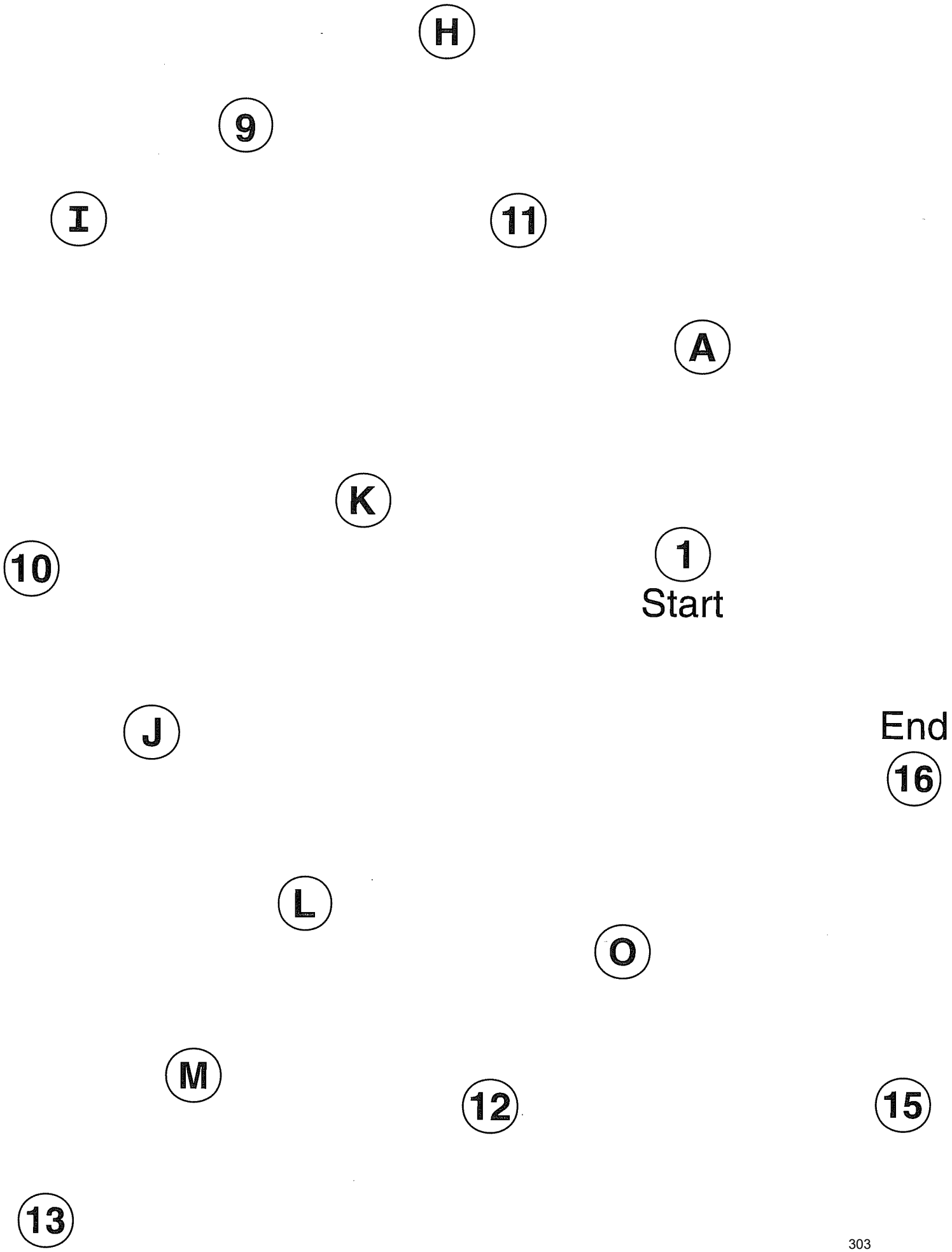


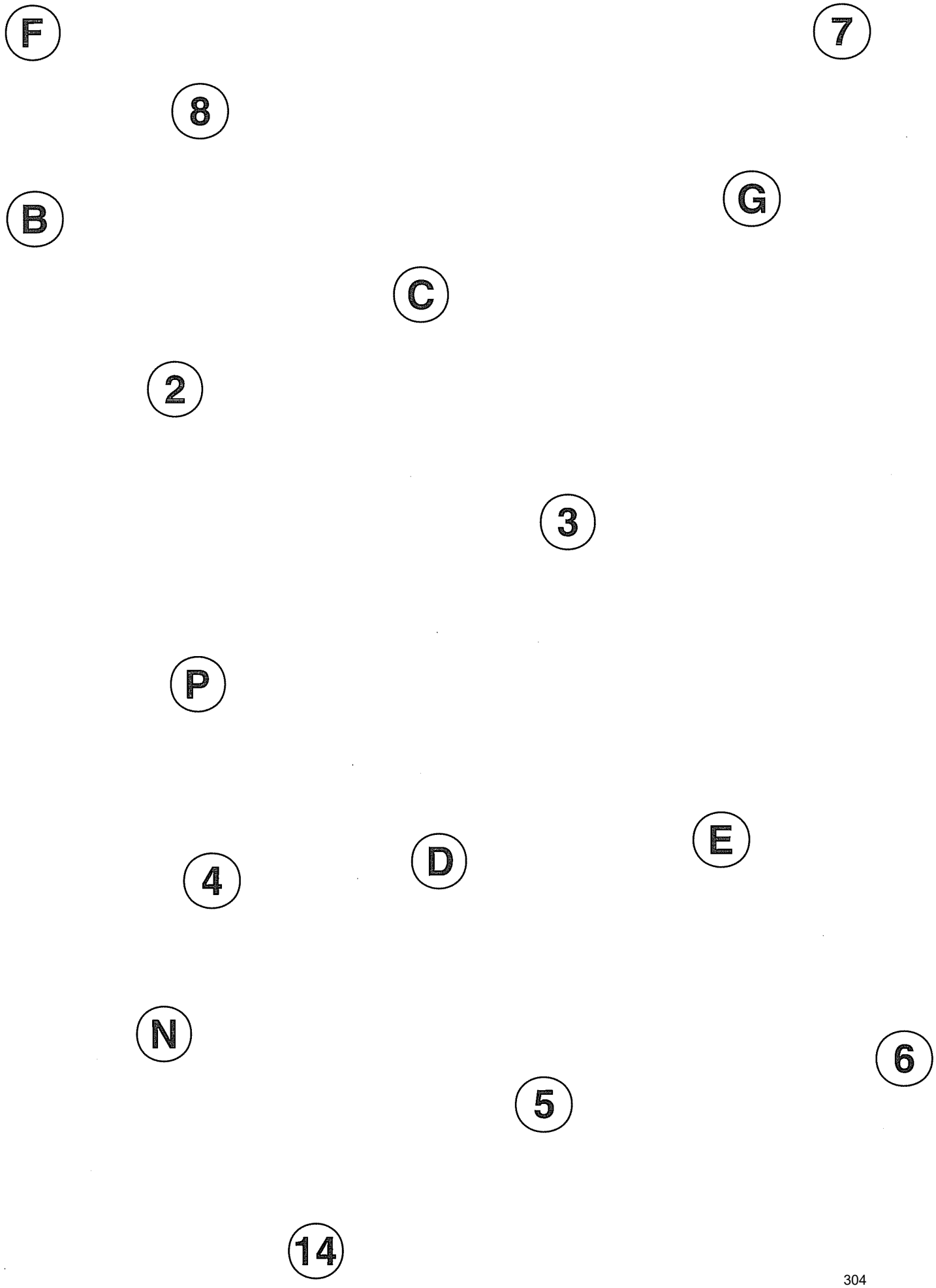
29 30 A B C D E

PEARSON

Copyright © 2001 by NCS Pearson, Inc. All rights reserved. Printed in the United States of America.

PsychCorp™


H
9
I
11
A
K
10
1
Start
J
End
16
L
O
M
12
15
13


F
7
8
G
B
C
2
3
P
E
D
4
N
6
5
14

DELIS • KAPLAN
D-KEFS™
Executive Function System™

Trail Making Test

Name _____ Age _____

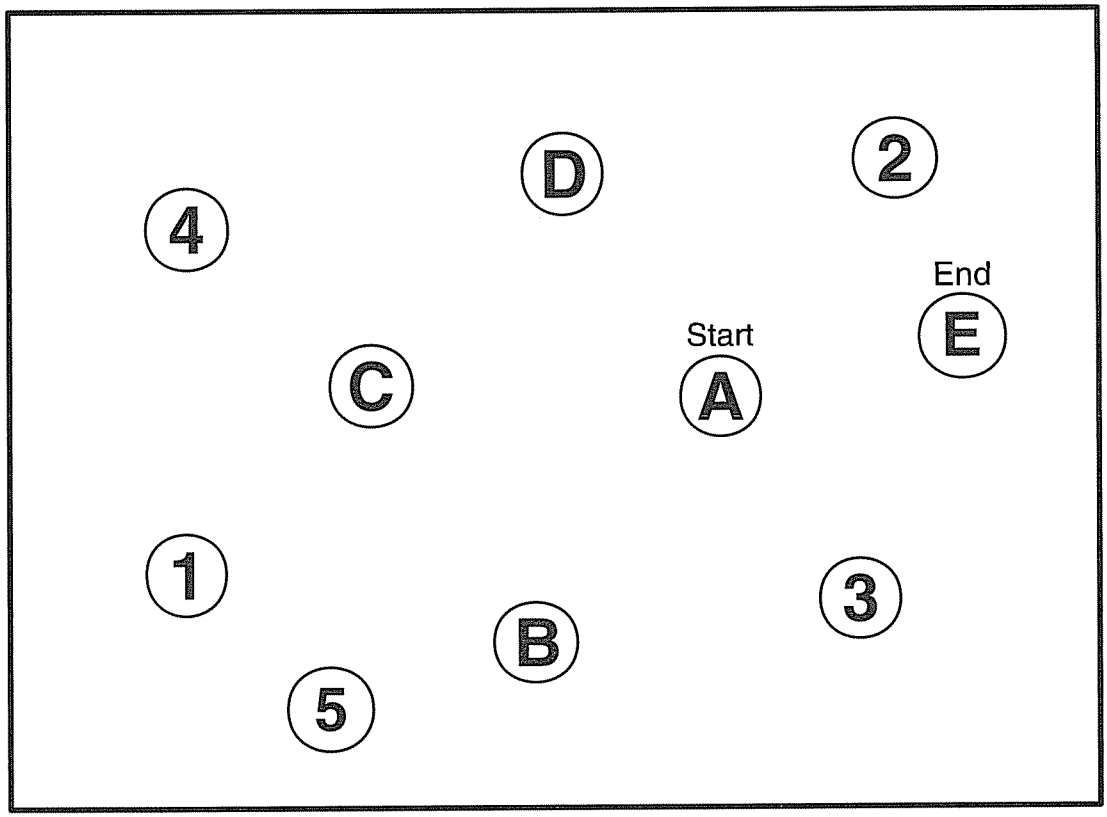
ID _____ Date _____

Examiner _____

Notes _____

Condition 3
Letter Sequencing

Practice

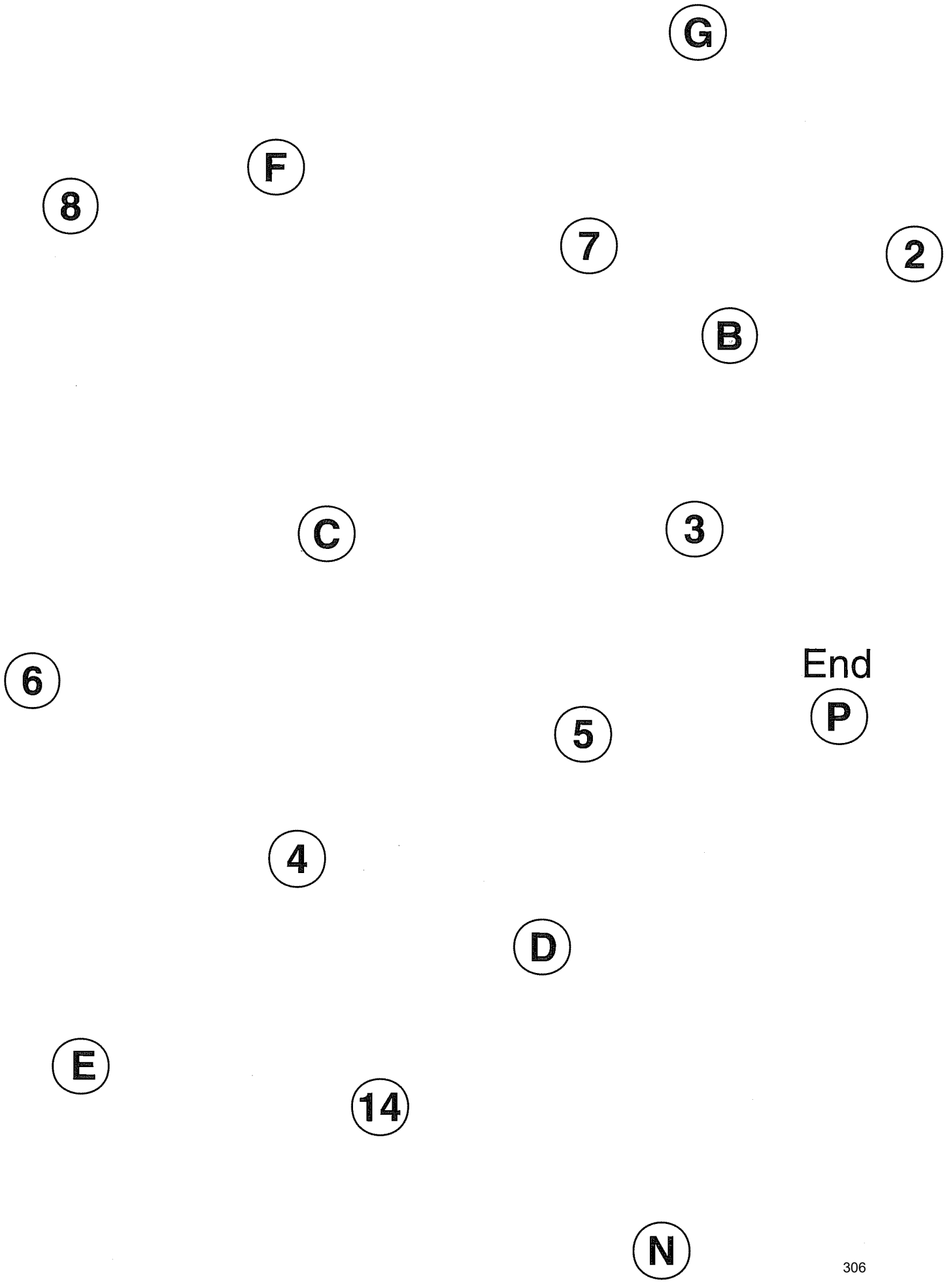


29 30 A B C D E

PEARSON

Copyright © 2001 by NCS Pearson, Inc. All rights reserved. Printed in the United States of America.

PsychCorp™


G
F
8
7
2
B
C
3
6
End
P
5
4
D
E
14
N


H
K
9
10
12
I
11
A
Start
J
1
13
16
O
15
L
M

DELIS • KAPLAN
D-KEFS™
Executive Function System™

Trail Making Test

Name _____ Age _____

ID _____ Date _____

Examiner _____

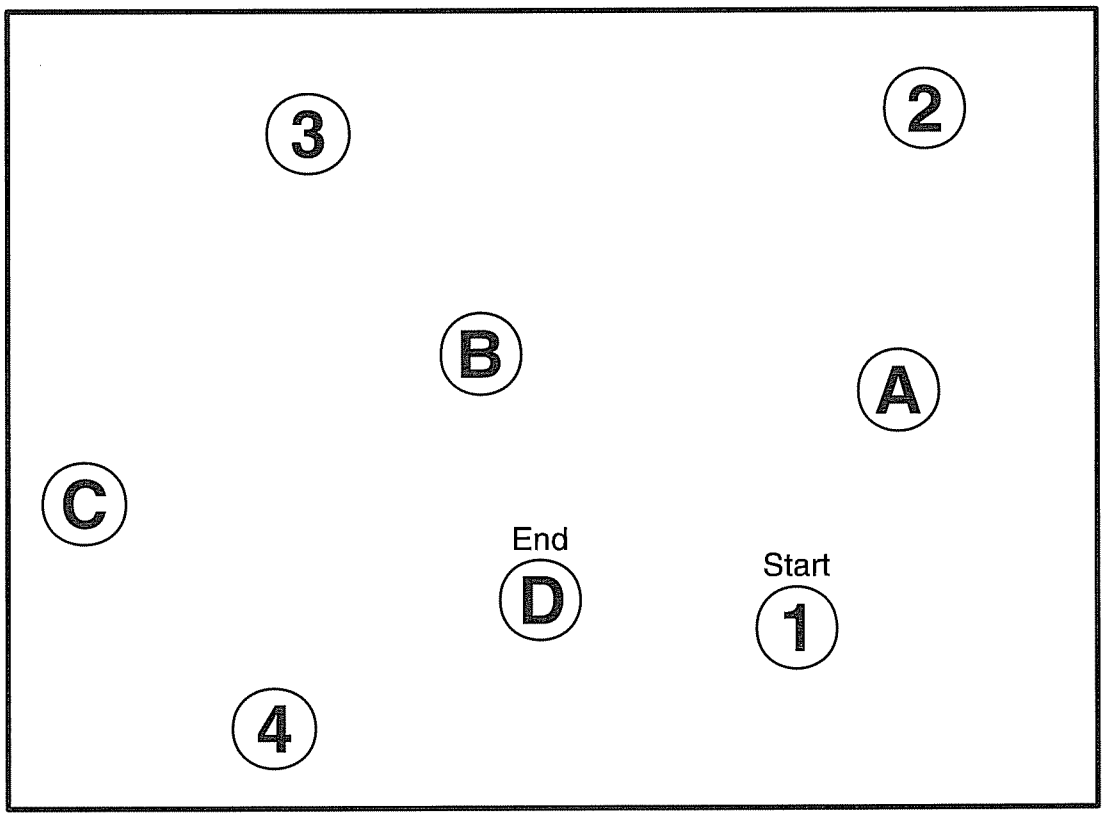
Notes _____

_____

_____

Condition 4
Number–Letter Switching

Practice

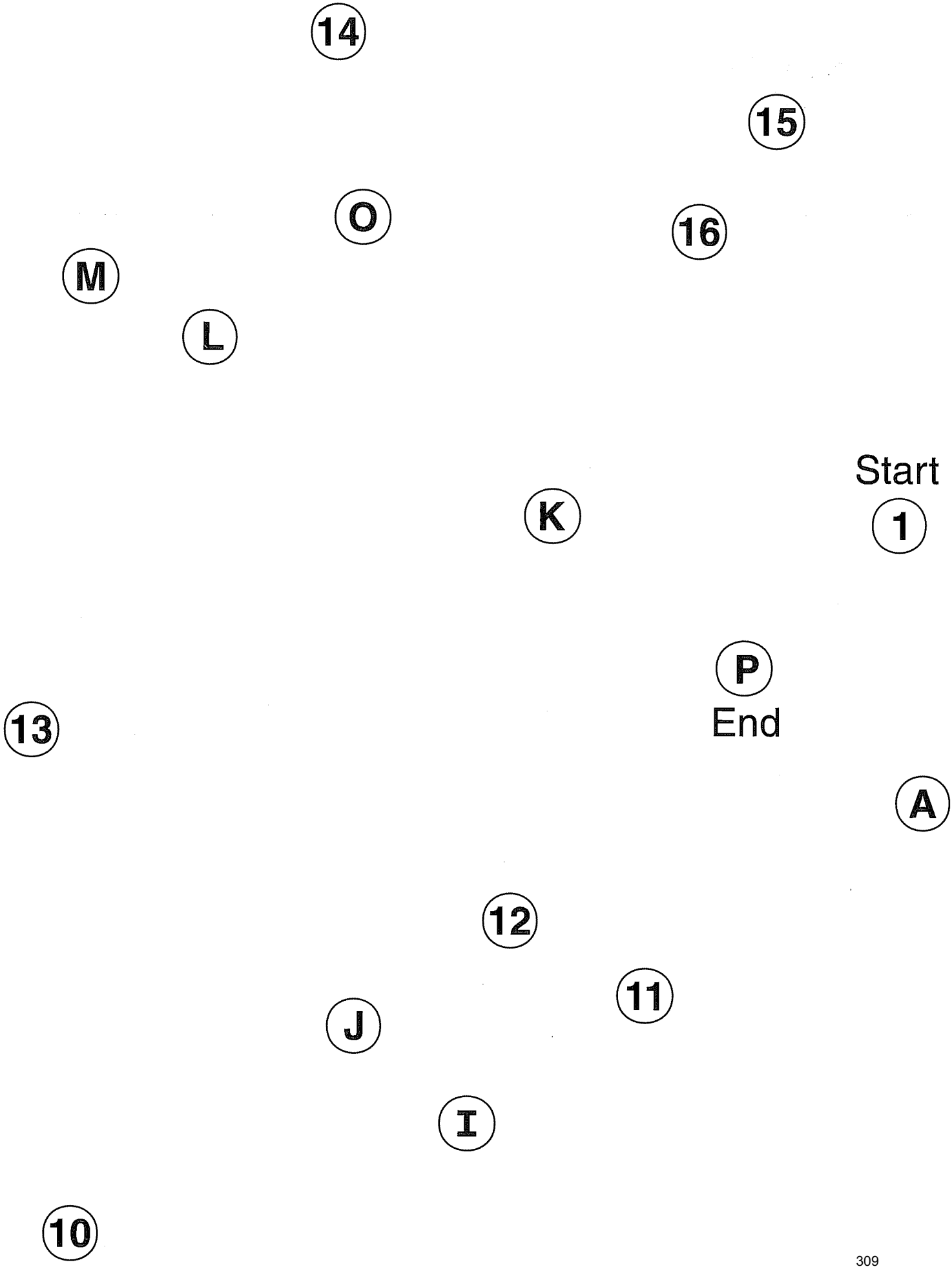


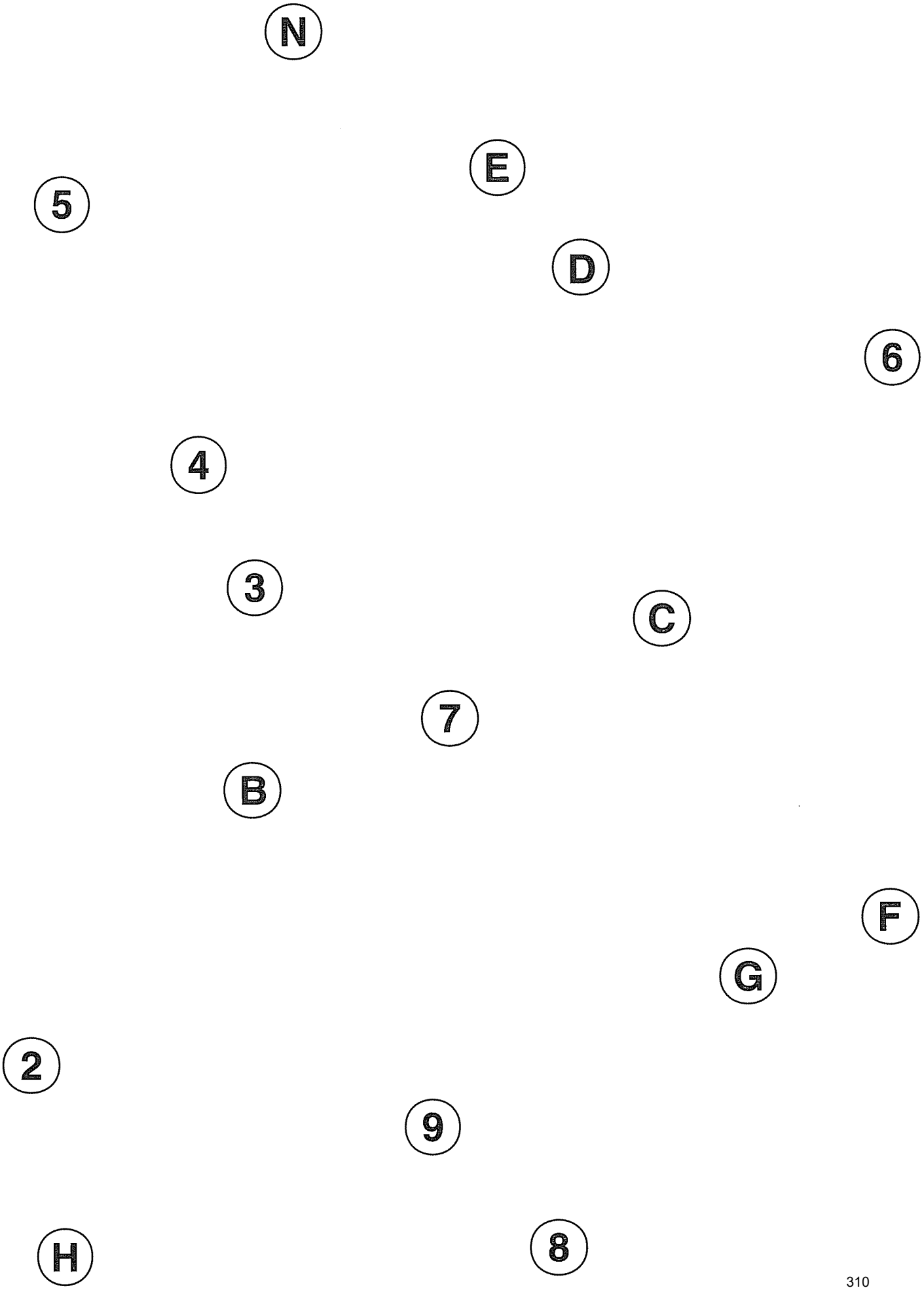
29 30 A B C D E

PEARSON

Copyright © 2001 by NCS Pearson, Inc. All rights reserved. Printed in the United States of America.

PsychCorp® 808


14
15
O
16
M
L
Start
K
1
P
End
13
A
12
11
J
I
10


N
E
5
D
6
4
3
C
7
B
F
G
2
9
H
8

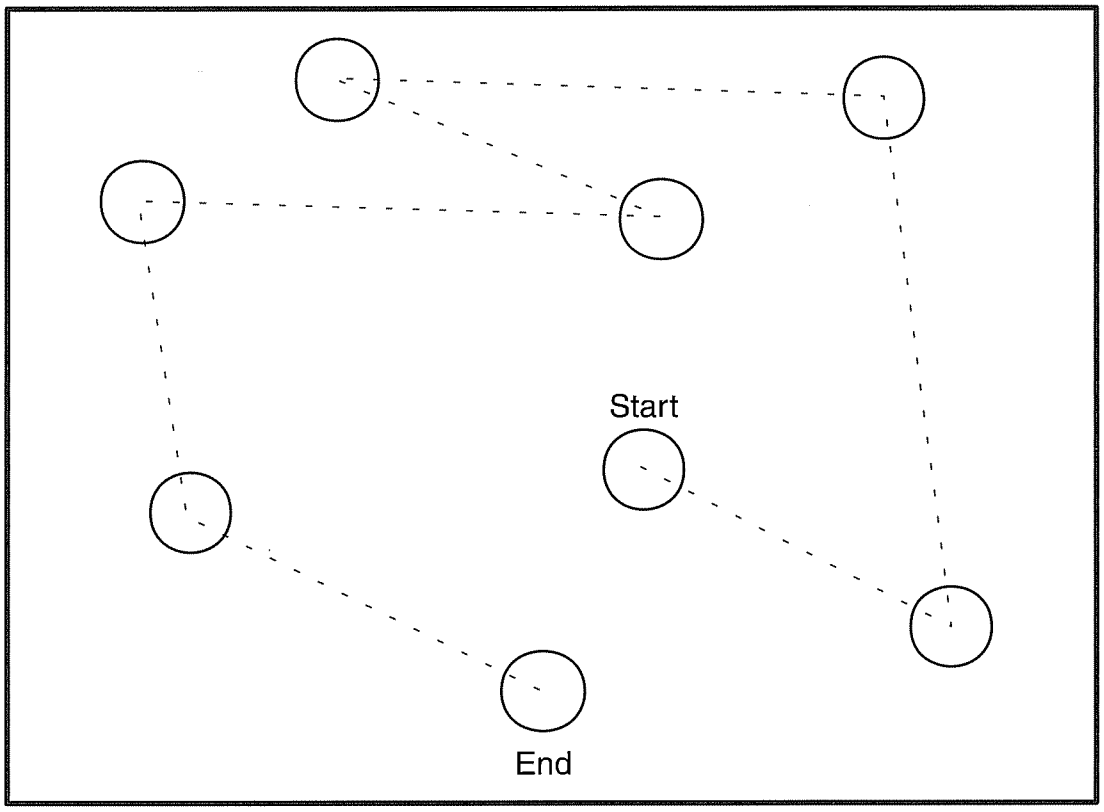
DELIS • KAPLAN
D-KEFS™
Executive Function System™

Trail Making Test

Name _____ Age _____
ID _____ Date _____
Examiner _____
Notes _____

Condition 5
Motor Speed

Practice

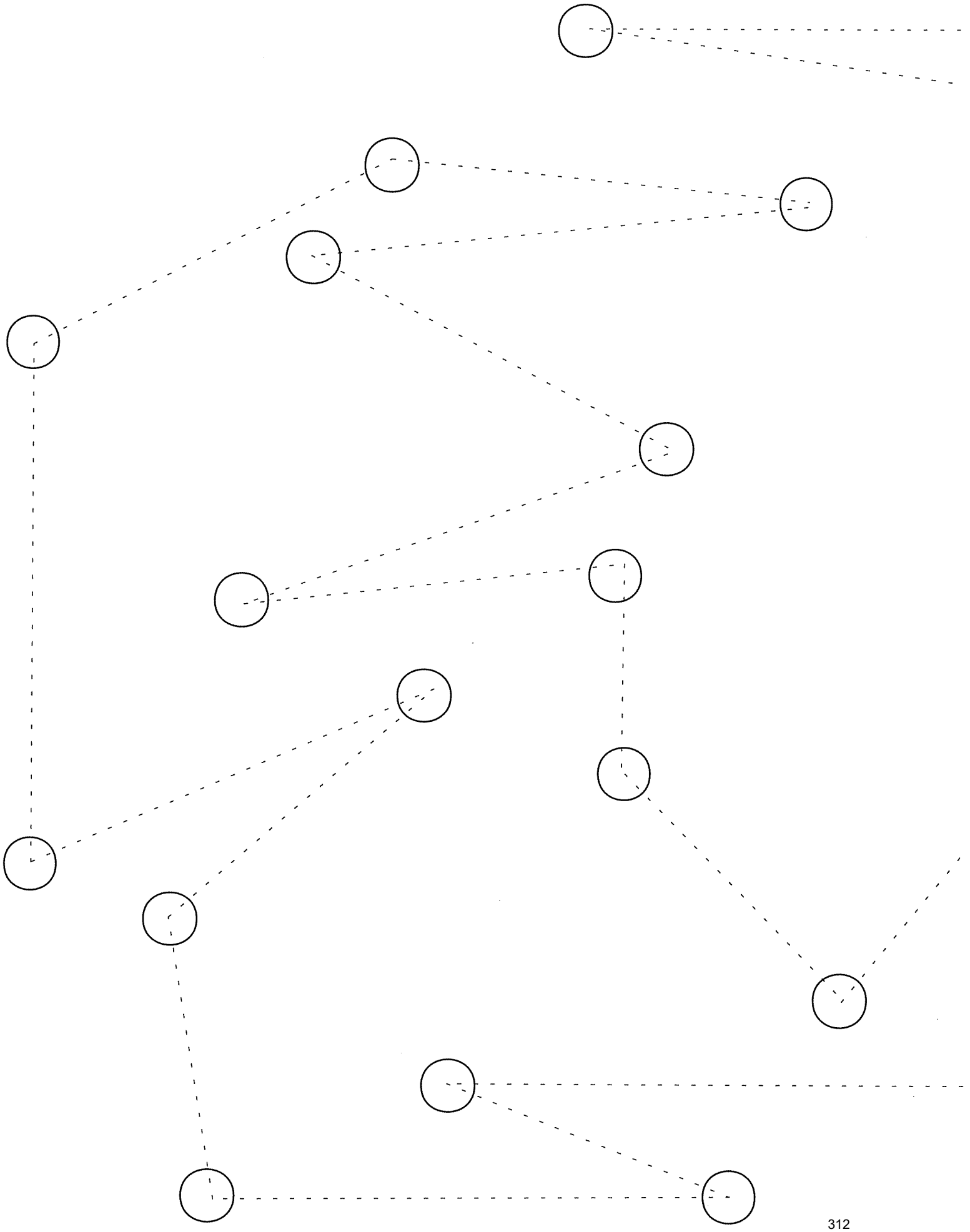


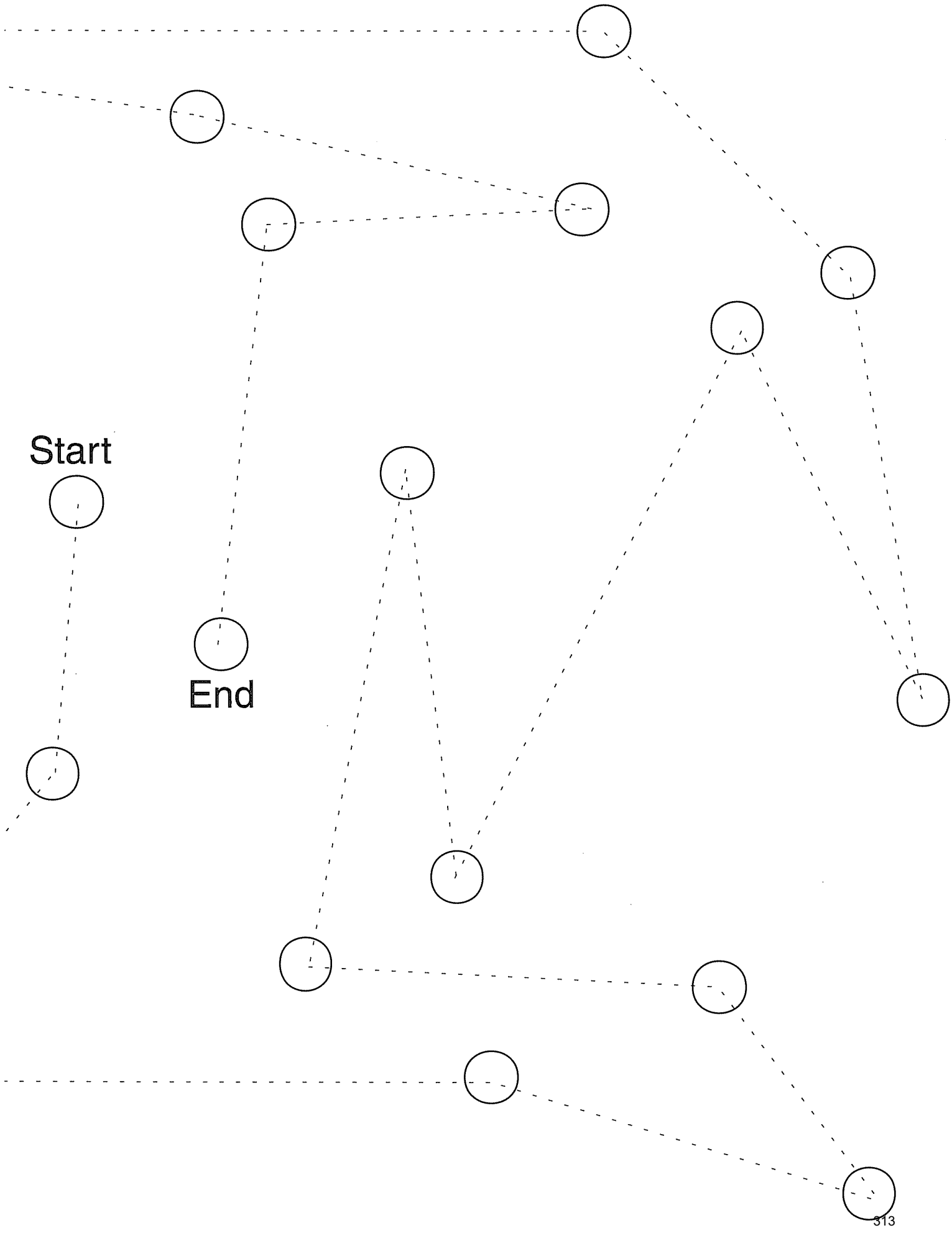
28 29 30 A B C D E

PEARSON

Copyright © 2001 by NCS Pearson, Inc. All rights reserved. Printed in the United States of America.

PsychCorp™




Start
End

DELIS • KAPLAN

D-KEFS™

Executive Function System™

Design Fluency Test

Name _____ Age _____

ID _____ Date _____

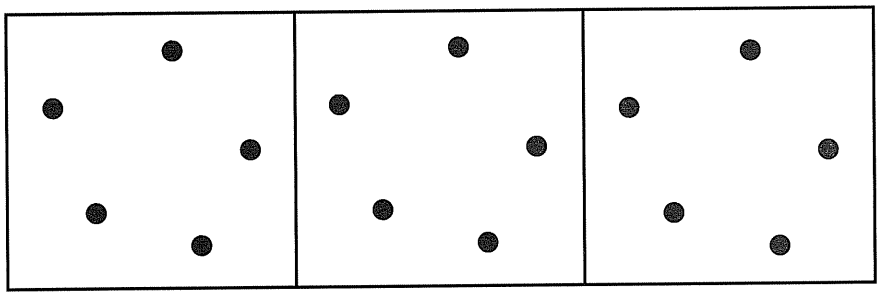
Examiner _____

Notes _____

Condition 1
Filled Dots



Practice



PEARSON

Copyright © 2001 NCS Pearson, Inc. All rights reserved.
Printed in the United States of America.

26 27 28 A B C D E 280832-1 121110

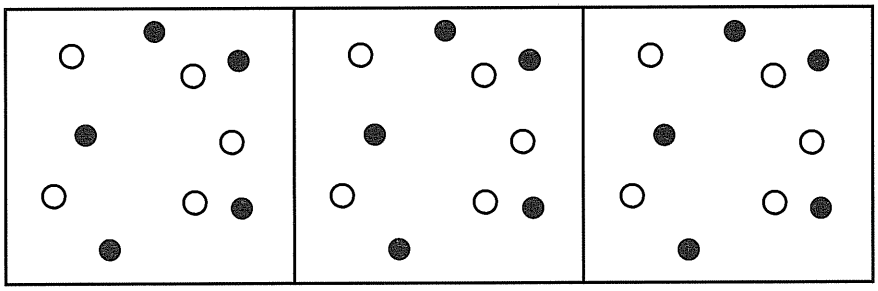
PsychCorp™

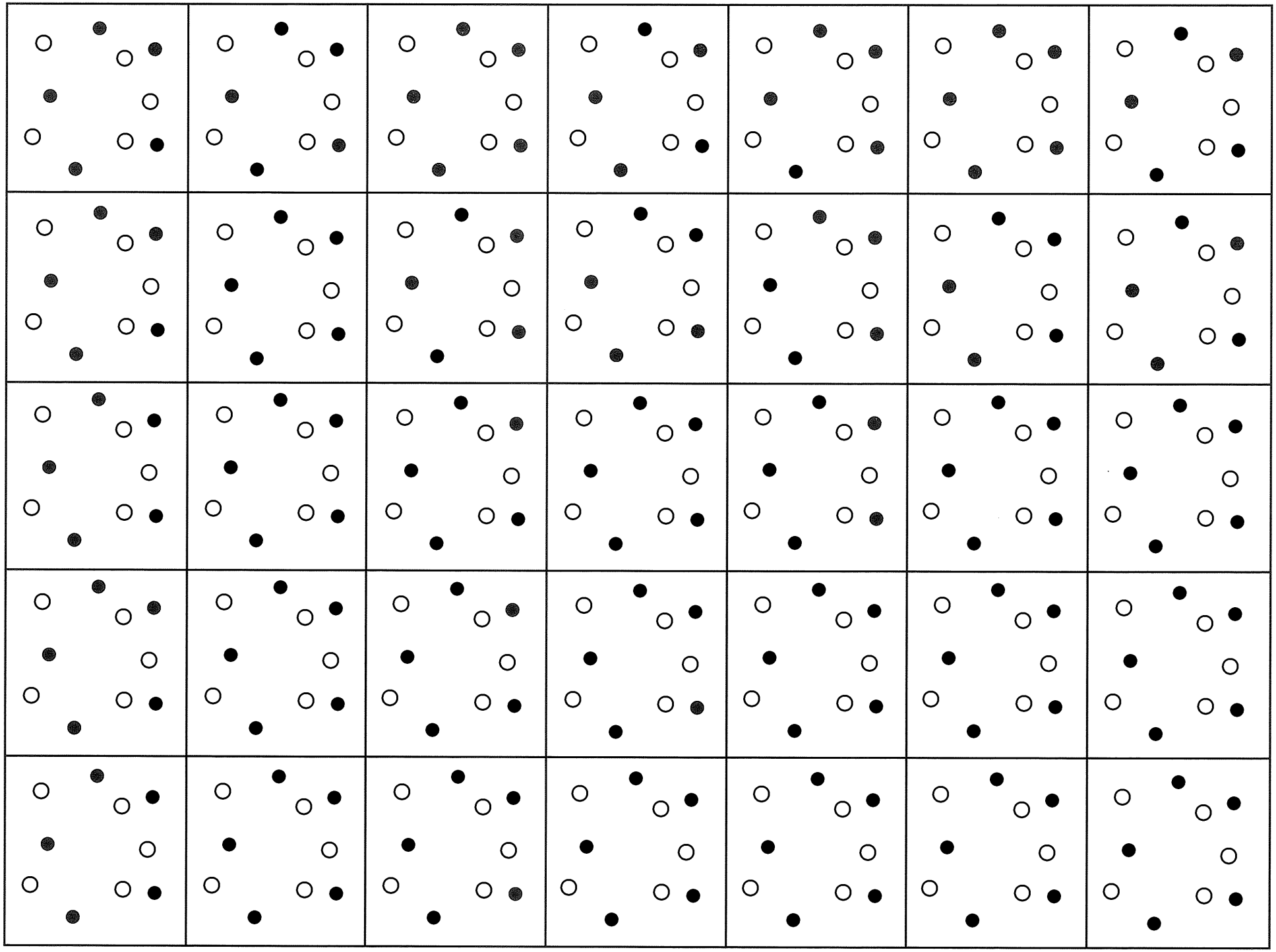
Product Number: 0154091170

Filled Dots

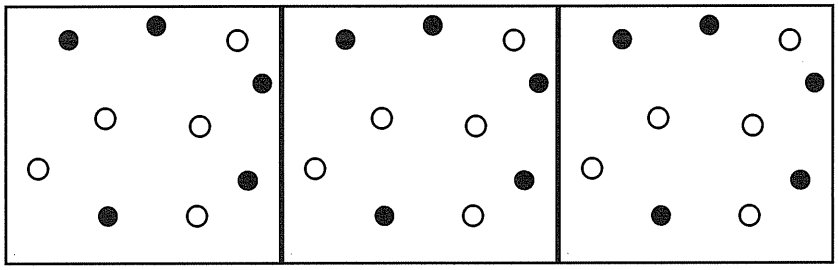
Top

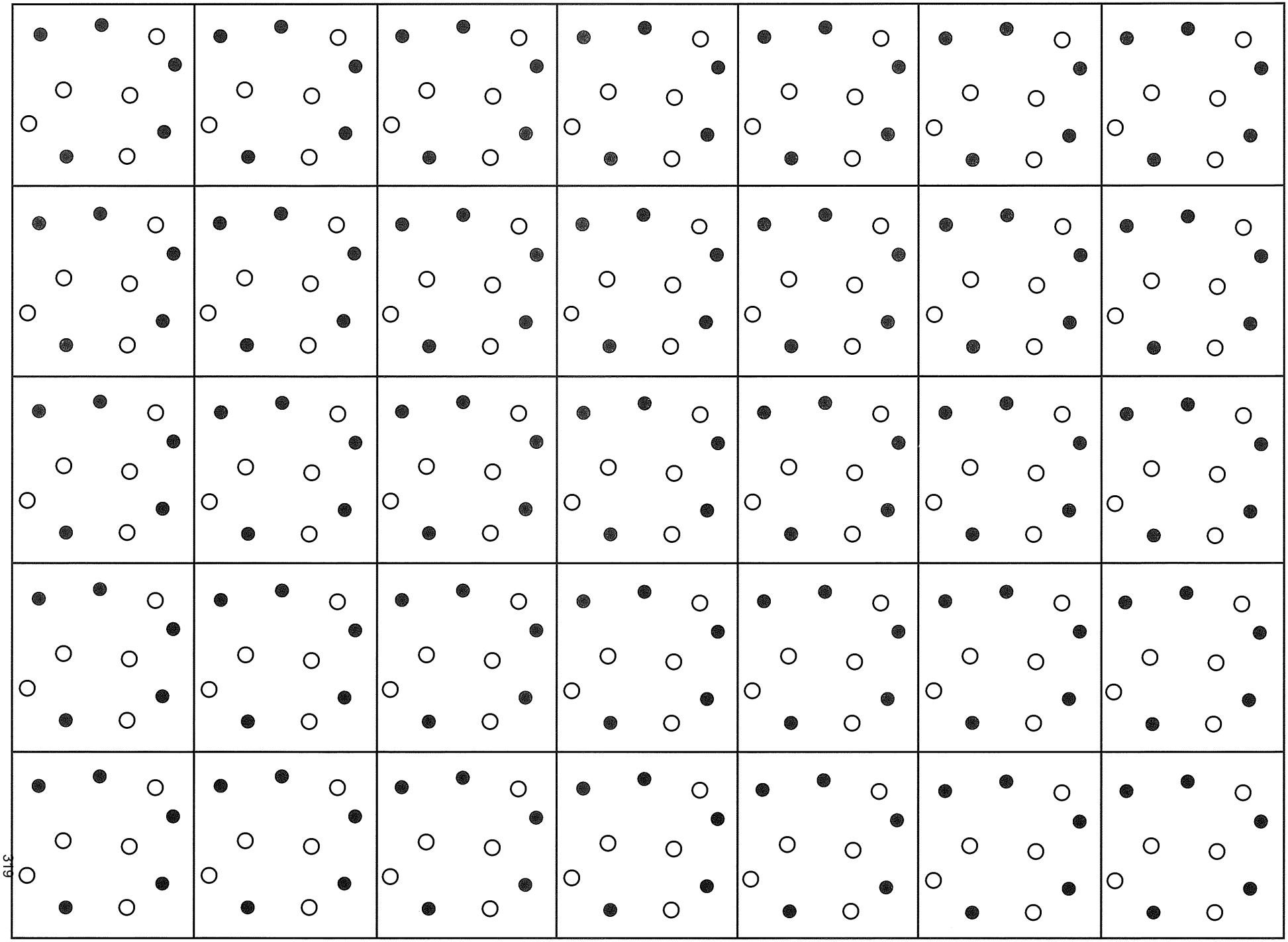
Practice



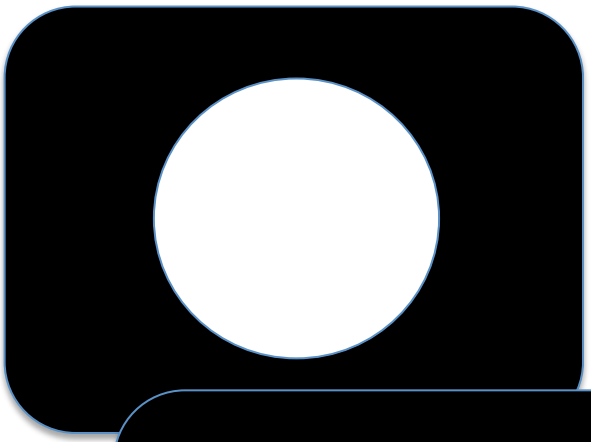


Practice

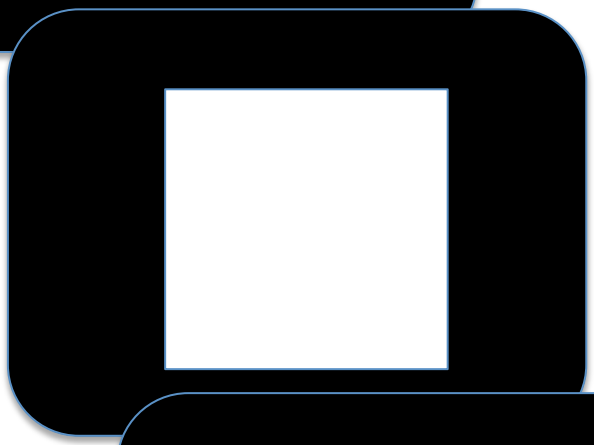




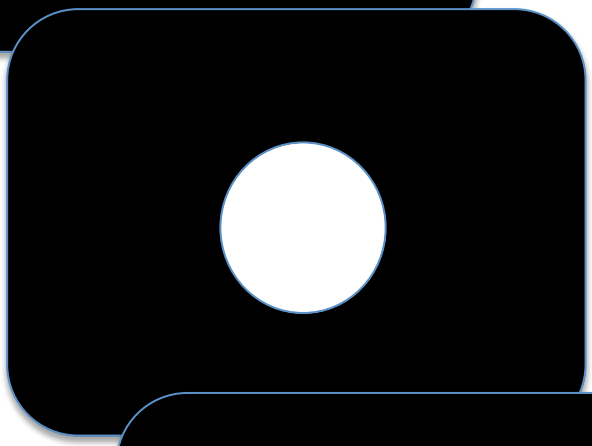
Go/No-Go Task



Go



Go



Go



No Go

Brief Visuospatial Memory Test-Revised

Response Form

Ralph H. B. Benedict, PhD

Test Date ____/____/____

ID# _____

Gender _____ Ethnicity _____ Handedness _____ Age _____

Education _____ Examiner _____

Form Administered: 1 2 3 4 5 6 (circle one)

	Raw score	*T* score	Percentile
Trial 1			
Trial 2			
Trial 3			
Total Recall[1]			
Learning[2]			
Delayed Recall			
Percent Retained[3]			
Recognition Hits			
Recognition False Alarms			
Recognition Discrimination Index[4]			
Recognition Response Bias			
Copy (optional)			

Normative table/comparison group _____

[1]Total Recall = (Trial 1 raw score + Trial 2 raw score + Trial 3 raw score).

[2]Learning = (Higher value of Trial 2 raw score or Trial 3 raw score) – Trial 1 raw score.

[3]Percent Retained = [Delayed Recall raw score ÷ (higher value of Trial 2 raw score or Trial 3 raw score)] x 100.

[4]Recognition Discrimination Index = Recognition Hits raw score – Recognition False Alarms raw score.

Delay Interval Table

Time Trial 3 completed	
Time Delayed Recall started	
Delay interval (minutes)	

Brief Visuospatial Memory Test–Revised

Response Form

Ralph H. B. Benedict, PhD

Test Date ____/____/____

ID# _____

Gender _____ Ethnicity _____ Handedness _____ Age _____

Education _____ Examiner _____

Form Administered: 1 2 3 4 5 6 (circle one)

	Raw score	*T* score	Percentile
Trial 1			
Trial 2			
Trial 3			
Total Recall[1]			
Learning[2]			
Delayed Recall			
Percent Retained[3]			
Recognition Hits			
Recognition False Alarms			
Recognition Discrimination Index[4]			
Recognition Response Bias			
Copy (optional)			

Normative table/comparison group _____

[1]Total Recall = (Trial 1 raw score + Trial 2 raw score + Trial 3 raw score).
[2]Learning = (Higher value of Trial 2 raw score or Trial 3 raw score) – Trial 1 raw score.
[3]Percent Retained = [Delayed Recall raw score ÷ (higher value of Trial 2 raw score or Trial 3 raw score)] x 100.
[4]Recognition Discrimination Index = Recognition Hits raw score – Recognition False Alarms raw score.

Delay Interval Table

Time Trial 3 completed	
Time Delayed Recall started	
Delay interval (minutes)	

Subject ID: _____ Date: _____

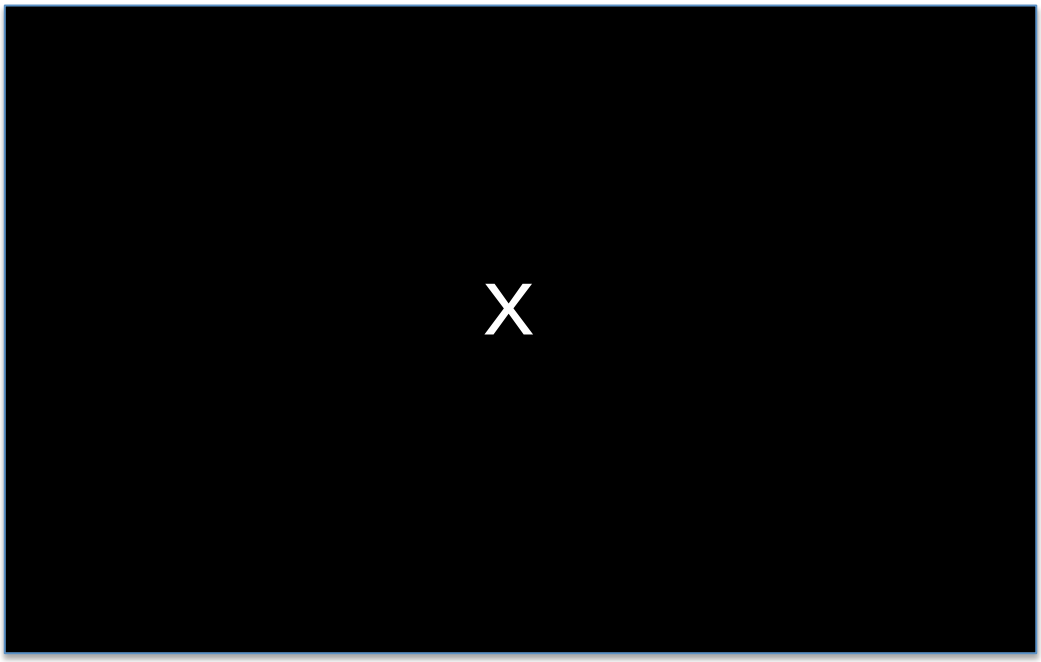
Please rate each of the following items in terms of how characteristic they are of you. Use the following scale for answering these items.

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

Psychomotor Vigilance Test

Press the spacebar every time an “x” appears on the screen.



Session 1 _____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_____

© 1989, University of Pittsburgh. All rights reserved. Developed by Buysse,D.J., Reynolds,C.F., Monk,T.H., Berman,S.R., and Kupfer,D.J. of the University of Pittsburgh using National Institute of Mental Health Funding.

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

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

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
© Copyright 2006-2007, Center for the Study of Human Operator Performance

Table of Contents

3 Requirements
3 Hardware Requirements
3 Software Requirements

4 Chapter 1: Installing and Running ANAM4™

5 Chapter 2: Starting ANAM4™
5 Starting ANAM4™
5 Selecting a Battery and Entering the User ID
6 Changing Data Directories (Folders)
6 Confirming Date, Time, ID, and Session Number
7 Restarting a Previously Cancelled Battery
7 Selecting Test Settings
8 Selecting a Specific Test or Subset of Tests
9 Proceeding through the Battery

10 Chapter 3: ANAM4™ Data
10 File Naming
10 ANAM4™ Data Directories

11 Chapter 4: ANAM4™ Tests
11 ANAM4™ Test Names, Modules, and Extensions

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

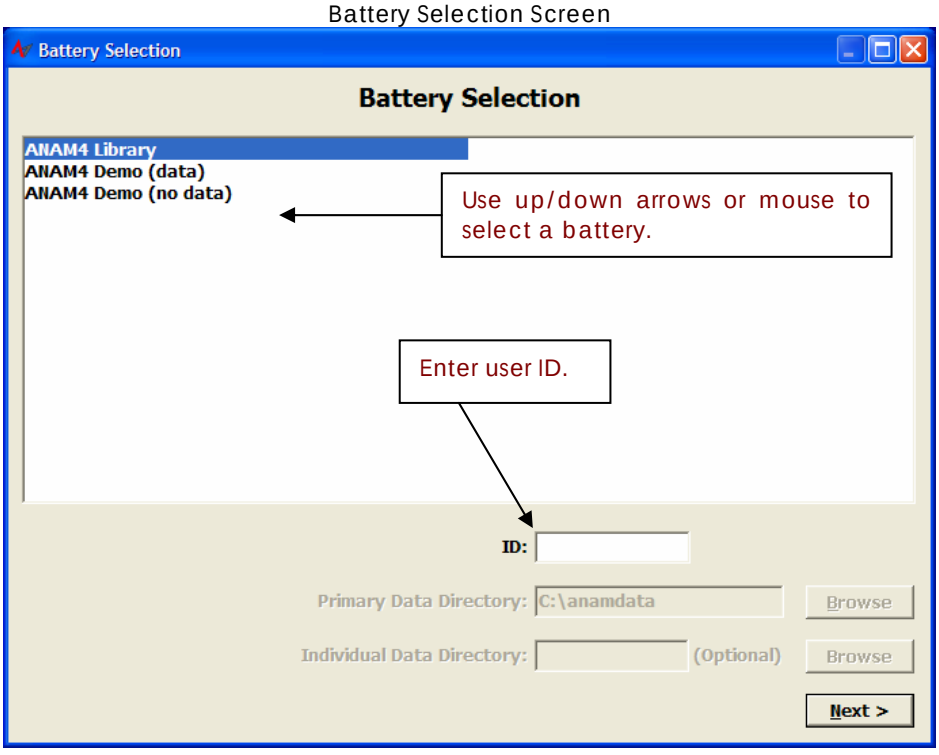


Selecting a Battery and Entering the User ID

The *Battery Selection* screen allows the user to choose a battery, specify an ID number, and specify data directories.

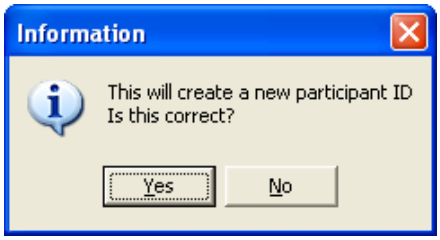
1. Use the up/down cursor keys or mouse to select the desired ANAM4™ battery.

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:

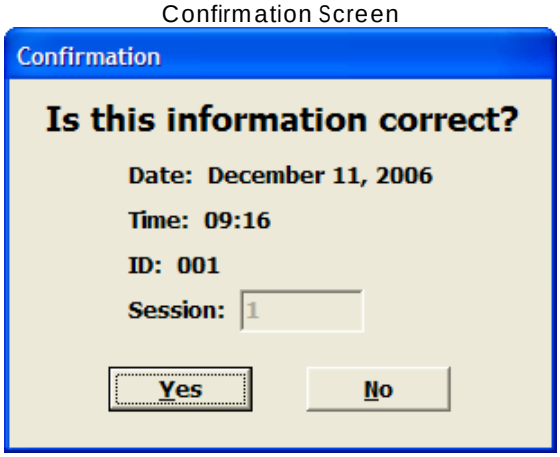
1. Press <**Alt**><**F1**>. This will unlock the *Primary Data Directory* and *Individual Data Directory* fields for modification.
2. Type the path location of the directory for data storage or click **Browse**. If you select Browse, navigate to the directory where you would like to store the ANAM data files.

After confirming all information on the *Battery Selection* screen, Press **Enter** or click **Next** to continue.

Confirming Date, Time, ID, and Session Number

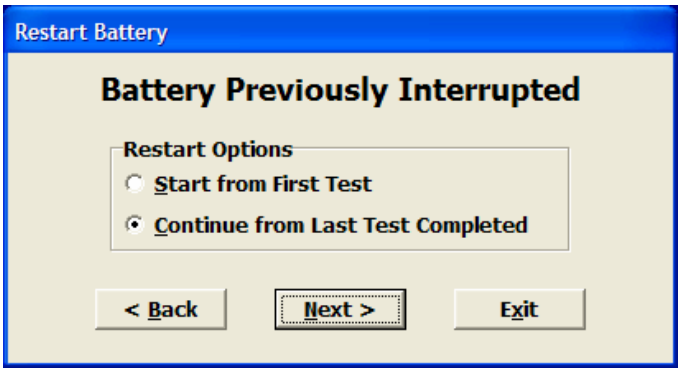
1. Confirm that the Date and Time on your computer are accurately set. If not, click on **No**, close the *Battery Selection* screen that reappears by clicking on the red close button at the upper right corner, correct the Date/Time setting, and restart ANAM4™.
2. Confirm that the correct Session number 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.

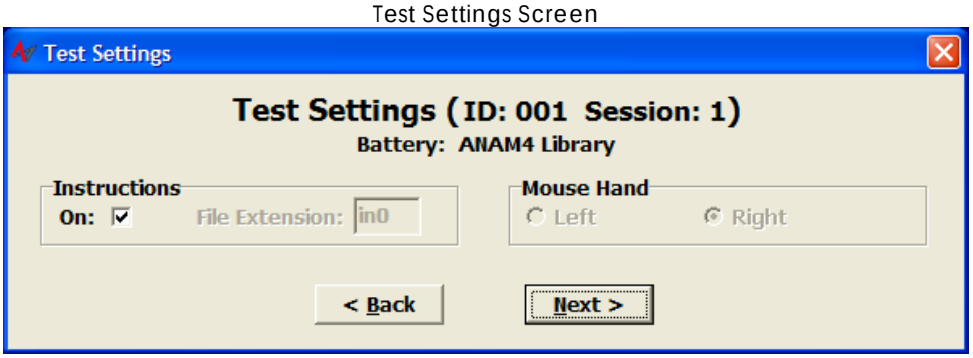


2. Once you have selected the desired option, click on **Next** to continue.

Selecting Test Settings

The *Test Settings* screen allows the user to customize the ANAM4™ test session.

Test Settings Screen



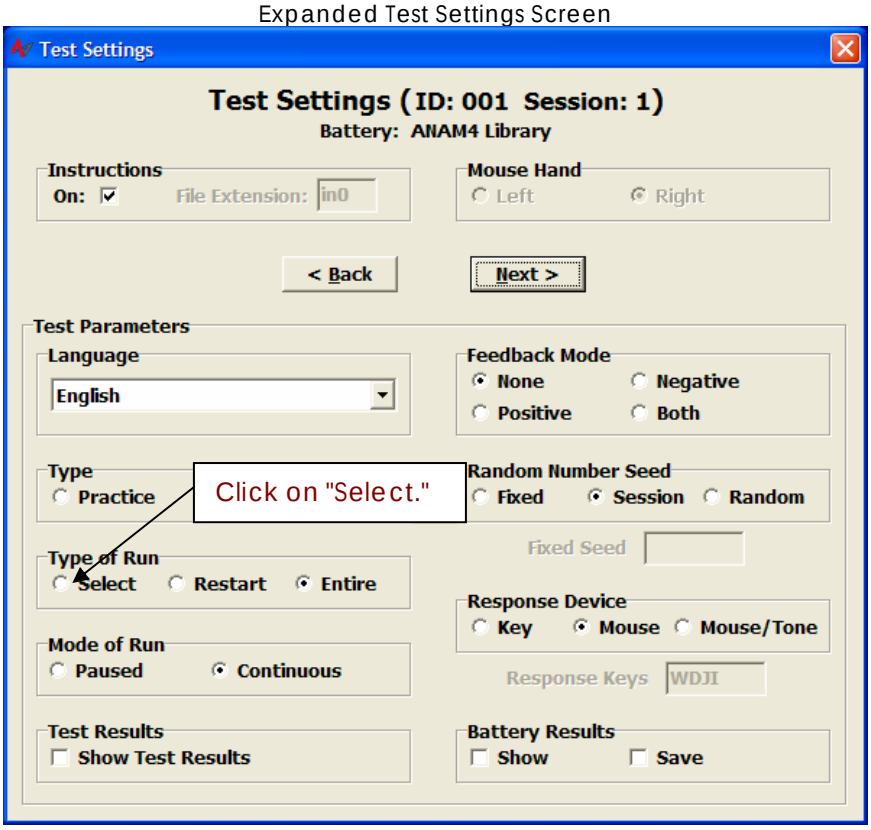
Note: After using the battery a few times for a particular person, you may wish to turn off instructions by deselecting the "Instructions" box. Make sure it is checked **On** the first time through.

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.

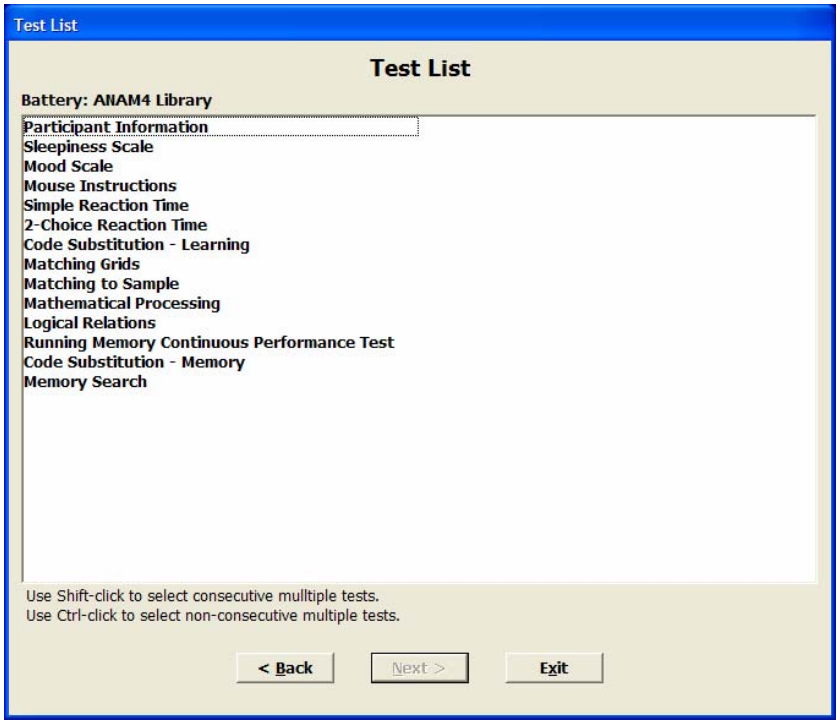
Selecting a Specific Test or Subset of Tests

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



Center for the Study of Human Operator Performance
University of Oklahoma
3200 Marshall Ave, Suite 260
Norman OK 73072 USA
www.c-shop.ou.edu

Copyright © 2006-2007 Center for the Study of Human Operator Performance. All rights reserved. ANAM4, the ANAM4 logo, specific device designations and all other words and logos that are identified as trademarks and/or service marks are, unless noted otherwise, the trademarks and service marks of C-SHOP in the U.S. and other countries. All other product or service names are the property of their respective holders. ANAM products are protected under numerous U.S. and foreign patents and pending applications, mask work rights, and copyrights.

BDI-II

Date:

Subject ID: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

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
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry any more than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

PEARSON

34 35 36 B C D E

Copyright © 1996 Aaron T. Beck. All rights reserved.

Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437
800.627.7271 www.PsychCorp.com

PsychCorp
344
Product Number 0154018392

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____	Subtotal Page 2
_____	Subtotal Page 1
_____	Total Score

NOTICE: This form is printed with blue and black ink. If your copy does not appear this way, it has been photocopied in violation of copyright laws.

281283-2 987

WASI-II Record Form

WECHSLER ABBREVIATED SCALE OF INTELLIGENCE — SECOND EDITION

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Test Age			

ID:

Sex: ☐ F ☐ M Handedness: ☐ R ☐ L

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:	☐	☐

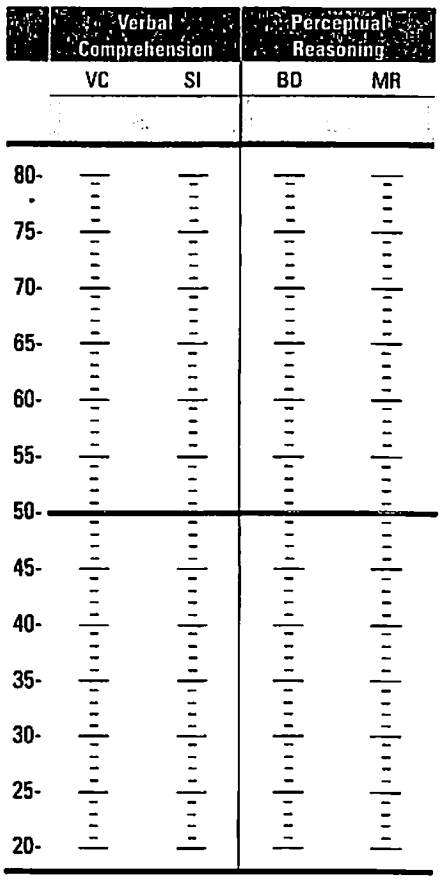
Sum of *T* Scores to Composite Score Conversion

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		–

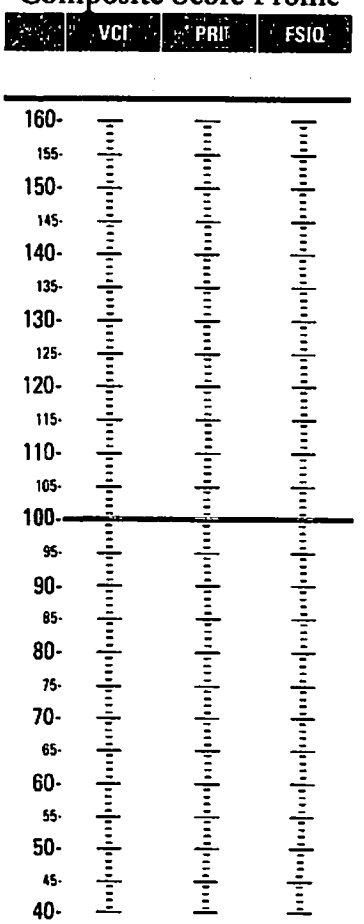
Ranges of Expected Scores

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

Subtest *T* Score Profile



Composite Score Profile



PEARSON

Copyright © 2011 NCS Pearson, Inc. All rights reserved.

PsychCorp

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			

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
6–8 STOP	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
	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 352

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)

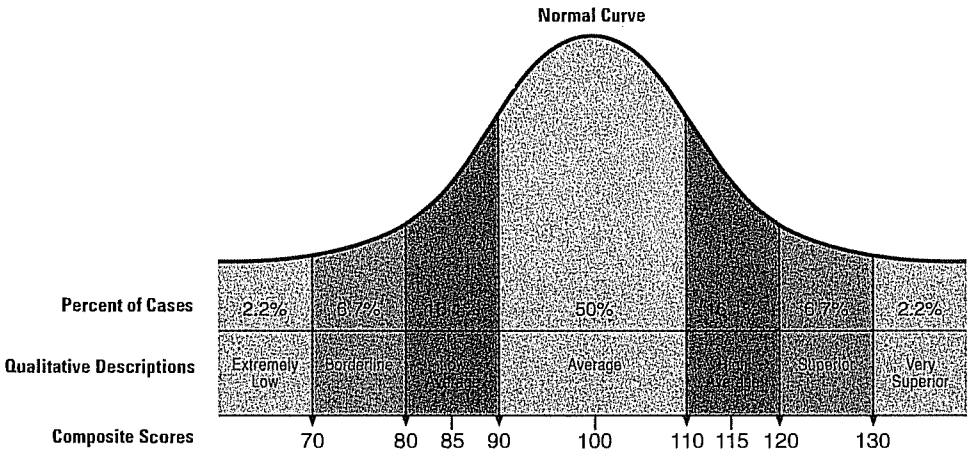
Attention and concentration

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

Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437

800.627.7271 www.PsychCorp.com

Copyright © 2011 NCS Pearson, Inc. All rights reserved.

Warning: No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the copyright owner.

Pearson, the **PSI logo**, **PsychCorp**, **WASI**, **Wechsler**, and **Wechsler Abbreviated Scale of Intelligence** are trademarks, in the U.S. and/or other countries, of Pearson Education, Inc., or its affiliate(s).

Portions of this work were previously published.

Printed in the United States of America.

CD-RISC

Subject #: Date: _____ Time: _____

_____

Think about how you have been feeling over the past month. Using the scale below, please rate each of the following statements for how <u>well they describe you</u> **DURING THE PAST MONTH**.

0	**1**	**2**	**3**	**4**
not true at all	**rarely true**	**sometimes true**	**often true**	**true nearly all the time**

1. _____ Able to adapt to change
2. _____ Close and secure relationships
3. _____ Sometimes fate or God can help
4. _____ Can deal with whatever comes
5. _____ Past success gives confidence for new challenge
6. _____ See the humorous side of things
7. _____ Coping with stress strengthens
8. _____ Tend to bounce back after illness or hardship
9. _____ Things happen for a reason
10. _____ Best effort no matter what
11. _____ You can achieve your goals
12. _____ When things look hopeless, I don't give up
13. _____ Know where to turn for help
14. _____ Under pressure, focus and think clearly
15. _____ Prefer to take the lead in problem solving
16. _____ Not easily discouraged by failure
17. _____ Think of self as strong person
18. _____ Make unpopular or difficult decisions
19. _____ Can handle unpleasant feelings
20. _____ Have to act on a hunch
21. _____ Strong sense of purpose
22. _____ In control of your life
23. _____ I like challenges
24. _____ You work to attain your goals
25. _____ Pride in your achievements

Craig Handicap Assessment and Reporting Technique Scoring Short Form

1. How many hours in a typical 24-hour day do you have someone with you to provide physical assistance for personal care activities such as eating, bathing, dressing, toileting and mobility?

_____ hours paid assistance _____ hours unpaid (family, others)

PHYSICAL INDEPENDENCE

A. Total the hours of paid and unpaid care, multiply by 4, and subtract that number from 100.

100
minus
_____.
=

2. How much time is someone with you in your home to assist you with activities that require remembering, decision making, or judgment?

1_____ Someone else is always with me to observe or supervise.
2_____ Someone else is always around, but they only check on me now and then.
3_____ Sometimes I am left alone for an hour or two.
4_____ Sometimes I am left alone for most of the day
5_____ I have been left alone all day and all night, but someone checks in on me.
6_____ I am left alone without anyone checking on me.

3. How much of the time is someone with you to help you with remembering, decision making, or judgment when you go away from your home?

1_____ I am restricted from leaving, even with someone else.
2_____ Someone is always with me to help with remembering, decision making or judgment when I go anywhere.
3_____ I go to places on my own as long as they are familiar.
4_____ I do not need help going anywhere.

COGNITIVE INDEPENDENCE

A. Assign points as follows: response #1 = 0 points; response #2 = 1 point; response #3 = 2 points; response #4 = 3 points; response #5 = 4 points; and response #6 = 5 points.

_____.
x11
=
_____.

B. Multiply points in “A" by 11. +

C. Assign points as follows: response #1 = 0 points; response #2 = 1 point; response #3 = 2 points; and response #4 = 3 points.

_____.
x15
=
_____.

D. Multiply points in “C" by 15. =

Add the sums of “B” and “D”. If the total sum is greater than 100, enter 100.

4. On a typical day, how many hours are you out of bed? _____ hours

5. In a typical week, how many days do you get out of your house and go somewhere?
_____days

6. In the last year, how many nights have you spent away from your home (excluding hospitalizations?)
_____ none _____ 1-2 _____ 3-4 _____ 5 or more

MOBILITY

A. Multiply the number of hours out of bed by 3. _____.

\+

B. Multiply the number of days per week out of the house by 7. _____.

\+

C. Assign points as follows: no nights out = 0; 1-2 nights out = 10; 3-4 nights out = 15; 5 or more nights = 20. If the total sum is greater than 100, enter 100. _____.

=

Add the sums of "A", "B", and "C". If the total sum is greater than 100, enter 100. [ ]

7. How many hours per week do you spend working in a job for which you get paid?
hours_____

8. How many hours per week do you spend in school working toward a degree or in an accredited technical training program (including hours in class and studying)?
hours

9. How many hours per week do you spend in active homemaking including parenting, housekeeping, and food preparation? _____ hours

10. How many hours per week do you spend in home maintenance activities such as gardening, house repairs or home improvement? _____ hours

11. How many hours per week do you spend in recreational activities such as sports, exercise, playing cards, or going to movies? Please do not include time spent watching TV or listening to the radio._____hours

OCCUPATION

A. Multiply the number of hours working by 2.5. _____.

\+

B. Multiply the number of hours in school by 2.5. _____.

\+

C. Multiply the number of hours in active homemaking by 2.5. _____.

\+

D. Multiply the number of hours in home maintenance by 2.5. _____.

\+

E. Multiply the number of recreational activities by 1.25 _____.

=

Add the sums of "A", "B", "C", "D", and "E". If the total sum is greater than 100, enter 100. [ ]

SOCIAL INTEGRATION

12. How many people do you live with?

13. Is one of them your spouse or significant other?

14. of the people you live with how many are relatives?

15. How many business or organizational associates do you visit, phone, or write to at least once a month? _____ Associates

16. How many friends (non-relatives contacted outside business or organizational settings) do you visit, phone, or write to at least once a month?_____Friends

17. With how many strangers have you initiated a conversation in the last month (for example, to ask information or place an order)?

    none ____ 1-2 ____ 3-5 ____ 6 or more

A. Assign 38 points if living with spouse/partner OR assign 25 points if living with unrelated roommate and/or an attendant.

Add an additional six points for every relative that lives in the household.

_____.
+

B. Multiply number of business associates by 2.5. A maximum score for this component is 25 points.

_____.
+

C. If living with more than one roommate, add extra roommate to number of friends contacted monthly. Multiply by 13. A Maximum score for this component is 65 points.

_____.
+

D. Assign points as follows: none = 0 points; 1-2 = 15 points; 3-5 = 23 points; 6 or more = 30 points.

_____.

=

Add the sums from "A", "B", "C", and "D". If the total sum is greater than 100, enter 100.

18. Approximately what was the combined annual income, in the last year, of **all family members in your household**? (consider all sources including wages and earnings, disability benefits, pensions and retirement income, income from court settlements, investments and trust funds, child support and alimony, contributions from relatives, and any other source.)

a. Less than 25,000 - If no ask e; if yes ask b
b. Less than 20,000 - If no code 22500; if yes ask c
c. Less than 15,000 - If no code 17500; if yes ask d
d. Less than 10,000 - If no code 12500; if yes code 5000
e. Less than 35,000 - If no ask f; if yes code 30000
f. Less than 50,000 - If no ask g; if yes code 42500
g. Less than 75,000 - If no code h; if yes code 62500
h. 75,000 or more code 80000

19. Approximately how much did you pay last year for medical care expenses? (Consider any amounts paid by yourself or the family members in your household and **not reimbursed** by insurance or benefits.)

a. Less than 1000 if "no" ask b if "yes" code 500.
b. Less than 2500 if "no" ask c if "yes" code 1750.
c. Less than 5000 if "no" ask d if "yes" code 3750.
d. Less than 10000 if "no" code e if "yes" code 7500.
e. 10000 or more code 15000

ECONOMIC SELF SUFFICIENCY

A. Calculate family size by adding respondent, plus partner (if living with respondent), plus other relatives in household.

_____.
Family size

_____.
(#19)
minus

B. Subtract the unreimbursed medical expenses from the annual income (amount in question #19 minus amount in question #20.

_____.
(#20)

C. Determine poverty level from family size calculated in "A".

=

D. Divide the value from "B" by the poverty level from "C".

_____.

divided by

E. Multiply by 50

_____.
Poverty level

*50
=

_____.

=

If the total sum is greater than 100, enter 100.

Personality Assessment Inventory (PAI)

99% of the products we distribute are in stock at all times.

Product Search

By All

Advanced Search

About PAR
Products
Request Catalog
Conferences/Workshops
Assessment Consultants
Research and Development
Opportunities at PAR
Community Involvement
Permissions and Licensing
PAR Report Card
Forms
Contact Us

Telephone 1.800.331.8378
Fax 1.800.727.9329
Tech Support 1.800.899.8378

Customer Comments:

"The speed with which you fill your orders is to be commended! This is very helpful for your customers. Thank you!"

Laura Liljequist, PhD
Murray, KY

facebook

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.

Subject ID: _____ Date: _____

The following questions concern your alcohol consumption. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

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

Subject ID: _____ Session: _____ Study: _____ Date: ____/____/____

Snaith-Hamilton Pleasure Scale

This questionnaire is designed to measure your ability to experience pleasure in the last few days.
It is important to read each statement very carefully.
Circle the answer that corresponds to how much you agree or disagree with each statement.

1.	I would enjoy my favorite television or radio program.	Strongly Disagree	Disagree	Agree	Strongly Agree
2.	I would enjoy being with my family or close friends.	Definitely Agree	Agree	Disagree	Strongly Disagree
3.	I would find pleasure in my hobbies and past-times.	Strongly Disagree	Disagree	Agree	Strongly Agree
4.	I would be able to enjoy my favorite meal.	Definitely Agree	Agree	Disagree	Strongly Disagree
5.	I would enjoy a warm bath or refreshing shower.	Definitely Agree	Agree	Disagree	Strongly Disagree
6.	I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.	Strongly Disagree	Disagree	Agree	Strongly Agree
7.	I would enjoy seeing other people's smiling faces.	Definitely Agree	Agree	Disagree	Strongly Disagree
8.	I would enjoy looking smart when I have made an effort with my appearance.	Strongly Disagree	Disagree	Agree	Strongly Agree
9.	I would enjoy reading a book, magazine, or newspaper.	Definitely Agree	Agree	Disagree	Strongly Disagree
10.	I would enjoy a cup of tea or coffee or my favorite drink.	Strongly Disagree	Disagree	Agree	Strongly Agree
11.	I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend.	Strongly Disagree	Disagree	Agree	Strongly Agree
12.	I would be able to enjoy a beautiful landscape or view.	Definitely Agree	Agree	Disagree	Strongly Disagree
13.	I would get pleasure from helping others.	Strongly Disagree	Disagree	Agree	Strongly Agree
14.	I would feel pleasure when I receive praise from other people.	Definitely Agree	Agree	Disagree	Strongly Disagree

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.

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: _____

Have you ever used marijuana?

For our purposes, marijuana usage is considered any instance in which you intentionally consumed (smoked, ingested, etc.) any quantity of marijuana.

☐ **NO** ☐ **YES**

At what age did you start? _____

At what specific age (in years) was your marijuana usage the heaviest? _____

During your lifetime, approximately how many occasions have you used marijuana?

☐ 0-50 ☐ 51-100 ☐ 101-500 ☐ 501s-1000 ☐ 1001-5000 ☐ over 5000

Consider the extent of marijuana use throughout your lifetime. Please approximate the number of times per month on average which you used marijuana at the following ages:

16-18 years of age	19-21 years of age	22-24 years of age	25-27 years of age	28-30 years of age	30+ years of age

During your lifetime, on average, how many times per month have you used marijuana?

_____

In the past <u>four weeks</u>, did you use marijuana?

☐ **NO** ☐ **YES**

How often? _____ daily / weekly (*circle one*)

On average, how much do you consume per occasion? _____

If YES, please review the printed calendar reflecting all the days in the past month. Indicate the number of times you used marijuana on each of these days. If you abstained from marijuana use during a given day, please write a “0” on that day. Please fill out every day in the calendar with your best guess of marijuana use.

Test 9 Sentence Reading Fluency

Administration Overview

- This test has a 3-minute time limit.
- You will need a stopwatch or a watch or clock with a second hand to administer this test.
- If you are not using a stopwatch, note the *exact starting time* in minutes and seconds.
- Give the subject *exactly 3 minutes* to complete as many items as possible.
- Record the *exact finishing time* in minutes and seconds on the Test Record.
- Use the Response Booklet and a pencil with eraser for this test.

Scoring

- 1 = Correct response
  0 = Incorrect response
- Use the Sentence Reading Fluency Scoring Guide to score this test.
- When calculating the number correct, do not include points for sample items or the practice exercise.
- Record *both* the Number Correct and the Number Incorrect on the Test Record. Do not count unattempted items as incorrect.

Starting Point

- Administer Sample Items A and B and the Practice Exercise to all subjects.

Sample Items

Open Response Booklet to Sentence Reading Fluency sample items and place directly in front of subject. Say: **I want you to read some sentences and decide if the answer is yes or no.**

Point to Sample Item A and say: **Look at this sentence. It says, "A cow is an animal."** (Pause.) **Is that true?** (Pause for response.) **Because the answer is yes, you would circle the letter** *Y* (point to circled *Y*). **Now look at the second sentence. It says, "A fish can read."** (Pause.) **Is that true?** (Pause for response.) **Because the answer is no, you would circle the letter** *N* (point to circled *N*).

A. A cow is an animal.	(Y)	N
B. A fish can read.	Y	(N)

Practice Exercise

Give subject a pencil with eraser and say: **Now look at the next four sentences. Draw a circle around the correct answer for each sentence. Work as quickly as you can without making mistakes. Go ahead.**

C. An apple is blue.	Y	(N)
D. A wheel is round.	(Y)	N
E. A man has two legs.	(Y)	N
F. Ice is hot.	Y	(N)

❖ ***C–F: Error***
Say: **Read the sentence aloud and tell me if the answer is "yes" or "no."** If subject still gives incorrect answer, explain sentence and correct answer.

❖ ***C–F: No Response***
Say: **Read the sentence aloud and tell me if the answer is "yes" or "no."** If subject cannot read sentence, point to next sentence and say: **Try the next one.**

❖ ***2 or Fewer Correct***
If subject has 2 or fewer items correct on Practice Exercise, record score of 0 for Test 9 Sentence Reading Fluency without administering test items.

Test Items

Open Response Booklet to Sentence Reading Fluency test items and hold up booklet so subject cannot study items. Say: **Start here** (point to first sentence) **and read as many sentences as you can. Decide if the answer is yes or no. After you get to the bottom** (point to bottom of first column), **go to the top** (point to top of second column). **There are three pages. Keep working until I tell you to stop. Work as quickly as you can without making mistakes. If you do make a mistake, cross out the one you do not want. If you have trouble reading a word or cannot think of the answer, skip that one and go on to the next one. You will have three minutes. Tell me if you finish before I say, "Stop."**

Place Response Booklet, opened to test items, directly in front of subject and say: **Go ahead.** Begin timing 3 minutes.

Make sure subject continues to top of next page after completing each page.

❖ ***No Stopwatch***
If not using stopwatch, record *exact starting time* in minutes and seconds.

❖ ***Early Finish***
If subject finishes test items in less than 3 minutes, record *exact finishing time* in minutes and seconds on Test Record.

Allow subject to work for *exactly 3 minutes* and then say: **Stop. Put your pencil down.** Collect pencil and Response Booklet.

Record *exact finishing time* in minutes and seconds on Test Record.

End of Test 9
Sentence Reading
Fluency

Test 9 Sentence Reading Fluency

Sample Items

A. A cow is an animal. ..... (Y) N

B. A fish can read. ..... Y (N)

Practice Exercise

C. An apple is blue. ..... Y N

D. A wheel is round. ..... Y N

E. A man has two legs. ..... Y N

F. Ice is hot. ..... Y N

1. Fire is hot. ..... Y N
2. Dogs can eat. ..... Y N
3. A bird can fly. ..... Y N
4. Cats have five legs. ..... Y N
5. A clock tells time. ..... Y N
6. A bus has wings. ..... Y N
7. Cars have four wheels. ..... Y N
8. People can drive cars. ..... Y N
9. Candy is sweet. ..... Y N
10. A penny is round. ..... Y N
11. Milk is always blue. ..... Y N
12. Some days are sunny. ..... Y N
13. Windows can be washed. ..... Y N
14. Lawn chairs love to dance. ..... Y N
15. Birds sleep in big beds. ..... Y N
16. Most snakes fly through trees. ..... Y N
17. People like to drink gum. ..... Y N
18. A table has six arms. ..... Y N
19. An eagle is a bird. ..... Y N
20. Tires are always flat. ..... Y N
21. Pilots fly red bikes. ..... Y N
22. A train goes on the track. ..... Y N
23. A shoe goes on your head. ..... Y N
24. A bird may build a nest. ..... Y N
25. Milk comes out of gas pumps. ..... Y N
26. A door may have a lock. ..... Y N
27. A hat goes on your foot. ..... Y N
28. Elephants are large animals. ..... Y N
29. Many spiders can spin webs. ..... Y N
30. A butterfly has ten wings. ..... Y N
31. Glasses help people to hear. ..... Y N
32. Most poodles graduate from school. ..... Y N
33. Some fish live in the ocean. ..... Y N
34. The color of grass is red. ..... Y N
35. A school bus has a driver. ..... Y N
36. A plumber may fix a leak. ..... Y N
37. Snow is often green in color. ..... Y N
38. May is the month after March. ..... Y N
39. Most houses have only one room. ..... Y N
40. A fan may produce a breeze. ..... Y N
41. Many people like to play games. ..... Y N
42. People love to swim in puddles. ..... Y N
43. A beaver roars like a lion. ..... Y N
44. Some children like to watch cartoons. .... Y N
45. Some children fly kites on windy days. ..... Y N
46. Some people take medicine for colds. .... Y N
47. Berries can be different colors. ..... Y N
48. A dog may bark at a cat. ..... Y N
49. A boat can talk to a man. ..... Y N

Go to the next page →

50. You can drink milk through a straw. ..... Y N

51. A bicycle needs gas each day. ..... Y N

52. Fish like to prepare gourmet dinners. ..... Y N

53. An ocean has plenty of water. ..... Y N

54. Candy is always bitter to taste. ..... Y N

55. A magazine has only fourteen pages. ..... Y N

56. Children may eat soup with a spoon. ..... Y N

57. A plant's roots are above the ground. ..... Y N

58. Most people smile when they are sad. ..... Y N

59. All monkeys talk in complete sentences. ..... Y N

60. May is the last day of the week. ..... Y N

61. Big horses often sleep in small garages. ..... Y N

62. Floodwaters can cause soil erosion. ..... Y N

63. Winter is a season of the year. ..... Y N

64. Most people drive airplanes to the store. ..... Y N

65. A monkey is an insect that flies. ..... Y N

66. All mountains are very flat on top. ..... Y N

67. Roosters like to ride the bus to school. ..... Y N

68. Some people buy new homes in small towns. ..... Y N

69. Most people use keys to comb their hair. ..... Y N

70. A highway can have more than one lane. ..... Y N

71. A carpenter may build things with wood. ..... Y N

72. A hospital has more than one doctor. ..... Y N

73. Plans cannot be revised in a meeting. ..... Y N

74. Mice run in marathon races on Saturdays. ..... Y N

75. There are many different types of jewelry. ..... Y N

76. Some adults rent apartments in large cities. ..... Y N

77. Squirrels always deposit their money in banks. ..... Y N

78. Photo albums may hold many pictures. ..... Y N

79. Games can be played with a deck of cards. ..... Y N

80. A pitcher may be used to pour water. ..... Y N

81. Many bears walk down the middle of streets. ..... Y N

82. A trailer can be used to transport horses. ..... Y N

83. An old flashlight may need batteries to operate. ..... Y N

84. Some librarians put books back in the oven. ..... Y N

85. Some boys like to go swimming on hot days. ..... Y N

86. A car is so much bigger than a bus. ..... Y N

Go to the next page →

87. Most dogs can fly over the tops of mountains. ..... Y N

88. Tennis is a game some people like to play. ..... Y N

89. Parts of a hidden cavern may be unexplored. ..... Y N

90. Money is often used to start forest fires. ..... Y N

91. Every year all cars need to have new engines. ..... Y N

92. A lion eats paper when it is hungry. ..... Y N

93. You can see only one color in a rainbow. ..... Y N

94. A talented athlete may like several different sports. ..... Y N

95. Most people fill their pillows with rocks before sleeping. ..... Y N

96. The letter *A* is the last letter of the alphabet. ..... Y N

97. Children and adults are all the same height and weight. ..... Y N

98. One may see flowers along a trail in the spring. ..... Y N

99. Drivers may use a map to find certain locations. ..... Y N

100. People can use credit cards to buy clothes and supplies. ..... Y N

101. Calendars display the months, weeks, and days of a year. ..... Y N

102. A classroom teacher works all day in a grocery store. ..... Y N

103. Large dinosaurs may be found roaming in most national parks. ..... Y N

104. Some people like to go to another country for vacation. ..... Y N

105. A hammer is often used to write a funny story. ..... Y N

106. A map is used to help you find some numbers. ..... Y N

107. You may see an acrobat walk a tightrope at the circus. ..... Y N

108. A person can make a hotel reservation for just one night. ..... Y N

109. A variety of animal species can be found in the jungle. ..... Y N

110. Drivers never get tickets when they go over the speed limit. ..... Y N



Date Injury Occurred (mm/dd/yyyy):

Time of Injury (24 hour clock):

Day of week of injury:
☐Monday ☐Tuesday ☐Wednesday ☐Thursday ☐Friday ☐Saturday ☐Sunday

Source of information: ☐Clinician
☐Player ☐ Parent ☐ Coach ☐ Other

Reliability of injury data: ☐Verified ☐Estimated ☐Unknown

1. Who was the clinical assessment completed by?
   ☐Athletic Trainer ☐Coach ☐ Physicians Assistant
   ☐Medical Doctor ☐Physical Therapist ☐ Other

2. How confident was clinician that injury was a concussion?
   ☐Not at all Confident ☐Barely Confident ☐Somewhat Confident
   ☐Fairly Confident ☐Very Confident

3. If injury data is ESTIMATED, injury data type (point in time):
   ☐Time participant became symptomatic
   ☐Time of first trauma activation
   ☐Time of presentation to emergency dept

4. How many hours after the injury did the first evaluation take place?

5. How many hours after the injury did the second evaluation take place?

6. How many hours after the injury did the third evaluation take place?

7. Does subject have a baseline? ☐Yes ☐No

8. Was athlete taken out of game? ☐Yes ☐No

9. Did the athlete immediately report the injury? ☐Yes ☐No
   a. If no, how many minutes/hours after injury did athlete report it to someone?

10. Did athlete continue participation after suspected injury event? ☐Yes ☐No
    a. If so, for how long?
    b. For how many plays?

11. Did athlete go to ER? ☐Yes ☐No

12. Treated at hospital before study center? ☐Yes ☐No

13. Date treated at hospital: mm/dd/yyyy

14. Time treated at hospital: 24 hour clock

15. Hospital admission date:
    ☐ NA

16. Hospital admission time (mm/dd/yyyy; 24 hour clock):

17. Symptom onset date: mm/dd/yyyy

18. Symptom onset time: 24 hr clock

19. Were initial medical services received immediately after injury? ☐Yes ☐No ☐Unknown

20. Medical Services received:
    ☐CT/MRI
    ☐Hospitalization
    ☐Specialized therapies
    ☐Evaluation (neuro, psych)
    ☐Medications
    ☐Education on symptoms or course of injury
    ☐Other, specify:

21. At the time of injury, was any protective equipment worn? Helmet, mouthguard, tape, brace, other

22. Sport at time of injury

23. Position at time of injury

24. Injury occurred during: Game, practice, dryland/fitness, other

25. Injury involved: Sudden onset and contact with another player; sudden onset and no contact with another player; Gradual onset/overuse; unknown

26. Cause of injury (will depend on sport) – body check, tackle, intentional player contact (elbowing, roughing, cross-check, dueling for header, etc)

27. Mechanism of injury: direct blow to head, fell and hit head, hit head on environment, non head injury

28. Was a penalty called directly related to the injury event: Yes/no if yes, describe; who received penalty

29. Describe events surrounding the injury:

30. Injury location for each type of injury (often more than one injury at time of injury- list of all injury types and body parts)

31. Mechanism of Injury: ☐ Contact with another player ☐ Impact with ground ☐ Impact with object (i.e. ball)

32. Likelihood participant under influence of alcohol:
    ☐None ☐Suspected ☐Confirmed ☐Unknown

33. Location of impact:
    ☐Frontal
    ☐L temporal
    ☐R temporal

☐L parietal
☐R parietal
☐Occipital
☐Neck
☐Indirect force

34. Injury Description:

SYMPTOMS

35. Loss of consciousness ☐Yes ☐No
    a. Duration: ☐< 1 min ☐1-30 min ☐30 - 24 hr

36. Dizziness ☐Yes ☐No
    a. Duration: ☐0-1hr ☐1-24hr ☐>24hr

37. Retrograde amnesia ☐Yes ☐No
    a. Duration: ☐0-1hr ☐1-24hr ☐>24hr

38. Amnesia of event ☐Yes ☐No
    a. Duration: ☐0-1hr ☐1-24hr ☐>24hr

39. Post traumatic amnesia ☐Yes ☐No
    a. Duration: ☐0-1hr ☐1-24hr ☐>24hr

40. Confusion/disorientation ☐Yes ☐No

41. How long did symptoms last after injury/impact? days, hours, minutes

42. Symptoms:
    ☐Dizziness
    ☐Off-balance
    ☐Fogginess/ confusion
    ☐Nausea/vomiting
    ☐Memory loss
    ☐Vision changes
    ☐Headache

43. Baseline headache impact test-6 (HIT-6)

44. Follow-up headache impact test-6 (HIT-6)

45. Brain imaging abnormality: ☐Yes ☐No ☐No imaging
    a. Type of imaging:

46. Pain Assessment :

Faces Rating Scale (Wong Baker):



Explanation:

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

CHAPTER

3

c0003 # White Matter Abnormalities in MS: Advances in Diffusion Tensor Imaging/Tractography

A. Klimova, P. Singh, W.D.S. Killgore [AU1]

University of Arizona, Tucson, AZ, United States [AU2]

OUTLINE

A Brief Overview of the Neuropathology of Multiple Sclerosis 1

Neuroimaging in MS 2
- *T1-Weighted Imaging* 3
- *T1-Weighted Contrast Imaging* 3
- *T2-Weighted Imaging and FLAIR* 3
- *Magnetic Resonance Spectroscopic Imaging* 4
- *Diffusion Tensor Imaging* 4
- *DTI Findings in MS* 5
- *Relationship Between DTI Measures and Cognitive Profile of MS* 6
- *Relationship Between DTI Measures and Psychiatric Profile of MS* 7

Conclusions 7

References 8

s0010 ## A BRIEF OVERVIEW OF THE NEUROPATHOLOGY OF MULTIPLE SCLEROSIS

p0045 Multiple sclerosis (MS) is an acquired progressive inflammatory demyelinating condition affecting the central nervous system (CNS) that often presents with a relapsing and remitting course. To understand the symptoms and presentation of MS, it is crucial to first understand the basic neuropathology and associated neuroanatomy that is affected by the disease. MS generally involves neuropathology affecting three primary features of the neuron and surrounding tissue. These features are lesions, inflammation, and damage to the myelin sheath that surrounds the axons of a neuron. As shown in Fig. 3.1, a neuron is composed of cell body with branch-like dendrites and a longer fiber projection called an axon. It is the axons that permit neural communication over significant distances within the nervous system. A neural signal originating in the cell body travels along the axon and terminates at the synaptic bouton, where neurotransmitters are released into the synapse to stimulate adjacent neurons. The terms gray matter (GM) and white matter (WM) are often used to describe various aspects of these neuronal tissues. Specifically, brain tissue such as the cerebral cortex is often labeled as GM because it comprises dense clustering of the cell bodies of neurons, leading to a characteristic grayish appearance to the naked eye or when seen on standard T1 magnetic resonance imaging (MRI) scans. WM comprises the axons and their surrounding myelin insulation. The axon is a protoplasmic projection from the cell body that allows rapid transduction of an electrochemical signal, known as an action potential, across longer distances of the nervous system. In humans, axons are insulated by a fatty white-appearing covering called myelin. The layer of myelin is produced by the attachment of glial cells to the axon (oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system, PNS). The myelin sheath covering is discontinuous and the gaps between the myelin sheath on axon are known as nodes of Ranvier. These gaps allow exchange of ions with the extracellular space which helps regeneration of action potential across the axon. The myelin covering enables faster conduction

© 2017 Elsevier Inc. All rights reserved.

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

f0010

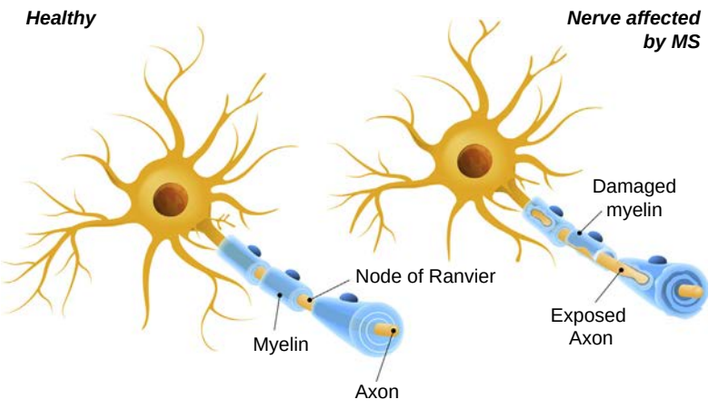


FIGURE 3.1 A graphical representation of the anatomical structure of a neuron and comparison between a healthy neuron and a neuron affected by multiple sclerosis (MS). As shown in the figure, the myelin sheath surrounding the axon is damaged in MS. *Reprinted with permission from* www.123rf.com*; designua © 123RF.com.*

[AU10]

of the action potential across neurons by permitting the neural impulse to propagate rapidly from node to node.

p0050 In brief, the pathology of MS involves damage to the myelin sheath, which results in disturbances in conduction of nerve impulses, which in turn affects motor, sensory, visual, and autonomic systems.[11] These disturbances may manifest in several ways. First, lesions (or plaques) to the WM, brain stem, basal ganglia, optic nerve, and spinal cord are among the most commonly observed.[12] These lesions are a result of demyelination and subsequent attempts of remyelination, which builds up plaques along the damaged axons eventually.[12] MS also is associated with the loss of oligodendrocytes, which are responsible for the production of myelin in the CNS.[12] Second, MS can lead to a disruption of the blood–brain barrier, which allows T cells to enter the CNS and initiate a cascade of other immune responses, which in turn commences inflammation.[12] There are four clinical subtypes of MS[8]: (1) relapsing remitting (RR) type—which is the most common pattern and involves periods of flair-ups followed by periods of relative dormancy; (2) secondary progressive (SP) type—which involves a slow worsening of symptoms over time, often with a relapsing and remitting progression; (3) primary progressive (PP) type—which involves a slow but fairly consistent worsening of symptoms over time, without a clear relapse/remission pattern; and (4) progressive relapsing type—which involves a progressive worsening of symptoms with acute periods of exacerbations without clear remissions.

s0015 NEUROIMAGING IN MS

p0055 MS is a challenging disease when it comes to diagnosis and treatment. Over the past decade, the development of new imaging modalities such as MRI has revolutionized the management of this disease, particularly with regard to diagnosis and monitoring disease progression. In this chapter, we briefly outline the use of standard clinical MRI scans for diagnosis and monitoring, and introduce the investigational use of newer cutting edge neuroimaging technologies, such as diffusion tensor imaging (DTI) and fiber tractography, which hold the promise of rapidly advancing understanding of this debilitating disease.

p0060 MRI is a widely used imaging modality that provides excellent resolution of the lesions common to MS. Standard MRI scans work on basic principles of quantum mechanics. In brief, during a typical MRI scan, the body part of interest is placed within a strong magnetic field, which aligns a large number of the hydrogen protons in the direction of the magnetic field. By applying a radio frequency (RF) pulse to the body part, the orientation of the protons can be momentarily reoriented. After cessation of the RF pulse, the realignment of the protons with the magnetic field will lead to a change in magnetic flux which can be captured by the receiver coil in the scanner and used to reconstruct three-dimensional images of the body part. Depending on the pulse sequences and imaging parameters used, the MRI can produce various sequences such as T1-weighted (T1WI), T1 contrast-enhanced (T1C), T2-weighted (T2WI), fluid-attenuated inversion recovery (FLAIR), DTI, and magnetic resonance spectroscopy (MRS), each providing meaningful information about the health and structure of the tissues and structures being imaged. Fig. 3.2 shows examples of T2WI scans showing MS lesions. MRI scans can be used clinically to make a diagnosis of MS. The McDonald criteria,[13] currently considered the most reliable method of MS diagnosis, rely upon MRI to demonstrate the dissemination of lesions in time and space. Table 3.1 represents the most recent (2011) version of these criteria for [AU4] using T2WI MRI images to diagnose MS.[18] In the next

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

f0015

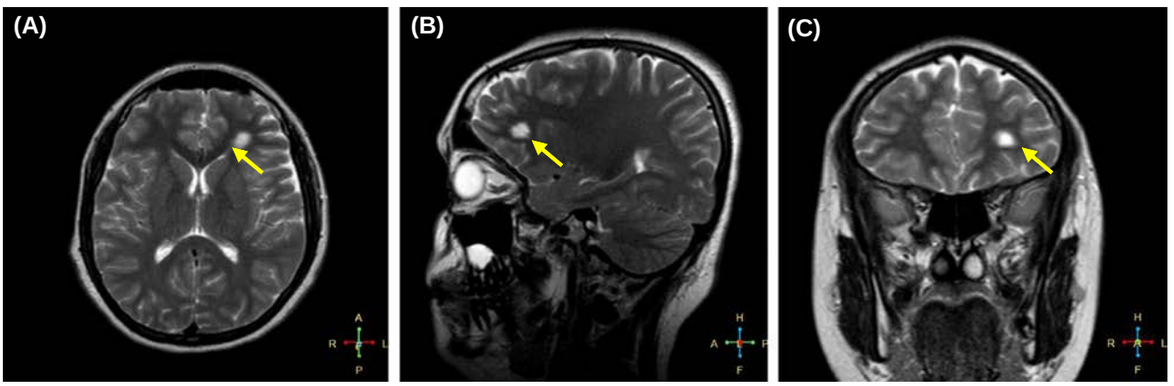


FIGURE 3.2 T2 weighted structural scans showing an oval shaped hyperintense lesion in the left forceps minor region on (A) axial view, (B) sagittal view, and (C) coronal view. *Reprinted with permission from* www.radiopaedia.org*; image courtesy of Dr. Ahmed Abd Rabou.*

t0010 **TABLE 3.1** Revised McDonald Criteria[18]

Dissemination in Space	Dissemination in Time
≥1 T2 lesions in two or more of the following locations: • Periventricular • Juxtacortical • Infratentorial • Spinal cord ◦ If a patient has a brain stem/spinal cord syndrome, the symptomatic lesion(s) are excluded from the criteria, not contributing to the lesion count	• A new lesion on follow-up MRI-T2 lesion and/or gadolinium enhancing or • Presence of asymptomatic gadolinium-enhancing lesion and a nonenhancing T2 lesion on any one scan

[AU5]

few paragraphs, we outline some of the major findings on each type of MRI scan in patients with MS.

s0020 ## T1-Weighted Imaging

p0065 While T1WI provide exquisite detail of the brain and show clear demarcation between GW and WM, they are not as sensitive as T2WI for detecting MS. In general, T1WI findings vary on the basis of duration and severity of the disease. Axonal loss or destruction in early stages of disease can appear as hypointense or isointense ovoid, rounded or linear shaped lesions, appearing as dark spots on the scan. These are usually seen along the callososeptal interface or periventricular area and are referred to as T1 *black holes*. Sometimes, as the disease progresses the black holes may be marked by a peripheral rim of hyperintensity due to macrophage infiltration and lipid peroxidation of the surrounding tissues. This gives the lesions a *beveled* or a *lesion-within-lesion appearance*. In advanced stages of disease, thinning of corpus callosum (CC) with or without generalized brain atrophy can be seen on T1WI.

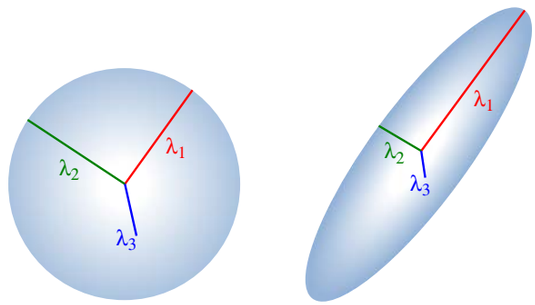
s0025 ## T1-Weighted Contrast Imaging

p0070 Adding a contrast agent to an MRI scan can help in identifying certain lesions or pathologies. In the case of MS, gadolinium contrast can be used with a T1 sequence to highlight the actively demyelinating lesions. The lesions can appear punctate, nodular, or rim shaped contrast-enhancing lesions in the cerebral WM. An incomplete rim with the open nonenhancing end facing toward the cortex resembling a horseshoe is a characteristic finding of MS seen on this sequence. The "horse shoe sign" represents active stage of disease. Treatment with steroids drastically suppresses the enhancement and appearance of these lesions.

s0030 ## T2-Weighted Imaging and FLAIR

p0075 The T2 sequence, especially FLAIR, is considered to be the most sensitive MRI scan for detecting MS plaques. These images are helpful for identifying lesions because they suppress the appearance of cerebrospinal fluid, which allows for greater resolution in detecting lesions in the periventricular regions. Multiple hyperintense lesions, sometimes surrounded by hypointense peripheral rim with perilesional edema, can be seen. The lesions can be ovoid (as shown in Fig. 3.2), linear, circular, or triangular in shape. A triangular shaped lesion with the base of triangle adjacent to the lateral ventricle and apex pointing toward the cortex is one of the typical findings of MS. Perivenular collection of inflammatory cells along medullary veins can be seen as hyperintensities

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.



f0020

FIGURE 3.3 Illustrative example of prototypical water diffusion. Isotropic diffusion means that water molecules can diffuse equally in all directions, as illustrated by a spherical pattern. Anisotropic diffusion means that water molecules are constrained and diffuse more readily in one direction (l_1) than in the other two directions (l_2 and l_3).

perpendicular to the lateral ventricles on axial and sagittal views. This finding is referred to as *Dawson fingers*. The callososeptal interface may show alternate areas of hyperintensity and hypointensity on FLAIR sagittal view giving a dot–dash appearance. This is known as the *dot–dash sign* and is one of the earliest characteristic finding of MS.

s0035 Magnetic Resonance Spectroscopic Imaging

p0080 Proton MRS is one of the unique applications of the MRI technique. It yields the information about the chemical composition of different metabolites in the tissues rather than information about anatomical structure or function. Biochemical changes are common within a tissue that is affected by certain disease states. These changes are then compared with the normal distribution of the chemicals to assess the degree and extent of damage within that tissue. While the range of neurochemicals that can be assessed with MRS is limited, there are some that may be particularly important in the case of MS. In particular, N-acetyl aspartate (NAA) is an extremely abundant chemical in the brain, particularly within myelin, so it could be an indicator of WM damage in MS. In fact, evidence reported in 2014 supports the suggestion that in primary and SP type of MS the MRS shows decreased levels of NAA, suggesting a biomarker of axonal damage.[27] Other neurochemicals have been found to be elevated in acute lesions of MS, including the levels of myoinositol, choline, and glutamate.[25]

s0040 Diffusion Tensor Imaging

p0085 DTI is a relatively new neuroimaging technique that has been used to study WM alterations in a great variety of conditions, ranging from depression, to traumatic brain injury, to MS. DTI measures the movement of water molecules within the living tissue,[2] permitting inference regarding the underlying structure of the tissues and their membranes. The motion of water molecules can be described in geometric terms as either resembling a sphere or an elongated ellipsoid and is characterized as being either isotropic or anisotropic in nature, respectively. Isotropic movement occurs when water molecules are unconstrained and free to move in any direction equally, and would thus be best defined as a spherical diffusion pattern. On the other hand, water moving in a tube or garden hose would move preferentially in one direction much more than in other directions, and would therefore be better characterized as anisotropic (i.e., an ellipsoid) pattern of diffusion.[2] For instance, due to the lack of axons within the brain ventricles that would have restricted the movement otherwise, the water is free to move in any direction and hence the movement within these structures would be described as being isotropic. In the brain WM, on the other hand, the presence of axons restricts the movement of water molecules in a particular direction and therefore movement within WM regions is predominantly anisotropic in nature.

p0090 Axons are not always perfectly aligned along one axis and in order to avoid having to measure diffusion along an impractically large number of axes, a concept of diffusion ellipsoid has been developed.[15] The diffusion ellipsoid is defined using three eigenvectors that have three corresponding eigenvalues (λ_1, λ_2, and λ_3) that describe their physical length.[16] The longest, medium, and shortest eigenvectors are represented by λ_1, λ_2, and λ_3, respectively.[16] Fig. 3.3 shows the relationships between these three eigenvectors for isotropic and anisotropic shapes.

p0095 A number of diffusion measurements have been developed in an attempt to characterize diffusion patterns within the brain WM. Fractional anisotropy (FA) is a global diffusivity measure that measures the degree of anisotropy and is used to evaluate WM integrity. FA is defined by the following formula[15]:

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

p0100 FA values range from 0 to 1, with higher values indicating higher anisotropy (i.e., water diffuses more along one axis relative to the others). Mean diffusivity (MD) has also frequently been used to measure the overall diffusivity and represents the average of the three eigenvalues[29]:

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}$$

p0105 Two other DTI metrics that have been proposed to further explain changes in the global measures (i.e., FA

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

and MD) are radial diffusivity (RD) and axonal diffusivity (AD). RD is used to measure diffusion across the axon whereas AD describes movement of water molecules along the axon. Changes within these metrics have been attributed to demyelination and axonal damage, respectively. In their pioneering studies, Song and colleagues showed that loss of myelin following retinal ischemia in mouse optic nerve was associated with increased RD and unchanged axial diffusivity. [22–24] Moreover, they showed that axonal degeneration observed during histological analysis was concurrently associated with reduced AD and unaltered RD.[22] Therefore, these metrics have been used to describe potential reasons for changes within the global diffusivity measures. RD is defined in the following way[23]:

$$\lambda\perp = \frac{(\lambda_2 + \lambda_3)}{2}$$

AD is represented by $\lambda\| = \lambda_1$[23].

DTI Findings in MS

Using conventional MRI, earlier studies were able to demonstrate macrostructural damage, such as WM lesions, that underlie the physical and cognitive disturbances that are commonly observed in MS. With application of DTI to a wider range of illnesses including MS, both physicians and scientists were able to better understand this condition on a microstructural level. One of the earliest studies by Werring, Clark, Barker, Thompson, and Miller[28] showed reduced FA and high MD in normal-appearing white matter (NAWM) in frontal, parietal, temporal, and occipital regions. Based on the earlier description, this suggests that MS is associated with regions of greater spherically shaped diffusion, potentially suggesting poorer axonal integrity or disruption of myelin (see Fig. 3.4B and C). An important implication from these findings is the notion that WM changes may start occurring before clinical symptoms emerge and remain undetectable using conventional MRI and hence potentially delay clinical interventions that could affect the onset of the illness or reduce its severity.

More recent studies have rectified this earlier limitation by investigating individual WM fiber bundles with the advent of WM tractography (Fig. 3.4A), an outgrowth of DTI procedures. This technique allows a more accurate identification and description of WM architecture. As shown in Fig. 3.4, it is possible to use the FA values at individual locations throughout the brain to determine the probable fiber pathways representing large bundles of axons and plot them for visual representation. Fink et al.[5] have investigated coherence within a number of WM regions including the uncinate fasciculus (UF), superior longitudinal fasciculus, fornix, and cingulum in a group of MS patients. The left UF showed reduced FA and increased MD while the right UF was characterized by increased RD. Increase in RD has been frequently interpreted to signal demyelination.[22] In addition, there was a bilateral reduction in FA within the fornix. Similar to the UF findings, increased RD was observed in the left cingulum.

Similarly, Hecke et al.[7] used voxel-based morphometry that implements whole-brain approach to studying brain WM to examine WM microstructure in RR and SP MS. They have demonstrated reduced FA in a number of WM tracts including the inferior longitudinal fasciculus (ILF), capsula interna, and forceps major in MS patients. There were also changes in AD that were consistent with the FA findings such that lower AD was observed in the ILF and capsula interna, as well as in the body of the CC and corona radiata (CR). Increased MD and RD were observed in the ILF, the capsula interna and externa, genu, body, and splenium of the CC, forceps major, and CR. These findings therefore indicate that MS is characterized by both axonal damage and demyelination, although the precise location of the damage varies by tract.

Kern, Sarcona, Montag, Giesser, and Sicotte[9] studied the relationship between WM integrity and motor function in RR MS using whole-brain DTI analysis as well as probabilistic tractography. This study observed 7.1% decrease in FA in the CC, CR, cingulum, and internal capsule, with concurrent 24.95% increase in RD within these regions, thus suggesting demyelination. Other regions with reduced RD included the cortico-spinal tract, right cerebellar peduncle, right external capsule, and left cerebellum. These changes in WM metrics were related to performance of motor tasks. In particular, reduced FA and increased RD in the body of the CC and mid-posterior CR was associated with reduced right-hand performance on the nine-hole peg test (NHPT). Increased RD in cortical WM adjacent to the left motor and right frontal cortices also predicted poor right-hand performance on the NHPT. Furthermore, worse left-hand performance was related to the reduced FA in the body of the CC and a region of occipital WM. These results suggest that at least motor dysfunction observed in MS is differentially affected by WM compromise due to asymmetry. Finally, increased RD at baseline predicted decrease in performance on the NHPT[9].

In 2015, Asaf, Evan, and Anat[1] studied a large sample of RR MS participants using whole-brain analysis approach in order to examine temporal timeframe of WM degeneration. This study included participants with MS at different stages of the disease duration: less than 1 year (short duration), 1 year (medium duration) and over 1 year (up to 6 years; long duration). Compared to medium disease duration, long disease duration was characterized by diffuse reduction in FA, especially in the body of the CC, by 22%. In the short disease duration

10003-WATSON-9780128052983

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

f0025

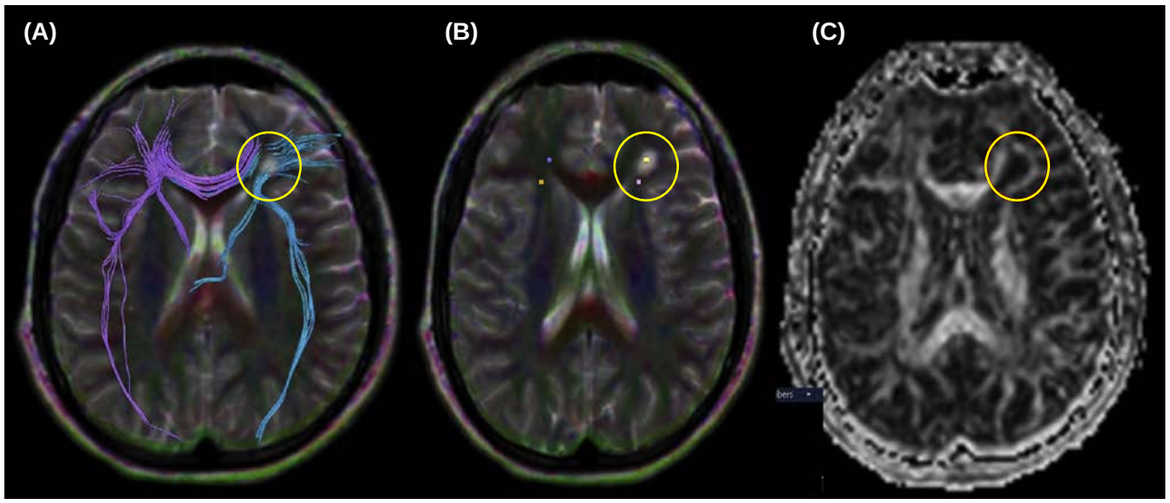


FIGURE 3.4 DTI findings for a plaque located in the left forceps minor region. (A) A tractographic image revealing destruction of white matter fibers at the site of plaque (*circled*). (B) A combination of anatomical color map with T2WI image with ROI markings at the site of plaque (*circled*) and normal appearing white matter. The circled ROI at the site of plaque shows decreased FA and increase ADC indicating increased diffusion of water molecules. (C) The FA map. White matter fibers appear bright except at the site of the plaque which appears dark as the diffusion becomes isotropic (*circled*). *Reprinted with permission from* www.radiopaedia.org*; image courtesy of Dr. Ahmed Abd Rabou.*

group, FA was reduced by 31% compared to healthy controls, especially in the ILF. There was no difference between the short disease duration and medium disease duration. Overall, disease duration negatively correlated with FA. This study provides evidence for a time-dependent WM atrophy that affects different tracts to a variable degree.

p0140 Similarly, Sigal, Shmuel, Mark, Gil, and Anat[21] showed an association between disease duration and changes in diffusivity measures. Specifically, this study observed a positive correlation between disease duration and rate of relapse and average diffusivity coefficient (ADC). Moreover, lower FA and increased AD and RD were observed in the MS group compared to healthy controls in the whole CC but not within its subregions. These findings further suggest that WM degeneration is temporally contingent. Taken together, these observations led researchers to explore the association between this trend and corresponding cognitive deterioration.

s0050 Relationship Between DTI Measures and Cognitive Profile of MS

p0145 Following the initial investigations into the WM changes in MS, researchers became interested in examining the effects that these neural changes have on the cognitive profile associated with this condition. Koenig et al.[10] used probabilistic tractography to investigate the relationship between the WM and cognitive function in RR and SP MS. This study observed reduced FA and increased RD, AD, and MD in the posterior cingulate bundle in the MS group compared to controls. The findings also indicated that episodic memory, as measured by the Brief Visuospatial Memory Test-R (BVMT), was a significant predictor of RD in the posterior cingulate bundle. Moreover, speed of processing, as measured by the Symbol Digit Modalities Test (SDMT), was a strong predictor of RD in the posterior limb of the internal capsule and posterior cingulate bundle. Taken together, these findings indicate that MS is associated with WM abnormalities within tracts that have traditionally been implicated in emotion, attention, and memory. These alterations were, in turn, manifested by memory and attention problems.

p0150 Memory problems are frequently observed in MS and have therefore been studied in relation to WM microstructure. Hecke et al.[7] studied working memory in a group of RR MS patients using whole-brain voxel-based morphometry. They observed reduction in FA in the group of MS patients compared to healthy controls in a number of major WM tracts, including the ILF, capsula interna, and forceps major and concurrently reduced AD in the ILF, capsula interna, body of CC, and CR. Additionally, there was an increase in RD and MD in the ILF, capsula interna and externa, genu, body, and splenium of the CC, forceps major, and CR. These diffusion measures were also shown to be related to performance on working memory tasks, such as Paced Auditory Serial Addition Test (PASAT). In particular, there was a significant positive correlation between PASAT and FA in the left ILF, forceps minor, the capsula interna and externa, genu of the CC, left cingulum, superior longitudinal fasciculus (SLF), and CR. This pattern of results was also observed in a study by Syc et al.[26] who used continuous

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

tractography method to study the microstructure of the cingulum and fornix. This study observed 19% reduction in FA in a group of RR, SP, and PP MS in the fornix, with a concurrent increase in RD, AD, and MD. There was also an increase in RD, AD, and MD within the left and right cingulum, with no significant changes within FA. In the left cingulum, there was a significant association between the diffusivity measures and performance on the PASAT of information processing and attention, where lower scores on the test were associated with lower FA and higher MD and RD.

p0155 Contrary to Syc et al.,[26] using the same tractography method, Ozturk et al.[17] studied microarchitecture of the subregions of the CC in relation to performance on the PASAT in a sample of RR, SP, and PP MS patients. The findings of that study showed reduced FA and increased RD and MD in the whole CC in MS compared to healthy controls. When subregions of the CC were studied individually, a positive correlation was observed between FA and the body and splenium of the CC. This finding not only suggests the involvement of multiple tracts in performance of PASAT but is also indicative of heterogeneous changes within different portions of the CC in this condition. Caligiuri et al.[3] have examined the role of the callosal subregions in cognitive function in MS. They observed an association between FA in the genu and splenium of the CC and cognitive function where cognitive impairment was significantly related to reduction in FA. Since the study by Caligiuri et al.[3] used a compound score to measure cognitive function, it cannot be directly compared to the results of the study by Ozturk et al.[17] who observed change in different subregions of the CC in relation to performance on the PASAT.

p0160 Another test that is frequently used to assess cognitive difficulties observed in MS is California Verbal Learning Test (CVLT), a task specifically designed to assess short- and long-term verbal memory. Performance on this assessment has recently been studied in conjunction with WM damage observed in MS. Using tractography, Fink et al.[5] studied microarchitecture of the UF, SLF, cingulum, and fornix and observed that RD within the UF predicted performance on the encoding subscale of the CVLT. Moreover, this study also showed a significant positive correlation between the recognition subscale of the CVLT and PD in the right fornix. These results indicate that in this clinical population, different aspects of verbal memory are differently affected depending on the specificity of WM damage as assessed by DTI techniques.

s0055 Relationship Between DTI Measures and Psychiatric Profile of MS

p0165 Apart from the cognitive complaints, emotional problems have also been observed in patients with MS. In particular, depression is one of the most frequently reported psychiatric sequelae. The lifetime prevalence of depression in MS is estimated to be 25–50%.[14] Pujol, Bello, Deus, Marti-Vilalta, and Capdevila[19] studied structural alterations in the frontal and temporal regions in depressed MS patients. Their results showed an association between lesions in the arcuate fasciculus and greater depressive symptoms. These lesions predicted approximately 17% of variance in depressive scores. Feinstein et al.[4] studied NAWM in MS patients. Their results showed greater reduction in FA in the left anterior NAWM in the depressed MS compared to nondepressed MS. Additionally, increased MD was observed in the right inferior frontal lobe.

p0170 In a DTI study reported in 2014, Gobbi et al.[6] performed a whole-brain analysis looking at both PP and SP forms of MS. They observed reduced FA in the forceps minor in the depressed subgroup compared to the nondepressed participants. This finding is of a particular significance given that this region of the CC connects parts of the dorso-medial prefrontal cortex (DMPFC) and has been implicated in the pathogenesis of depression.[6]. Pujol et al.[19] studied the microstructure of the arcuate fasciculus in patients with MS and showed that lesions within this tract were associated with cognitive expression of mood in these patients. After controlling for cognitive deficits, lesions in the arcuate fasciculus predicted 26% of variance in the Beck Depression Inventory (BDI) scores[19] Shen et al.[20] used whole-brain analysis to examine the association between WM architecture and the Hamilton Rating Scale for Depression (HAM-D). This study has showed a positive association between the scores on HAM-D and FA in a number of WM regions including the right precentral gyrus, cingulate gyrus, and posterior cingulate. This is inconsistent with past research showing decreased WM integrity with increased depressive symptoms. This finding may be attributable to the compensatory mechanisms that have been previously observed.

CONCLUSIONS s0060

p0175 MS is a progressive and debilitating disease that affects the myelin sheath of axonal pathways. Traditional clinical imaging, particularly T2-weighted MRI, has revolutionized the ability of researchers and clinicians to diagnose and track disease progression. These types of MRI scans provide clear evidence of the characteristic lesions of MS. Nonetheless, advances in MRI technology, particularly DTI and fiber tractography are providing even greater resolution and understanding of how MS affects specific fiber tracts and may allow an even more precise monitoring of disease progression. While these

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter TNQ Books and Journals Pvt Ltd. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is until formal publication.

newer DTI methods are still primarily investigational, they hold great promise for furthering understanding of MS and its underlying pathology.

References

1. Asaf A, Evan S, Anat A. Injury to white matter tracts in relapsing–remitting multiple sclerosis: a possible therapeutic window within the first 5 years from onset using diffusion-tensor imaging tract-based spatial statistics. *Neuroimage Clin* 2015;**8**:261–6.
2. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci* 2008;**34**(1):51–61.
3. Caligiuri ME, Barone S, Cherubini A, Augimeri A, Chiriaco C, Trotta M, et al. The relationship between regional microstructural abnormalities of the corpus callosum and physical and cognitive disability in relapsing–remitting multiple sclerosis. *Neuroimage Clin* 2015;**7**:28–33.
4. Feinstein A, O'Connor P, Akbar N, Moradzadeh L, Scott C, Lobaugh N. Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. *Mult Scler* 2009.
5. Fink F, Eling P, Rischkau E, Beyer N, Tomandl B, Klein J, et al. The association between California Verbal Learning Test performance and fibre impairment in multiple sclerosis: evidence from diffusion tensor imaging. *Mult Scler* 2010;**16**(3):332–41.
6. Gobbi C, Rocca M, Pagani E, Riccitelli G, Pravatà E, Radaelli M, et al. Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis. *Mult Scler J* 2014;**20**(12):1633–40.
7. Hecke WV, Nagels G, Leemans A, Vandervliet E, Sijbers J, Parizel PM. Correlation of cognitive dysfunction and diffusion tensor MRI measures in patients with mild and moderate multiple sclerosis. *J Magn Reson Imaging* 2010;**31**(6):1492–8.
8. Hooper K. *Managing progressive MS*. New York: National Multiple Sclerosis Society; 2011.
9. Kern KC, Sarcona J, Montag M, Giesser BS, Sicotte NL. Corpus callosal diffusivity predicts motor impairment in relapsing–remitting multiple sclerosis: a TBSS and tractography study. *Neuroimage* 2011;**55**(3):1169–77.
10. Koenig KA, Sakaie KE, Lowe MJ, Lin J, Stone L, Bermel RA, et al. The relationship between cognitive function and high-resolution diffusion tensor MRI of the cingulum bundle in multiple sclerosis. *Mult Scler J* 2015. http://dx.doi.org/10.1177/1352458515576983.
11. Lassmann H, Brück W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol* 2007;**17**(2):210–8.
12. Lumsden C. The neuropathology of multiple sclerosis. In: Vinker P, Bruyn G, editors. *Handbook of clinical neurology*. Amsterdam: North Holland; 1970. p. 217–309.
13. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;**50**:121–7.
14. Minden SL, Schiffer RB. Affective disorders in multiple sclerosis review and recommendations for clinical research. *Arch Neurol* 1990;**47**(1):98–104.
15. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 2006;**51**(5):527–39.
16. O'Donnell LJ, Westin C-F. An introduction to diffusion tensor image analysis. *Neurosurg Clin N Am* 2011;**22**(2):185–96.
17. Ozturk A, Smith S, Gordon-Lipkin E, Harrison D, Shiee N, Pham D, et al. MRI of the corpus callosum in multiple sclerosis: association with disability. *Mult Scler* 2010;**16**(2):166–77.
18. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;**69**:292–302.
19. Pujol J, Bello J, Deus J, Marti-Vilalta J, Capdevila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* 1997;**49**(4):1105–10.
20. Shen Y, Bai L, Gao Y, Cui F, Tan Z, Tao Y, et al. Depressive symptoms in multiple sclerosis from an in vivo study with TBSS. *Biomed Res Int* 2014;**2014**.
21. Sigal T, Shmuel M, Mark D, Gil H, Anat A. Diffusion tensor imaging of corpus callosum integrity in multiple sclerosis: correlation with disease variables. *J Neuroimaging* 2012;**22**(1):33–7.
22. Song S-K, Sun S-W, Ju W-K, Lin S-J, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 2003;**20**(3):1714–22.
23. Song S-K, Sun S-W, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 2002;**17**(3):1429–36.
24. Song S-K, Yoshino J, Le TQ, Lin S-J, Sun S-W, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 2005;**26**(1):132–40.
25. Srinivasan R, Sailasuta N, Hurd R, Nelson S, Pelletier D. Evidence of elevated glutamate in multiple sclerosis using magnetic resonance spectroscopy at 3 T. *Brain* 2005;**128**:1016–25.
26. Syc SB, Harrison DM, Saidha S, Seigo M, Calabresi PA, Reich DS. Quantitative MRI demonstrates abnormality of the fornix and cingulum in multiple sclerosis. *Mult Scler Int* 2013;**2013**.
27. Trentini A, Comabella M, Tintore M, Koel-Simmelink MJ, Killestein J, Roos B, et al. N-acetylaspartate and neurofilaments as biomarkers of axonal damage in patients with progressive forms of multiple sclerosis. *J Neurol* 2014;**261**:2338–43.
28. Werring D, Clark C, Barker G, Thompson A, Miller D. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. *Neurology* 1999;**52**(8):1626.
29. Whitford TJ, Kubicki M, Shenton ME. Structural neuroimaging of schizophrenia. In: Shenton ME, Turetsky BI, editors. *Understanding neuropsychiatric disorders: insights from neuroimaging*. Cambridge: Cambridge University Press; 2011. p. 1–30.

WATSON: 03

Non-Print Items

Abstract

Multiple sclerosis (MS) is a chronic debilitating disorder affecting the central nervous system (CNS), particularly the white matter. Over the years, there have been significant advances made in the management of MS including diagnosis and treatment. Magnetic resonance imaging (MRI) is one if the neuroimaging modalities which has revolutionized the diagnosis and early detection of the disease. MRI has also proven useful to monitor disease progression in patients with MS and estimate its prognosis. In this chapter we have described the neuroimaging findings in MS using various methods of MRI. On the basis of sequence and imaging parameters applied, MRI scans can provide T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (MRS) images, all of which may have applicability in the evaluation of patients with MS. Some of these sequences, especially DTI and MRS, have proven particularly helpful in understanding the pathology of this disease from a new perspective. We focus extensively on the recent development and application of DTI and fiber tractography in understanding and characterizing the white matter lesions that occur in MS. The application of these methods holds considerable promise for advancing our understanding of MS.

[AU3]

Keywords: Autoimmune; Demyelination; Diffusion tensor imaging (DTI); Diffusion weighted imaging (DWI); Fluid-attenuated inversion recovery (FLAIR); Fractional anisotropy (FA); Magnetic resonance imaging (MRI); Multiple sclerosis; Neuroimaging; Neuron; Tractography.

Disrupted Thalamocortical Connectivity following Mild Traumatic Brain Injury: Associations with Daytime Sleepiness

Natalie S. Dailey[1,*], Brieann C. Satterfield[1], Adam C. Raikes[1], Michael J. Strong[1], Brittany Forbeck[1], Michael A. Grandner[2], & William D. S. Killgore[1,]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

[2]Sleep and Health Research Program, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

**E-mail:* ndailey@psychiatry.arizona.edu

Introduction
Changes in sleep are commonly reported by upwards of 70% of individuals who have experienced a mild traumatic brain injury (mTBI). Among those with mTBI, increased daytime sleepiness is one of the most frequent self-reported complaints. Previous research demonstrates changes to thalamocortical connectivity associated with daytime sleepiness in healthy populations. The present study focused on identifying this association following a mTBI. We hypothesized that thalamocortical connectivity and daytime sleepiness associations would differ significantly between adults with mTBI and healthy controls (HC).

Methods
A total of 64 individuals participated in the study, including 23 HC and 41 individuals with mTBI. Individuals in the mTBI group had a documented injury sustained within the past 12 months. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), while functional connectivity was measured using resting-state functional magnetic resonance imaging (rs-fMRI). A seed-to-voxel analysis, using bilateral thalamic seed regions, was conducted in the CONN toolbox to identify differences in the association between thalamocortical connectivity and ESS between the two groups.

Results
Daytime sleepiness was significantly greater in those with mTBI (M = 9.83, SD = 3.86) compared to HCs (M = 5.35, SD = 3.58) (t = -4.57, p<.001). Significant anticorrelations between thalamocortical connectivity and ESS were found in the HC compared to limited associations in the mTBI group (whole-brain height threshold p < .001 uncorrected, two-sided; cluster threshold p < .05 FWE-corrected). Specifically, lower ESS scores were associated with greater functional connectivity between the thalamus and bilateral premotor cortices (BA6; R, p<.001; L, p<.05), left primary somatosensory cortex (BA1; p<.001), left primary motor cortex (BA4; p<.01), right hippocampus (p<.05), an association that was weaker in mTBI.

Conclusion: Lower daytime sleepiness was associated with greater thalamocortical connectivity, specifically to somatosensory and motor regions, in healthy controls, but not in those with mTBI. It is well established that thalamocortical projections are critically involved in sleep and arousal states. Our findings suggest well-established thalamocortical associations with sleepiness are disrupted following mTBI. These findings may reflect a neurobiological underpinning for sleep disturbances in mTBI.

Supported by USAMRMC grant (W81XWH-12-0386) awarded to WDS Killgore.

Self-Initiated Verbal Recall Strategies Following Mild Traumatic Brain Injury

Corinne Meinhausen[1], Simon Esbit[1], Natalie S. Dailey[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective

Impaired memory is frequently reported following an mTBI, yet little is known about the recovery timeline. This study sought to identify the self-initiated memory retrieval strategies used at different timepoints post mTBI. We predicted poorer total verbal recall and differences in recall strategy utilization during the sub-acute stage compared to the chronic stage and healthy controls (HCs). We evaluated two verbal recall strategies, serial clustering (recalling words in the order in which they were heard) and semantic clustering (grouping words by meaning) as well as recall distribution.

Participants and Methods

One hundred and eight adults completed this study. Groups consisted of those 2-12 weeks post-mTBI (sub-acute, n=40), 6-12 months post-mTBI (chronic, n=39), and healthy controls (HC, n=29). Serial clustering (SRC) and semantic clustering (SMC) utilization and the percentage of words recalled from the beginning (PR), middle (MR), and end (RR) was assessed using the California Verbal Learning Test, 2nd Edition (CVLT-II). A Multivariate Analysis of Variance (MANOVA) was calculated to determine whether the three groups differed on total words recalled, PR, MR, and RR. Due to non-normality, the non-parametric Kruskal-Wallis test was used to assess SMC, SRC, and recall distribution.

Results

Overall performance on the CVLT-II was similar across groups. There were no significant differences in PR, MR or RR. There was a significant main effect of group on semantic ($\chi^2(2) = 8.54$, $p = .01$) and serial clustering ($\chi^2(2) = 9.07$, $p = .01$). Post-hoc analyses of significant effects indicated the sub-acute group produced significantly more semantic clusters than the HC group ($p = .03$,) and the chronic mTBI group ($p = .05$) and significantly fewer serial clusters than the HC group ($p = .03$) and chronic mTBI ($p = .03$) groups.

Conclusions

The findings indicate differences in verbal recall strategy utilization in the early stages of mTBI recovery, compared to later stages of recovery and healthy controls. This may suggest semantic clustering is used as a compensatory strategy in response to serial clustering deficits present during the first three months of mTBI recovery.

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

Sahil Bajaj[1] | Natalie S. Dailey[1] | Isabelle M. Rosso[2] | Scott L. Rauch[2] | William D. S. Killgore[1,2]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, University of Arizona, Tucson, Arizona

[2]McLean Hospital, Department of Psychiatry, Harvard Medical School, Belmont, Massachusetts

Correspondence
William D. S. Killgore, Ph.D., 1501 N Campbell Avenue, Department of Psychiatry, Room # 7303B, University of Arizona, Tucson, AZ 85724.
Email: killgore@psychiatry.arizona.edu

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.

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.

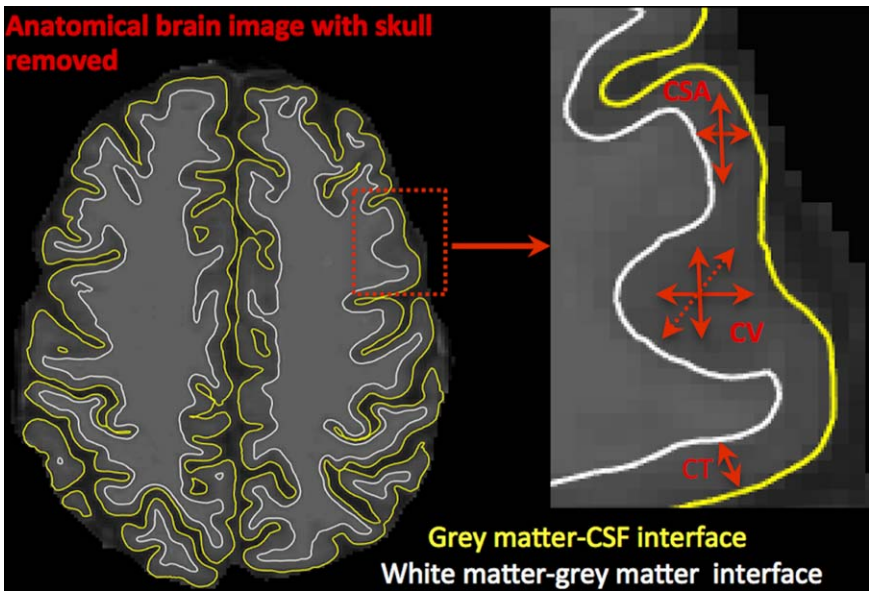


FIGURE 1 Cortical thickness (CT), cortical volume (CV), and cortical surface area (CSA). Representation of cortical measures (CT, CV, and CSA) within original anatomical brain image [Color figure can be viewed at wileyonlinelibrary.com]

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

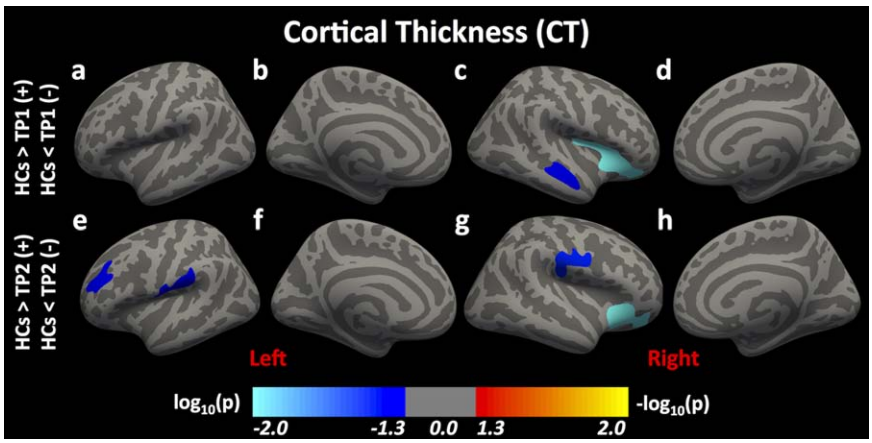


FIGURE 2 Differences in cortical thickness (CT) following mTBI. Here, we report significant differences in CT between HCs and individuals with mTBI at time-points (TPs) 1 and 2 [Color figure can be viewed at wileyonlinelibrary.com]

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

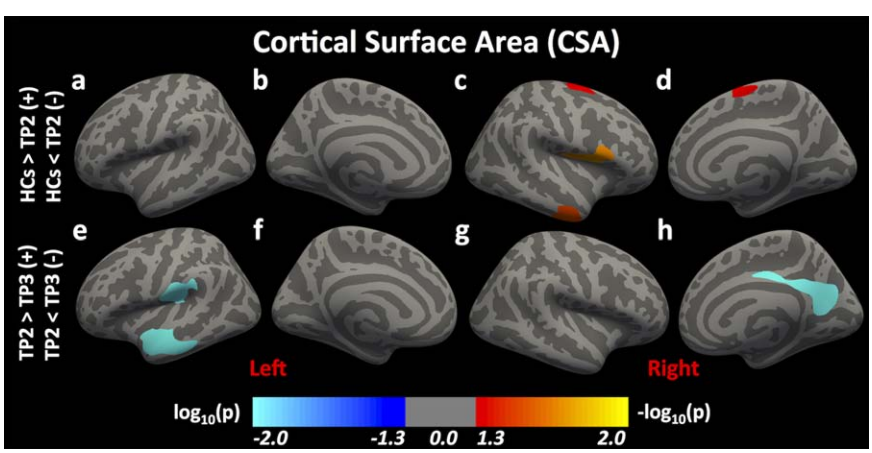


FIGURE 3 Differences in cortical surface area (CSA) following mTBI. Here, we report significant differences in CSA between HCs and individuals with mTBI at time-point (TP) 2 and between mTBI groups at TPs 2 and 3 [Color figure can be viewed at wileyonlinelibrary.com]

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	(−)

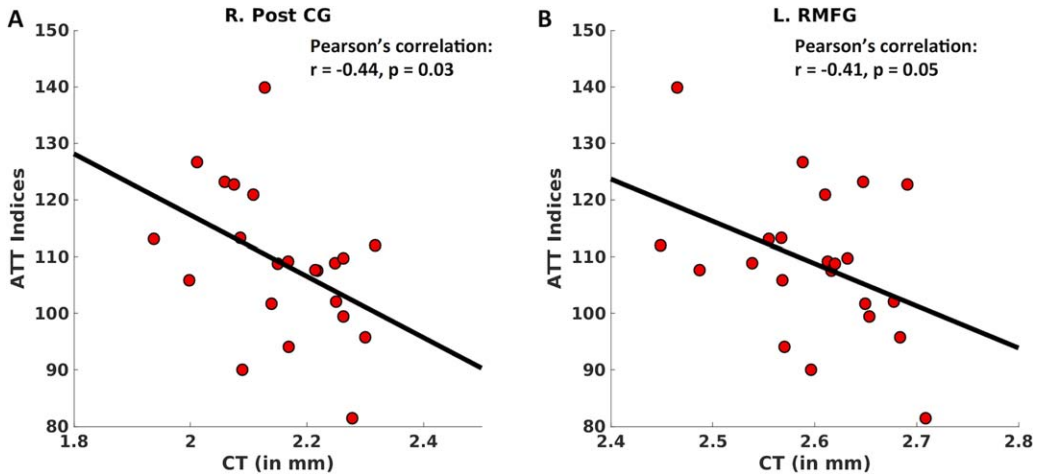


FIGURE 4 Significant partial correlations between RBANS ATT and cortical thickness (CT). After regressing out the effects of age, gender, and whole-brain CT, here we plot significant correlations found between RBANS ATT and CT for both the ROIs (a) the right postcentral gyrus (R. PostCG) ($r = -.44$, $p = .03$) 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.

ORCID

Sahil Bajaj http://orcid.org/0000-0003-0629-6036

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;39:1886–1897. https://doi.org/10.1002/hbm.23951

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 27 June 2018
doi: 10.3389/fnbeh.2018.00118

Elevated Aggression and Reduced White Matter Integrity in Mild Traumatic Brain Injury: A DTI Study

*Natalie S. Dailey, Ryan Smith, Sahil Bajaj, Anna Alkozei, Melissa K. Gottschlich, Adam C. Raikes, Brieann C. Satterfield and William D. S. Killgore**

Social, Cognitive and Affective Neuroscience Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States

Mild traumatic brain injury (mTBI) remains the most commonly reported head injury in the United States, and is associated with a wide range of post-concussive symptoms including physical, cognitive and affective impairments. Elevated aggression has been documented in mTBI; however, the neural mechanisms associated with aggression at the chronic stage of recovery remain poorly understood. In the present study, we investigated the association between white matter integrity and aggression in mTBI using diffusion tensor imaging (DTI). Twenty-six age-matched adults participated in the study, including 16 healthy controls (HCs) and 10 individuals in the chronic stage of recovery (either 6-months or 12 months post-mTBI). Psychological measures of aggression included the Buss-Perry Aggression Questionnaire and the Personality Assessment Inventory (PAI). Axonal pathways implicated in affective processing were studied, including the corpus callosum, anterior thalamic radiation, cingulum and uncinate fasciculus, and measures of white matter integrity included fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). We found that adults with mTBI in the chronic stage of recovery had higher levels aggression. Individuals with mTBI also had greater RD in the corpus callosum compared to HCs, indicating reduced fiber integrity. Furthermore, we observed a significant association between reduced white matter integrity in the corpus callosum and greater aggression. Our findings provide additional evidence for underlying neuroanatomical mechanisms of aggression, although future research will be necessary to characterize the specific relationship between aggression and the white matter pathways we identified.

Keywords: mild traumatic brain injury, aggression, white matter integrity, diffusion tensor imaging, corpus callosum, post-concussive symptoms

OPEN ACCESS

Edited by:
Nuno Sousa, Instituto de Pesquisa em Ciências da Vida e da Saúde (ICVS), Portugal

Reviewed by:
Robert Schulz, Universitätsklinikum Hamburg-Eppendorf, Germany
Chang-hyun Park, Catholic University of Korea, South Korea

***Correspondence:**
William D. S. Killgore
killgore@psychiatry.arizona.edu

Received: *10 November 2017*
Accepted: *28 May 2018*
Published: *27 June 2018*

Citation:
Dailey NS, Smith R, Bajaj S, Alkozei A, Gottschlich MK, Raikes AC, Satterfield BC and Killgore WDS (2018) Elevated Aggression and Reduced White Matter Integrity in Mild Traumatic Brain Injury: A DTI Study. Front. Behav. Neurosci. 12:118. doi: 10.3389/fnbeh.2018.00118

INTRODUCTION

Mild traumatic brain injury (mTBI) accounts for roughly 75% of the 1.5 million head injuries reported annually in the United States (Centers for Disease Control and Prevention, 2003). However, not all individuals who sustain a mTBI seek medical treatment, making it difficult to identify and track post-concussive symptomology and long-term disabilities in this population. During the acute and subacute phases of recovery, symptoms generally fall into one of three categories, including physical (i.e., headaches, dizziness and sleep disruptions), cognitive

(i.e., impaired attention and memory, reduced processing speed and poor concentration) and affective (i.e., increased irritability, anxiety and depression) disruptions (Prince and Bruhns, 2017). Furthermore, aggression is one of the most common affective symptoms, with upwards of 40% of individuals reporting increased aggression, hostility, or irritability after sustaining a mTBI (Kim et al., 1999; Bailie et al., 2015; Epstein et al., 2016; Roy et al., 2017).

One possible avenue through which to gain a better understanding of aggression in mTBI is to examine acquired pathology within the neural systems that contribute to affective/emotional behavior. Emotional episodes are believed to arise from interactions between cognitive, physiological and behavioral processes, such that bodily/behavioral reactions are first initiated in response to a situation (and its cognitive interpretation), and these reactions are then perceived and interpreted at multiple levels—leading to the behavioral expression, experience, recognition and subsequent regulation of the elicited emotion (Lindquist et al., 2012; Barrett and Satpute, 2013; Smith and Lane, 2015; Smith et al., 2017). Several large-scale neural networks have been implicated in the emotion-related processes described above, with contributing regions within distinct prefrontal, cingulate and subcortical areas (Barrett and Satpute, 2013). As individuals with a history of mTBI have been found to exhibit problems with the experience, expression and control of anger, this suggests that such individuals may exhibit pathology in these emotion-related processes, and within the neural networks that appear to implement them (Bailie et al., 2015). However, the potential neural mechanisms that underlie the expression and regulation of anger/aggression, and the relationship between neuronal injury sustained during mTBI and affective dysregulation, have not yet been thoroughly examined.

Of the many interconnected large-scale neural networks embedded within association cortices, white matter pathways connecting the temporal lobe, amygdala and orbitofrontal, medial prefrontal, and cingulate cortices are believed to play especially important roles in the emotion-related processes mentioned above (Barrett and Satpute, 2013). One such pathway is the anterior thalamic radiation, a fiber bundle connecting the thalamus, orbitofrontal cortex and anterior cingulate cortex, which is believed to be involved in affective response generation/regulation. Damage to this pathway is associated with emotional dysfunction (e.g., depression) and reduced self-awareness of emotion in clinical populations (Sussmann et al., 2009; Kubota et al., 2012). Another important pathway is the uncinate fasciculus, which connects the anterior temporal lobe, amygdala and orbitofrontal cortex. This pathway may facilitate top-down prefrontal modulation of the amygdala, which is believed to be important for promoting context-appropriate affective responses (Gershman et al., 2013; Chan et al., 2016). Reductions in white matter integrity within the uncinate fasciculus have also been found in populations that exhibit patterns of aggression and/or deficits in emotional regulation, including adults with multiple concussions (Goswami et al., 2016) and specific psychiatric disorders (Sundram et al., 2012). Yet another relevant pathway is the cingulum, which contains fibers connecting medial prefrontal, cingulate, and medial parietal regions. These regions support a network often termed the "default network", and is thought to play an important role in the conceptualization of affective states through the integration of prior experiences (Binder et al., 2009). Finally, the corpus callosum connects left and right hemisphere components of a range of cortical systems, including those subserving motor, perceptual, and cognitive functions. Furthermore, there is some evidence that interhemispheric signal transfer through the corpus callosum may play an integral role in cognitive processes that contribute to aggressive behavior (Schutter and Harmon-Jones, 2013).

When considering acquired neural network pathology in mTBI, time since injury and injury severity are likely key factors for understanding affective symptomology. Neurobehavioral symptoms are often dynamic in the early stages of injury, with the majority of individuals recovering quickly from mTBI (Binder et al., 1997; McCrea et al., 2003). However, there is evidence to suggest that a significant proportion of individuals experience persistent and potentially disruptive symptoms months and years after their injury (see Ruff, 2005). Findings related to affective disruption are also inconsistent in the few studies that directly investigate mTBI-related aggression. For example, some studies report diminished irritability and/or anger with increased time since injury (Kim et al., 1999; Bailie et al., 2015), suggesting improvements in neurobehavioral symptoms over time. In contrast, Baguley et al. (2006) found that the prevalence of aggression was similar at 6, 24 and 60 months post-injury, while another study by Roy et al. (2017) documented elevated aggression 6 months to 1-year post-injury—suggesting aggression is a persistent symptom associated with brain injury. Moreover, individuals who experience persistent symptoms, including affective disruption, may be prime candidates for clinical intervention. Similar discrepancies have been found regarding injury severity. An inverse relationship between injury severity and aggression has been documented, where individuals with mild to moderate TBI were more likely to report post-injury irritability/aggression (Kim et al., 1999). However, other studies report no significant relationship between injury severity and aggression (Rao et al., 2009; Bailie et al., 2015). The use of mixed samples (e.g., time since injury and/or injury severity) may account for the discrepancies in the current literature and complicate the interpretations regarding mTBI-related aggression.

The manifestation and duration of mTBI-related aggression beyond the acute and subacute stages of recovery is not well understood, nor are the underlying neural mechanisms. Given the inconsistencies in the literature, the present study focused exclusively on individuals in the chronic phase of recovery (6-months and 12-months post-injury) and with a TBI that was classified as mild. The purpose of the present study was twofold: (1) to assess chronic post-concussive aggression in those with mTBI; and (2) to identify fiber pathways associated with aggression. We hypothesized that adults with mTBI would

exhibit elevated levels of aggression relative to healthy controls (HCs). Using neural models of emotion to guide the selection of targeted white matter pathways, white matter integrity of the corpus callosum, cingulate, anterior thalamic radiation and uncinate fasciculus was hypothesized to show reduced integrity in the mTBI population, and these white matter integrity reductions were predicted to show associations with aggression.

MATERIALS AND METHODS

Participants

Twenty-six age-matched young adults were enrolled in the present study, including 16 HCs and 10 individuals with mTBI; three at 6-months post-injury and seven at 12-months post-injury. Eligibility criteria required participants to be between 18 years and 45 years of age, native English speakers and right handed. For those in the chronic mTBI group, brain injury documentation from a doctor, physician, or other qualified witness to the injury was required prior to enrollment in the study. Severity was classified as mild based on the ACRM and the Department of Veterans Affairs, Department of Defense (2016), where mTBI was defined as a physiological disruption of brain function resulting in temporary loss of consciousness (<30 min), transient posttraumatic amnesia (<24 h), altered mental state (i.e., feeling dazed, disoriented, or confused), and/or focal neurological damage that may or may not be transient (American Congress of Rehabilitation Medicine, 1993). Exclusionary criteria included: (1) a history of psychiatric or neurological disease; (2) pregnancy; (3) previous or ongoing alcoholism or substance abuse; (4) more than three TBIs in a lifetime; or (5) contraindication to MRI. In the present sample, mTBI was the result of sports related injuries (70%), vehicular accidents (20%) and falls (10%). Participants in this study are part of a larger ongoing study, investigating neuropsychological function across multiple stages of recovery from mTBI. The current study was approved by the Institutional Review Board at the University of Arizona and the U.S. Army Human Research Protections Office (HRPO), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Neuropsychological Assessments

Participants completed a battery of neuropsychological assessments on the same day and prior to the collection of neuroimaging data. Paper and pencil assessments were administered by a trained full-time research technician in a quiet testing room located in the laboratory.

Wechsler Abbreviated Scale of Intelligence Test (WASI-II)

All participants completed the Wechsler Abbreviated Scale of Intelligence test (WASI-II; Wechsler, 1999). The WASI-II is highly correlated (r = 0.92) with the longer Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2008) and was used to obtain a measure of general intellectual ability or "IQ". Full Scale IQ was used to assess overall intelligence and ensured participants enrolled in the study exhibited cognitive functioning within normal limits.

Buss-Perry Aggression Questionnaire

Aggression was measured using two different questionnaires. The Buss-Perry Aggression Questionnaire (BPAQ; Buss and Perry, 1992) consists of 29 items, rated on a 5-point scale from "extremely uncharacteristic" to "extremely characteristic". The BPAQ provides an overall measure of aggression (total aggression) and four subscales including physical aggression, verbal aggression, anger and hostility. BPAQ-Physical measures one's tendency to use threats, and/or physical harm towards others and objects. BPAQ-Verbal measures disagreements and argumentative behavior, while BPAQ-Anger assesses irritability and control over one's temper. Finally, BPAQ-Hostility refers to feelings of jealousy, suspicion and resentment. Moderate to high reliability has been established for the BPAQ (Harris, 1997) and participants were given as much time as needed to complete the assessment.

Personality Assessment Inventory

The personality assessment inventory (PAI; Morey, 1991) was the second self-report measure of aggression. The PAI was administered on the computer and required roughly 45 min to complete. This 344-item inventory uses a four-alternative scale ranging from "Totally False" to "Very True", to assess 22 non-overlapping scales, including aggression. Total aggression on the PAI measures characteristics and attitudes related to anger, assertiveness and hostility. The PAI has three subscales which include aggressive attitude (hostility and poor control over anger), verbal aggression (assertiveness and readiness to express anger to others), and physical aggression (tendency to be involved in physical altercations). The PAI has been found to be a valid and clinically useful measure of psychiatric and emotional disturbances in adults with TBI (Till et al., 2009). Due to time restrictions and computer error, PAI scores were incomplete for one HC and three mTBI participants.

Beck Depression Inventory

Given the strong association between depression and aggression (Rapoport et al., 2003), the Beck Depression Inventory (BDI-II; Beck et al., 1961) was used to assess post-injury depression. The BDI-II has been shown to discriminate well between clinical and non-clinical populations, where a score of 13 or greater is indicative of mild clinical depression (Lasa et al., 2000). Participants scored the 21-item inventory using a 4-point scale ranging in severity from 0 to 3 for each item. Clinical levels of depression have been shown to be a comorbid symptom of mTBI (Jorge et al., 2004; Baguley et al., 2006), therefore, BDI-II scores were used as a covariate in subsequent analyses, allowing for the comparison of aggressive tendencies while controlling for behaviors associated with depression.

Neuroimaging

Magnetic resonance imaging (MRI) data were collected at the University of Arizona, using a whole-body Siemens Skyra 3.0 Tesla with 32-channel head coil (MAGNETO Skyra Siemens

Healthcare). Diffusion weighted data were acquired using single-shot echo planar imaging (TR = 9600; TE = 88; acquisition matrix = 128 × 128; FOV: 256 × 256; slice thickness = 2 mm, no gap). Diffusion gradients were applied along 72 directions, with b = 1000 s/mm^2 and six non-diffusion weighted images (b_0). A preprocessing pipeline consisted of artifact and head motion correction using TOPUP eddy in the FMRIB Software Library (FSL; Andersson and Sotiropoulos, 2016). The FMRIB Diffusion Toolbox was used for brain extraction (Smith, 2002), and fitting of the diffusion tensor model (DTIFIT; Behrens et al., 2003). DTIFIT calculates fractional anisotropy (FA) and mean diffusivity (MD), while axial diffusivity (AD) and radial diffusivity (RD) were calculated from DTIFIT outputs using the following formulas:

$$AD = \lambda_1 \quad (1)$$

$$RD = (\lambda_2 + \lambda_3)/2 \quad (2)$$

Measured differences in anisotropy can result from axonal density and/or myelination, where AD and RD have been associated with axonal integrity and demyelination, respectively (Song et al., 2002, 2005). Thus, these metrics allow for the quantification of fiber pathway integrity, and may provide reliable biomarkers of mTBI-related symptoms. Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) was used for nonlinear registration to a standard template (FMRIB-58) and affine-aligned to 1 × 1 × 1 mm Montreal Neurological Institute (MNI) space using FNIRT (de Groot et al., 2013). Individually aligned images were then merged to create a single 4D image for each DTI metric, resulting in a total of four separate 4D images. White matter was identified using whole-brain skeletonized masks with a threshold of 0.20, a process that reduces voxels in the periphery where inter-subject variability or partial volume effects tend to be high.

Targeted White Matter Tracts

Binary template masks were created to extract voxels from targeted pathways including the corpus callosum, and bilateral cingulate, uncinate fasciculus and anterior thalamic radiation. Template masks were based on the ICBM-DTI-81 white-matter labels atlas overlaid on a standard template in MNI space (MNI_152_T1 1 × 1 × 1 mm; see **Figure 1**). The population-based atlas includes 48 labeled tracts from hand-segmented white matter parcellation maps based on averaged tensor maps derived from 81 subjects (Mori et al., 2008). Voxels from the 4D skeletonized images which overlapped a given white matter mask were included in subsequent analyses for that tract (see **Figure 2**). White matter integrity was quantified using diffusion and anisotropy properties, resulting in FA, MD, RD and AD values for all targeted tracts. Mean values for a given tract were obtained by averaging all values from voxels extracted from the white matter mask. By extracting values from the skeletonized data and targeting specific tracts of interest, this DTI-approach eliminates superfluous comparisons and provides higher detection power of white matter differences between the two groups.

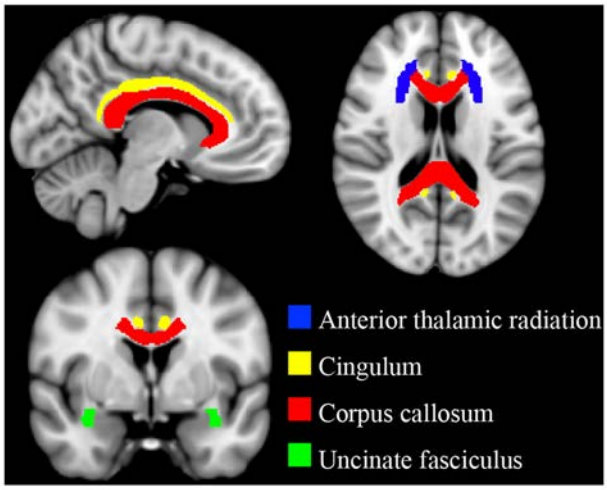


FIGURE 1 | Targeted white matter tracts. Binary template masks from the ICBM-DTI-81 atlas were used to delineate white matter pathways of interest. Anterior thalamic radiation (blue), cingulum (yellow), corpus callosum (red) and uncinate fasciculus (green). Template masks are overlaid on a standard T1 montreal neurological institute (MNI) template (1 × 1 × 1 mm).

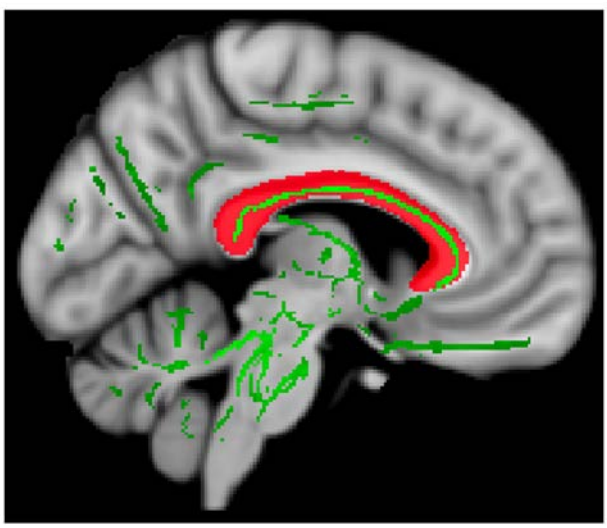


FIGURE 2 | Extracting diffusion values. Data from a representative participant showing whole-brain 4D skeletonized data (green) overlaid on the mask of the corpus callosum (red). Only voxels from 4D data (green) overlapping with white matter mask (red) were extracted and included in subsequent analyses.

Statistical Analysis

Analyses were conducted using IBM SPSS Statistics (version 24.0). Independent sample *t*-tests were performed to identify group differences on continuous demographic measures, and a chi-square was used to test that group and gender were independent. General linear models (GLMs) were used to test whether the two groups differed on measures of aggression and DTI metrics, while controlling for potential effects of age, gender and depression (i.e., covariates). Group was entered into each

GLM as a categorical independent variable, where the HCs was coded as "0" and individuals with mTBI were coded as "1".

To test our first hypothesis addressing aggression in chronic mTBI, we fit individual GLMs with group as a categorical independent variable and BPAQ and PAI total aggression as dependent variables. Age, gender and depression were entered into each model as covariates. Based on significant findings, *post hoc* analyses were conducted to determine which aggression subscales contributed significantly to the overall between-group effect. Separate GLMs were calculated, with group as the independent variable and BPAQ or PAI subscales as the dependent variables, controlling for age, gender and depression.

To test our second hypothesis addressing group differences in the microstructure of targeted fiber pathways, individual GLMs were fit for each tract in the left and right hemisphere separately, with group as a categorical independent variable and DTI metrics (FA, MD, AD and RD) as the dependent variables, while accounting for the effects of age, gender and depression. False discovery rate (FDR; $\alpha = 0.05$) was used to minimize Type I error associated with multiple comparisons (Benjamini and Yekutieli, 2001). For comparisons of microstructure integrity, pathways of interest were selected *a priori* and FDR-correction was adjusted within tract. Finally, Pearson's partial correlations were calculated to quantify the unique relationship between white matter integrity and aggression. Given our interest in determining whether a relationship exists between white matter integrity and aggression, we computed these partial correlations within our whole sample, without stratifying by group. Partial correlation covariates included age, gender and depression and the correlations were restricted to overall aggression measures and tracts which showed significant between-group differences in the previous analyses.

RESULTS

Neuropsychological

Demographic characteristics are summarized in **Table 1**. Adults with mTBI reported significantly higher levels of aggression on the BPAQ ($F_{(1,21)} = 13.22$, $p < 0.05$; $\eta^2 = 0.39$; FDR-corrected) and the PAI ($F_{(1,17)} = 10.86$, $p < 0.05$; $\eta^2 = 0.39$; FDR-corrected), as compared to HCs (see **Figure 3**). In addition, BPAQ scores differed based on gender ($F_{(1,21)} = 8.28$, $p < 0.01$; $\eta^2 = 0.28$).

To better understand the driving factors associated with elevated aggression, *post hoc* analyses were conducted separately for BPAQ and PAI subscales (see **Table 2**). *post hoc* results were FDR-corrected at $p < 0.05$, within test. Adults with mTBI reported significantly higher aggressive attitude on the PAI and significantly higher levels of physical aggression and anger on the BPAQ. In the GLM for the BPAQ, gender was significantly associated with physical aggression ($F_{(1,21)} = 9.28$, $p < 0.01$; $\eta^2 = 0.31$). Follow-up analyses were conducted to further explore these findings. An analysis of covariance was calculated with physical aggression as the dependent variable, group and gender as the independent variables, with age and depression as covariates. There was a significant main effect of group ($F_{(1,20)} = 19.08$, $p < 0.001$; $\eta^2 = 0.49$), a significant main effect of gender ($F_{(1,20)} = 15.64$, $p < 0.001$; $\eta^2 = 0.44$), and a significant group × gender interaction ($F_{(1,20)} = 5.49$, $p < 0.05$; $\eta^2 = 0.22$). **Figure 4** shows the *post hoc* results, in that males with mTBI reported significantly higher physical aggression ($M = 25.67$; $SD = 4.04$) than females with mTBI ($M = 15.86$; $SD = 3.13$), a result not observed in HCs.

Neuroanatomical

The microstructure of targeted fiber pathways was compared between mTBI and HCs. In the corpus callosum, individuals with mTBI exhibited higher RD compared to HCs ($F_{(1,21)} = 7.71$, $p < 0.05$; $\eta^2 = 0.27$; FDR-corrected), indicating reduced fiber integrity within the corpus callosum after an mTBI. Lower FA in the corpus callosum was also found in the mTBI group, however this finding did not survive FDR-correction. White matter integrity (FA, MD, RD and AD) within the anterior thalamic radiation, cingulum, and uncinate fasciculus showed no significant between-group differences (see Supplementary Table S1).

Neural Correlates of Aggression

Neural correlates of aggression were restricted to overall aggression measures and fiber pathways that showed significant between-group differences in the previous analyses. Therefore, we assessed the relationship between white matter integrity in the corpus callosum (RD) and aggression (BPAQ-total aggression and PAI-total aggression). A significant positive correlation was

TABLE 1 | Demographic characteristics by group.

	Healthy Controls ($n = 16$)	Chronic mTBI ($n = 10$)	Statistic	p-value
Age, in years	22.69 (3.40)	22.40 (6.38)	$t_{(24)} = 0.15$	0.88
Gender – %female	50%	70%	$\chi^2_{(1)} = 1.01$	0.43
Education, in years	14.19 (2.43)	12.80 (1.55)	$t_{(24)} = 1.61$	0.12
WASI-II Full-Scale IQ	111.31 (9.69)	111.90 (12.90)	$t_{(24)} = -0.12$	0.90
BDI	2.50 (3.08)	6.10 (7.64)	$t_{(24)} = -1.69$	0.10
Time Since Injury, in days				
6-months ($n = 3$)		184.67 (2.08)		
12-months ($n = 7$)		363.57 (2.99)		

Note: Values are Mean (Standard Deviation), unless otherwise noted. mTBI, mild traumatic brain injury; WASI-II, Wechsler Abbreviated Scale of Intelligence – 2nd Edition; BDI, Beck Depression Inventory.

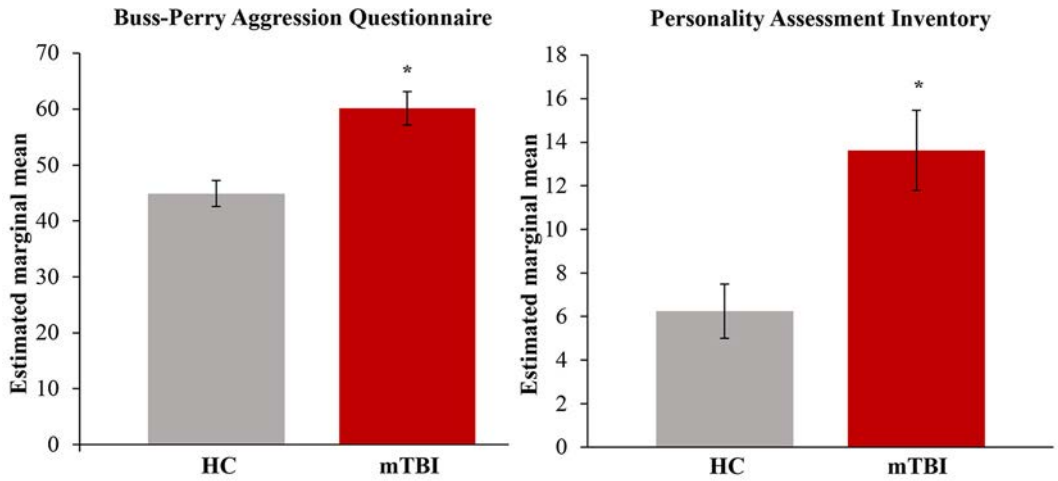


FIGURE 3 | Total aggression by group. Significantly higher aggression on the Buss-Perry Aggression Questionnaire (BPAQ) and Personality Assessment Inventory (PAI) was found in those with mild traumatic brain injury (mTBI). Estimated marginal means represent the group means after adjusting for covariates in the model (age, gender and depression). HC, healthy controls; mTBI, mild traumatic brain injury. Error bars represent standard error of the mean. *$p < 0.05$; FDR-corrected.

found between RD in the corpus callosum and BPAQ-total aggression ($r = 0.49$; $p < 0.05$; FDR-corrected; see **Figure 5**).

Post hoc analyses were conducted to determine whether findings related aggression in the corpus callosum were widespread, or restricted to specific regions. Therefore, the corpus callosum was subdivided into the genu, body and splenium and template masks were created using the procedures previously described in the Materials and Methods: "Targeted White Matter Tracts" section. Similar to previous GLMs, between-group comparisons of white matter integrity in the corpus callosum were calculated for the three subdivisions separately (controlling for age, gender, and depression). Results are summarized in **Table 3**. Significantly higher RD was found in the body and the splenium of the corpus callosum in adults with mTBI compared to HCs ($p < 0.05$, uncorrected). While not significant across the entire corpus callosum, FA was significantly lower in the splenium for those with mTBI ($p < 0.05$, uncorrected). Partial correlations (controlling for age, gender and depression) were then calculated to determine which aspects of aggression were associated with the body and the splenium of the corpus callosum. Given the exploratory nature of these analyses, uncorrected *p*-values are reported. Physical aggression was only associated with white matter integrity in the splenium, in that higher reports of physical aggression were significantly correlated with higher RD ($r = 0.42$, $p < 0.05$) and lower FA ($r = -0.43$, $p < 0.05$). In contrast, aggressive attitude was significantly correlated with higher RD in the body of the corpus callosum ($r = 0.64$, $p < 0.01$).

DISCUSSION

In this study, we investigated post-concussive aggression in individuals who were in the chronic stage of recovery from mTBI, as well as the neural correlates of aggression. We hypothesized that individuals with mTBI would exhibit higher aggression relative to HCs, and that white matter integrity in the corpus callosum, cingulum, anterior thalamic radiation and uncinate fasciculus would be reduced in the mTBI population. In addition, we hypothesized that white matter integrity in these tracts would

TABLE 2 | *Post hoc* group comparisons on aggression subscales.

	Healthy Controls ($n = 16$)	Chronic mTBI ($n = 10$)	*F-statistic*[a,b]	*p*-value	*Partial* η^2[‡]
BPAQ					
Physical Aggression	14.19 (3.73)	18.80 (5.71)	13.22[a]	0.01*	0.39
Verbal Aggression	10.69 (2.92)	12.40 (4.01)	2.39[a]	0.14	0.10
Anger	9.75 (1.98)	12.20 (2.97)	9.44[a]	0.01*	0.31
Hostility	11.63 (4.02)	14.60 (4.38)	0.25[a]	0.05	0.17
PAI					
Aggressive Attitude	1.27 (1.53)	4.14 (2.80)	15.94[b]	0.01*	0.48
Verbal Aggression	4.47 (3.09)	7.43 (2.64)	4.56[b]	0.05	0.21
Physical Aggression	0.80 (1.37)	1.43 (1.62)	2.06[b]	0.17	0.11

Note: Values are Mean (Standard Deviation). Statistics are from separate general linear models on the BPAQ and PAI, controlling for age, gender and depression. [a]*df(1,21);* [b]*df(1,17);* η^2 *= partial eta squared;* [‡]*Small effect size: 0.01 ≤* η^2 *< 0.05; medium effect size: 0.06 ≤* η^2 *< 0.13; large effect size:* $\eta^2 \geq 0.14$*. mTBI, mild traumatic brain injury; BPAQ, Buss-Perry Aggression Questionnaire; PAI, Personality Assessment Inventory. Unadjusted p-values reported. *Significant at FDR-corrected p < 0.05.*

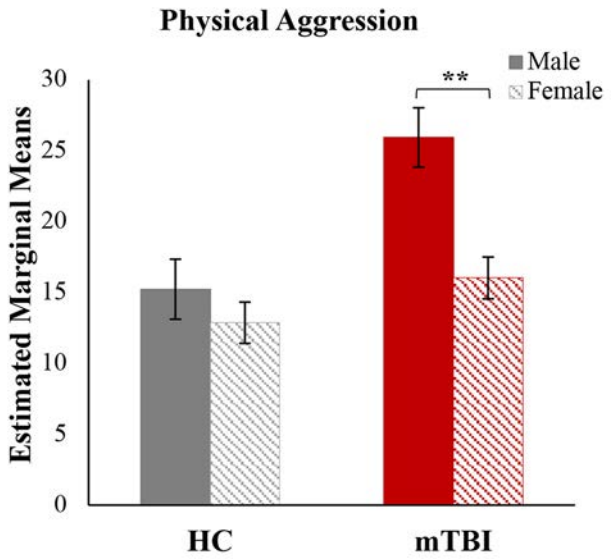


FIGURE 4 | Physical aggression by group and gender. A significant group by gender interaction was found for physical aggression. Estimated marginal means for the physical aggression subscale of the Buss-Perry Aggression Questionnaire, after adjusting for covariates (age and depression). HC, healthy controls; mTBI, mild traumatic brain injury. Error bars represent standard error of the mean. $^{**}p < 0.01$.

be associated with aggression. In support of our first hypothesis, we found significantly elevated levels of aggression in the mTBI group. Partial support was found for our second hypothesis, in that microstructure differed between the two groups, but only in the corpus callosum. We found significantly higher RD in the corpus callosum of adults with mTBI, which is indicative of reduced white matter integrity. Furthermore, a significant positive correlation was found between aggression and RD of the corpus callosum.

Numerous studies have reported increased aggression following traumatic brain injury (Kim et al., 1999; Bailie et al., 2015; Epstein et al., 2016; Roy et al., 2017), yet few have restricted participant samples to chronic mTBI to investigate the presence of persistent and potentially long-lasting symptoms associated with brain injury. Consistent with a recent study by Epstein et al. (2016), we found increased physical aggression, anger, and total aggression on the BPAQ following mTBI. Additionally, measures of aggressive attitude and total aggression on the PAI were elevated in those with mTBI. While not a focus of the present study, we found interesting gender differences following mTBI. In our sample, males with mTBI reported higher levels of physical aggression compared to females with mTBI. While some studies report no relationship between gender and aggression (Baguley et al., 2006; Johansson et al., 2008), our findings are consistent with a recent study focused exclusively on mild TBI. McGlade et al. (2015) investigated sex differences associated with functional connectivity following mTBI, and found that males exhibited increased physical aggression, which was associated with decreased left orbitofrontal functional connectivity. These findings may have important theoretical and clinical implications regarding the manifestation of aggression in the chronic recovery phase.

The BPAQ-anger and PAI-aggressive attitude subscales assess an individual's tendency to become easily frustrated or lose control of one's temper. High endorsement of these constructs by those with mTBI might be due to difficulties with the generation or subsequent understanding of affective responses (Lindquist et al., 2012; Smith et al., 2017). For example, it may be that individuals struggle to appropriately understand the causes and/or emotional meaning of felt somatovisceral changes during an affective response, which would be expected to hinder effective regulation of such responses. Thus, incomplete conceptualization of negative affect may manifest in initial frustration. On the other hand, increased levels of BPAQ-physical aggression suggest those with mTBI might struggle more with top-down control processes, which are important for appropriately adjusting behavioral responses within a particular context; if so, greater levels of dysregulated aggression would also be expected. In healthy adults, physical aggression is often higher in males than females (Archer, 2004; Cleverley et al., 2012). Although we did not observe this relationship exclusively in our healthy control group, we did find elevated physical aggression in males compared to females in those with mTBI. Based on our results, it may be that mTBI exacerbates a pre-existing gender difference, leaving males particularly prone to dysregulated emotional responses. Together, the current findings suggest persistent and variable manifestations of dysregulated aggression and frustration, perhaps related to impaired affect generation, conceptualization, and top-down control processes in chronic mTBI.

From this study, we provide preliminary findings regarding possible loci of pathology within neural networks that plausibly contribute to affective processing. Reduced integrity in the corpus callosum has previously been reported in mTBI (Lipton et al., 2008; Lo et al., 2009; Sugiyama et al., 2009). In line with these previous studies, we found increased RD in the corpus callosum in adults with chronic mTBI. The diffusivity pattern of increased RD is proposed to reflect a loss of structural integrity, resulting from myelination abnormalities and/or reduced axonal density (Beaulieu, 2002; Song et al., 2002; Concha et al., 2009). The lack of observed significant between-group differences for other diffusivity measures, particularly FA, is unclear. It is important to note that FA in the corpus callosum was reduced in the mTBI group compared to HCs. Although these findings did not survive correction for multiple comparisons, this was possibly the result of low power within our relatively small sample size. Overall, our findings provide preliminary evidence of persistent and/or dynamic loss of structural integrity within the corpus callosum in those who have experienced a mild TBI, and are in the chronic stage of recovery.

A major aim of our study was to evaluate the relationship between neuropsychological function and structural integrity of white matter pathways. The association between aggression and white matter integrity offers several potential implications regarding the underlying systems responsible for affective states. Cortical networks connected by the corpus callosum are known to play an integral role in the

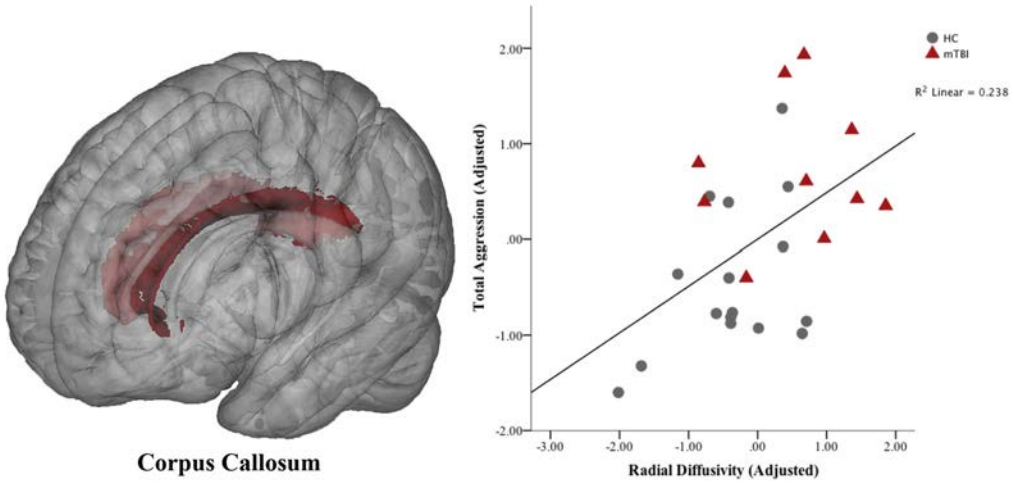


FIGURE 5 | Association between aggression and white matter in the corpus callosum. Voxels of the corpus callosum included in the analysis are shown in red overlaid on a standard brain. Means are the standardized residuals after adjusting for covariates (age, gender and depression). A significant partial correlation (controlling for age, gender and depression) was found between total aggression on the Buss-Perry Aggression Questionnaire and radial diffusivity (RD) in the corpus callosum ($p < 0.05$; FDR-corrected). HC, healthy controls; mTBI, mild traumatic brain injury.

generation, conceptualization/representation, and regulation of affective/emotional responses (Lindquist et al., 2012; Smith and Lane, 2015). For example, one interpretation could be that reduced white matter in the corpus callosum might disrupt one's ability to integrate exteroceptive and interoceptive percepts with conceptualization processes during an emotional episode, potentially contributing to situationally inappropriate aggressive responses and a poor conceptual understanding of those responses (i.e., low emotional awareness or alexithymia)—both of which would be expected to contribute to sustained dysregulation (Paul, 2004; Kubota et al., 2012). Considering previous findings implicating the corpus callosum (Kubota et al., 2012), as well as the interconnected cortical regions (Kalisch et al., 2006) in emotional awareness (or the related construct of alexithymia), our results suggest disruption in such cognitive-emotional processes might contribute to frustration or agitation in individuals with mTBI. This interpretation is also consistent with our *post hoc* analyses indicating reduced

TABLE 3 | Diffusion characteristics for the corpus callosum.

	Healthy Controls (n = 16)	Chronic mTBI (n = 10)	*F-statistic* df (1, 21)	*p*-value	*Partial* $\eta^{2\ddagger}$
CC					
FA	0.80456 (0.01415)	0.79500 (0.01073)	4.32	0.05	0.17
MD	0.00072 (0.00002)	0.00074 (0.00002)	2.76	0.11	0.12
RD	0.00027 (0.00002)	0.00028 (0.00002)	7.71	0.01*	0.27
AD	0.00162 (0.00007)	0.00164 (0.00003)	0.16	0.69	0.01
CC Genu					
FA	0.80530 (0.02682)	0.79903 (0.01414)	0.13	0.72	0.01
MD	0.00071 (0.00002)	0.00072 (0.00003)	1.31	0.27	0.06
RD	0.00026 (0.00003)	0.00028 (0.00002)	0.53	0.48	0.02
AD	0.00159 (0.00008)	0.00162 (0.00007)	0.45	0.51	0.02
CC Body					
FA	0.78165 (0.01648)	0.77022 (0.02114)	3.60	0.07	0.15
MD	0.00074 (0.00003)	0.00076 (0.00002)	2.64	0.12	0.11
RD	0.00029 (0.00002)	0.00032 (0.00003)	5.68	0.03	0.21
AD	0.00163 (0.00007)	0.00165 (0.00003)	0.16	0.69	0.01
CC Splenium					
FA	0.83502 (0.01310)	0.82553 (0.01385)	4.94	0.04	0.19
MD	0.00070 (0.00003)	0.00071 (0.00002)	1.20	0.29	0.05
RD	0.00023 (0.00002)	0.00025 (0.00002)	4.95	0.04	0.19
AD	0.00164 (0.00008)	0.00164 (0.00003)	0.00	1.00	0.00

*Note: Mean (Standard Deviation) in mm²/s. Values extracted from overlapping voxels in the 4D skeletonized image and template mask, for each region of the corpus callosum. General linear models were calculated for each interhemispheric tract separately, controlling for age, gender and depression. df, degrees of freedom. ‡Small effect size: 0.01 ≤ η^2 < 0.05; medium effect size: 0.06 ≤ η^2 < 0.13; large effect size: η^2 ≥ 0.14. mTBI, mild traumatic brain injury; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; CC, corpus callosum. Unadjusted p-values reported. *Significant at FDR-corrected p < 0.05.*

white matter integrity in the body and splenium of the corpus callosum, which have been associated with sensorimotor and perception/conceptualization processes, respectively (Paul, 2011).

An alternative interpretation of our findings could be that reduced white matter integrity in the corpus callosum results in decreased behavioral inhibition. Prior studies have documented increased aggression in patients with orbitofrontal damage (Coccaro et al., 2007; Epstein et al., 2016). Our findings indicate similar behavioral tendencies (increased aggression) associated with reduced structural integrity in the corpus callosum, which may disrupt interhemispheric signal transfer and impede cortically mediated inhibitory processes necessary for context-appropriate behavioral regulation. The different mechanistic interpretations we have proposed could also interact, such that difficulty integrating internal and external cues during conceptualization, combined with a lack of inhibitory control during the regulatory process, could result in the selection of inappropriate behaviors such as physical or verbal aggression. It should be mentioned, however, that disruptions within frontal (genu) subregions of the corpus callosum would be most consistent with deficits in inhibitory control; thus, the fact that alterations within posterior subregions of the corpus callosum appear to drive our findings, this is probably most consistent with deficits in recognizing and understanding one's own emotions. Regardless of the detailed mechanisms involved, our findings suggest that alterations in the corpus callosum may play an important role in promoting dysregulated affect, leading to the observed increases in aggressive tendencies.

Limitations and Future Directions

It is important to acknowledge methodological limitations of the current study. First, we assessed aggression at a single point in time (i.e., during the chronic stage of recovery). As such, we are unable to determine whether aggression manifests differently throughout various stages of recovery. For example, those in the acute phase might exhibit more outward aggression (i.e., physical or verbal aggression) as a result of reduced executive control, while those in the chronic phase might have relearned aspects of executive function, gaining more control over behavioral inhibition but continue to exhibit deficits with the context-appropriate generation or conceptualization of affective responses. While we are unable to answer this particular question about the role of different mechanistic contributions at different recovery stages, our current findings provide new insights into the manifestation of aggression in chronic mTBI.

We acknowledge the relatively small sample size of the present study. Although we implemented methodological approaches aimed at minimizing small sample effects (i.e., partial volume effects and targeted pathways), we may have lacked the statistical power necessary to detect group-differences in certain tracts. This is especially problematic for anatomical regions with a considerable number of crossing fibers (i.e., the uncinate fasciculus), as crossing fibers are another source of inherent noise in DTI studies (Jeurissen et al., 2013). Furthermore, the link between aggression and white matter integrity was calculated across all participants. As such, a disease-specific effect of brain structure on aggression cannot be inferred. Future studies with larger sample sizes are needed to confirm our preliminary findings and further examine the reliability of the reported relationship between aggression and fiber tracts in systems contributing to affective processing.

Limitations notwithstanding, the clinical implications of this study should not be overlooked. Aggressive behavior can have devastating impacts on the home environment, social and interpersonal functioning, and could result in the loss of employment or criminal violence. Therefore, therapeutic interventions aimed at ways to more effectively manage affective states may be particularly beneficial to individuals who experience persistent affective symptoms. Understanding the association between neural systems and behavior could potentially lead to interventions targeting the range of emotion-related processes that might be particularly affected by damage sustained from mTBI.

CONCLUSION

In conclusion, we found higher levels of aggression in adults with a chronic mTBI, when compared to HCs. Additionally, elevated aggression was associated with reduced white matter integrity in the corpus callosum, regardless of group. As this pathway is known to play an important role in multiple affective processes, our results suggest that alterations in this tract may play an important role in accounting for dysregulated aggression. This may be associated with the generation of situationally inappropriate affective responses and/or poor awareness/understanding of such responses (i.e., both linked to disrupted conceptualization processes). Alternatively, it could be directly associated with reduced top-down cognitive/behavioral regulatory processes. Future research should focus on disambiguating which of these processes, or what combination of them, best accounts for such mTBI symptoms. This may be especially important, given that our findings also highlight the potentially persistent nature of such post-concussive symptoms in mTBI.

AUTHOR CONTRIBUTIONS

ND assisted with MRI data acquisition, conducted MRI data processing, statistical analysis and drafted the initial manuscript. RS and SB assisted with data analysis and interpretations, and manuscript revisions. AA assisted with the statistical analysis and manuscript revisions. MG conducted participant recruitment, data acquisition, MRI preprocessing and assisted with manuscript revisions. AR assisted with data interpretation and manuscript revisions. BS assisted with manuscript revisions. WK designed the study, assisted with data interpretation and critique, as well as manuscript review and revisions.

FUNDING

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 Medical Research and Materiel Command (USAMRMC) under Award No. (W81XWH-12-0386) to WK. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

REFERENCES

American Congress of Rehabilitation Medicine. (1993). Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* 8, 86–87. doi: 10.1097/00001199-199309000-00010

Andersson, J. L. R., and Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage* 125, 1063–1078. doi: 10.1016/j.neuroimage.2015.10.019

Archer, J. (2004). Sex differences in aggression in real-world settings: a meta-analytic review. *Rev. Gen. Psychol.* 8, 291–322. doi: 10.1037/1089-2680.8.4.291

Baguley, I. J., Cooper, J., and Felmingham, K. (2006). Aggressive behavior following traumatic brain injury how common is common. *J. Head Trauma Rehabil.* 21, 45–56. doi: 10.1097/00001199-200601000-00005

Bailie, J. M., Cole, W. R., Ivins, B., Boyd, C., Lewis, S., Neff, J., et al. (2015). The experience, expression, and control of anger following traumatic brain injury in a military sample. *J. Head Trauma Rehabil.* 30, 12–20. doi: 10.1097/htr.0000000000000024

Barrett, L. F., and Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. *Curr. Opin. Neurobiol.* 23, 361–372. doi: 10.1016/j.conb.2012.12.012

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed.* 15, 435–455. doi: 10.1002/nbm.782

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., and Erbaugh, J. (1961). An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., et al. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn. Reson. Med.* 50, 1077–1088. doi: 10.1002/mrm.10609

Benjamini, Y., and Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Ann. Stat.* 29, 1165–1188. doi: 10.1214/aos/1013699998

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–2796. doi: 10.1093/cercor/bhp055

Binder, L. M., Rohling, M. L., and Larrabee, G. J. (1997). A review of mild head trauma. Part I: meta-analytic review of neuropsychological studies. *J. Clin. Exp. Neuropsychol.* 19, 421–431. doi: 10.1080/01688639708403870

Buss, A. H., and Perry, M. (1992). The aggression questionnaire. *J. Pers. Soc. Psychol.* 63, 452–459. doi: 10.1037/0022-3514.63.3.452

Centers for Disease Control and Prevention. (2003). *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem.* Atlanta, GA: Centers for Disease Control and Prevention.

Chan, S. C., Niv, Y., and Norman, K. A. (2016). A probability distribution over latent causes, in the orbitofrontal cortex. *J. Neurosci.* 36, 7817–7828. doi: 10.1523/JNEUROSCI.0659-16.2016

Cleverley, K., Szatmari, P., Vailancourt, T., Boyle, M., and Lipman, E. (2012). Developmental trajectories of physical and indirect aggression from late childhood to adolescence: sex differences and outcomes in emerging adulthood. *J. Am. Acad. Child Adolesc. Psychiatry* 51, 1037–1051. doi: 10.1016/j.jaac.2012.07.010

Coccaro, E. F., McCloskey, M. S., Fitzgerald, D. A., and Phan, K. L. (2007). Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biol. Psychiatry* 62, 168–178. doi: 10.1016/j.biopsych.2006.08.024

Concha, L., Beaulieu, C., Collins, D. L., and Gross, D. W. (2009). White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. *J. Neurol. Neurosurg. Psychiatry* 80, 312–319. doi: 10.1136/jnnp.2007.139287

Department of Veterans Affairs, Department of Defense (2016). VA/DoD clinical practice guideline for the management of concussion-mild traumatic brain injury. Version 2.0. Available online at: https://www.healthquality.va.gov/guidelines/Rehab/mtbi

de Groot, M., Vernooij, M. W., Klein, S., Ikram, M. A., Vos, F. M., Smith, S. M., et al. (2013). Improving alignment in tract-based spatial statistics: evaluation and optimization of image registration. *Neuroimage* 76, 400–411. doi: 10.1016/j.neuroimage.2013.03.015

Epstein, D. J., Legarreta, M., Bueler, E., King, J., McGlade, E., and Yurgelun-Todd, D. (2016). Orbitofrontal cortical thinning and aggression in mild traumatic brain injury patients. *Brain Behav.* 6:e00581. doi: 10.1002/brb3.581

Gershman, S. J., Jones, C. E., Norman, K. A., Monfils, M. H., and Niv, Y. (2013). Gradual extinction prevents the return of fear: implications for the discovery of state. *Front. Behav. Neurosci.* 7:164. doi: 10.3389/fnbeh.2013.00164

Goswami, R., Dufort, P., Tartaglia, M. C., Green, R. E., Crawley, A., Tator, C. H., et al. (2016). Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct. Funct.* 221, 1911–1925. doi: 10.1007/s00429-015-1012-0

Harris, J. K. (1997). A further evaluation of the aggression questionnaire: issues of validity and reliability. *Behav. Res. Ther.* 35, 1047–1053. doi: 10.1016/s0005-7967(97)00064-8

Jeurissen, B., Leemans, A., Tournier, J. D., Jones, D. K., and Sijbers, J. (2013). Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum. Brain Mapp.* 34, 2747–2766. doi: 10.1002/hbm.22099

Johansson, S. H., Jamora, C. W., Ruff, R. M., and Pack, N. M. (2008). A biopsychosocial perspective of aggression in the context of traumatic brain injury. *Brain Inj.* 22, 999–1006. doi: 10.1080/02699050802530573

Jorge, R. E., Robinson, R. G., Moser, D., Tateno, A., Crespo-Facorro, B., and Arndt, S. (2004). Major depression following traumatic brain injury. *Arch. Gen. Psychiatry* 61, 42–50. doi: 10.1097/00001199-200407000-00010

Kalisch, R., Wiech, K., Critchley, H. D., and Dolan, R. J. (2006). Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. *Neuroimage* 30, 1458–1466. doi: 10.1016/j.neuroimage.2005.11.011

Kim, S. H., Manes, F., Kosier, T., Baruah, S., and Robinson, R. G. (1999). Irritability following traumatic brain injury. *J. Nerv. Ment. Dis.* 187, 327–335. doi: 10.1097/00005053-199906000-00001

Kubota, M., Miyata, J., Sasamoto, A., Kawada, R., Fujimoto, S., Tanaka, Y., et al. (2012). Alexithymia and reduced white matter integrity in schizophrenia: a diffusion tensor imaging study on impaired emotional self-awareness. *Schizophr. Res.* 141, 137–143. doi: 10.1016/j.schres.2012.08.026

Lasa, L., Ayuso-Mateos, J. L., Vázquez-Barquero, J. L., Díez-Manrique, F. J., and Dowrick, C. F. (2000). The use of the beck depression inventory to screen for depresssion in the general population: a preliminary analysis. *J. Affect. Disord.* 57, 261–265. doi: 10.1016/s0165-0327(99)00088-9

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., and Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 35, 121–143. doi: 10.1017/s0140525x11000446

Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K., et al. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: a voxel-wise analysis of diffusion tensor imaging. *J. Neurotrauma* 25, 1335–1342. doi: 10.1089/neu.2008.0547

Lo, C., Shifteh, K., Gold, T., Bello, J. A., and Lipton, M. L. (2009). Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. *J. Comput. Assist. Tomogr.* 33, 293–297. doi: 10.1097/RCT.0b013e31817579d1

McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., et al. (2003). Acute effects and recovery time following concussion in collegiate football players. *JAMA* 290, 2556–2563. doi: 10.1001/jama.290.19.2556

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2018.00118/full#supplementary-material

McGlade, E., Rogowska, J., and Yurgelun-Todd, D. (2015). Sex differences in orbitofrontal connectivity in male and female veterans with TBI. *Brain Imaging Behav.* 9, 535–549. doi: 10.1007/s11682-015-9379-3

Morey, L. C. (1991). *Personality Assessment Inventory Professional Manual*. 2nd Edn. Lutz, FL: Psychological Assessment Resources, Inc.

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., et al. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 40, 570–582. doi: 10.1016/j.neuroimage.2007.12.035

Paul, L. (2004). Social processing deficits in agenesis of the corpus callosum: narratives from the thematic apperception test. *Arch. Clin. Neuropsychol.* 19, 215–225. doi: 10.1016/s0887-6177(03)00024-6

Paul, L. K. (2011). Developmental malformation of the corpus callosum: a review of typical callosal development and examples of developmental disorders with callosal involvement. *J. Neurodev. Disord.* 3, 3–27. doi: 10.1007/s11689-010-9059-y

Prince, C., and Bruhns, M. E. (2017). Evaluation and treatment of mild traumatic brain injury: the role of neuropsychology. *Brain Sci.* 7:E105. doi: 10.3390/brainsci7080105

Rao, V., Rosenberg, P., Bertrand, M., Salehinia, S., Spiro, J., Vaishnavi, S., et al. (2009). Aggression after traumatic brain injury prevalence and correlates. *J. Neuropsychiatry Clin. Neurosci.* 21, 420–429. doi: 10.1176/jnp.2009.21.4.420

Rapoport, M. J., McCullagh, S., Streiner, D., and Feinstein, A. (2003). The clinical significance of major depression following mild traumatic brain injury. *Psychosomatics* 44, 31–37. doi: 10.1176/appi.psy.44.1.31

Roy, D., Vaishnavi, S., Han, D., and Rao, V. (2017). Correlates and prevalence of aggression at six months and one year after first-time traumatic brain injury. *J. Neuropsychiatry Clin. Neurosci.* 29, 334–342. doi: 10.1176/appi.neuropsych.16050088

Ruff, R. M. (2005). Two decades of advances in understanding of mild traumatic brain injury. *J. Head Trauma Rehabil.* 20, 5–18. doi: 10.1097/00001199-200501000-00003

Schutter, D. J., and Harmon-Jones, E. (2013). The corpus callosum: a commissural road to anger and aggression. *Neurosci. Biobehav. Rev.* 37, 2481–2488. doi: 10.1016/j.neubiorev.2013.07.013

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155. doi: 10.1002/hbm.10062

Smith, R., and Lane, R. D. (2015). The neural basis of one's own conscious and unconscious emotional states. *Neurosci. Biobehav. Rev.* 57, 1–29. doi: 10.1016/j.neubiorev.2015.08.003

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505. doi: 10.1016/j.neuroimage.2006.02.024

Smith, R., Thayer, J. F., Khalsa, S. S., and Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neurosci. Biobehav. Rev.* 75, 274–296. doi: 10.1016/j.neubiorev.2017.02.003

Song, S.-K., Sun, S.-W., Ramsbottom, M. J., Chang, C., Russell, J., and Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429–1436. doi: 10.1006/nimg.2002.1267

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., et al. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 26, 132–140. doi: 10.1016/j.neuroimage.2005.01.028

Sugiyama, K., Kondo, T., Oouchida, Y., Suzukamo, Y., Higano, S., Endo, M., et al. (2009). Clinical utility of diffusion tensor imaging for evaluating patients with diffuse axonal injury and cognitive disorders in the chronic stage. *J. Neurotrauma* 26, 1879–1890. doi: 10.1089/neu.2008.0839

Sundram, F., Deeley, Q., Sarkar, S., Daly, E., Latham, R., Craig, M., et al. (2012). White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex* 48, 216–229. doi: 10.1016/j.cortex.2011.06.005

Sussmann, J. E., Lymer, G. K. S., McKirdy, J., Moorhead, T. W. J., Muñoz Maniega, S., Job, D., et al. (2009). White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar Disord.* 11, 11–18. doi: 10.1111/j.1399-5618.2008.00646.x

Till, C., Christensen, B. K., and Green, R. E. (2009). Use of the personality assessment inventory (PAI) in individuals with traumatic brain injury. *Brain Inj.* 23, 655–665. doi: 10.1080/02699050902970794

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. 2nd Edn. San Antonio, TX: Pearson.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale*. San Antonio, TX: Pearson.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Dailey, Smith, Bajaj, Alkozei, Gottschlich, Raikes, Satterfield and Killgore. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Resting-state functional connectivity as a biomarker of aggression in mild traumatic brain injury

Natalie S. Dailey, Ryan Smith, John R. Vanuk, Adam C. Raikes and William D.S. Killgore

Mild traumatic brain injury (mTBI) can alter the structure of the brain and result in a range of symptoms, including elevated aggression. Neurological damage associated with mTBI is traditionally viewed as transient, yet a growing number of studies suggest long-lasting psychological and neurological changes following mTBI. However, research examining the neural basis of emotion processing in the chronic stage of mTBI recovery remains sparse. In the current study, we utilized resting state functional MRI to explore the association between default mode network connectivity and aggression in 17 healthy controls and 17 adults at least 6 months post-mTBI. The association between within-network connectivity and aggression was examined using general linear models, controlling for the effects of depression. Increased connectivity between the right hippocampus and midcingulate cortex was associated with elevated aggression in adults with mTBI, but not in healthy controls. The results provide evidence for a link between intrinsic functional network disruptions and the manifestation of postconcussive symptoms within chronic stages of recovery following mTBI. These findings expand upon the current research, providing evidence for the use of resting state functional connectivity as a potential biomarker of postconcussive aggression in chronic mTBI. *NeuroReport* **29:1413–1417 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

NeuroReport 2018, **29**:1413–1417

Keywords: aggression, default mode network, functional connectivity, mild traumatic brain injury, postconcussive symptoms, resting state functional magnetic resonance imaging

Department of Psychiatry, College of Medicine, University of Arizona, Tucson, Arizona, USA

Correspondence to Natalie S. Dailey, PhD, Department of Psychiatry, College of Medicine, University of Arizona, 1501N Campbell Avenue, Tucson, AZ 85701, USA
Tel: + 1 520 626 8710; fax: + 1 520 626 6050; e-mail: ndailey@email.arizona.edu

Received 13 August 2018 **accepted** 21 August 2018

Introduction

Mild traumatic brain injury (mTBI) is exceedingly prevalent [1,2], yet the heterogeneous nature of mTBI, combined with a dynamic recovery process, presents challenges in accurate diagnosis and treatment. Neurological damage associated with mTBI is traditionally viewed as transient, followed by rapid symptom reduction in the days and weeks following injury [3]. Nonetheless, recent studies have documented a range of persistent symptoms in individuals at least 6 months after injury [4–6], alluding to potentially long-lasting psychological and neurological changes following mTBI. One persistent symptom is elevated aggressive tendencies, which is the focus of the present study.

Disruptions within the neural systems associated with aggression following mTBI, especially in the chronic stage of recovery, are not well understood. Specific large-scale networks are implicated in different aspects of emotion processing and can be explored through the use of resting state functional MRI (rs-fMRI). One particular network, the default mode network (DMN), consists of medial regions in prefrontal, parietal, and temporal cortices [7], and plays an important role in recognizing and understanding emotions [8–11]. Reduced understanding of one's own emotions promotes inefficient conceptualization [11], suggesting that DMN dysfunction could promote elevated aggression. Findings are mixed in terms of the influences of mTBI on DMN function, but, previous work suggests that functional connectivity in the DMN is disrupted in acute [12–14] and chronic stages [13,15,16] of mTBI, and that such disruption relates to impaired control of affective responses in mixed severity TBI [17].

Research examining the neural basis of recognizing/understanding emotion in the chronic stage of mTBI recovery remains sparse. The aim of the present study was to explore the association between DMN function and self-reported aggression in individuals at least 6 months post-mTBI. The metric of network function we chose to examine was within-network functional connectivity. On the basis of the critical role played by the DMN in understanding emotion, we hypothesized that connectivity within this network would be altered in individuals with mTBI, compared with healthy controls (HCs), and that connectivity within the DMN would be associated with differences in post-mTBI aggression.

Participants and methods

Participants

The present study included 17 individuals with mTBI and 17 HCs and is part of a larger, on-going study

0959-4965 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/WNR.0000000000001127

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

investigating neuropsychological function at various stages of mTBI recovery. Previous aggression findings from the larger study were previously published [6], yet this manuscript reports on novel connectivity findings. All participants were between 18 and 45 years of age, native English speakers, and right-handed. Exclusionary criteria included a history of psychiatric/neurological disease, alcohol/substance abuse, or contraindication for MRI. Individuals in the mTBI group presented at least 6 months after injury and provided brain injury documentation before study enrollment. Injury severity was based on the American Congress of Rehabilitation Medicine [18] and VA/DoD Guidelines [19], where mTBI was defined as a physiological disruption of brain function, a Glasgow Coma Scale between 13 and 15, temporary loss of consciousness less than 30 min, transient post-traumatic amnesia less than 24 h, and altered mental state that may be transient.

Participants underwent neuropsychological testing followed by rs-fMRI data acquisition. The Buss–Perry Aggression Questionnaire was used to measure aggression [20] and the Beck Depression Inventory [21] was used to measure depression. The study was approved by the Institutional Review Board at the University of Arizona and the US Army Human Research Protections Office, and participants provided prior written informed consent in accordance with the Declaration of Helsinki.

MRI data acquisition

Neuroimaging data were acquired on a 3.0-Tesla Siemens Skyra scanner (MAGNETOM Skyra; Siemens Healthcare, Malvern, Pennsylvania, USA) equipped with a 32-channel head coil. A high-resolution T1-weighted MPRAGE anatomical scan was collected first (repetition time = 2100 ms, echo time = 2.33 ms, field-of-view = 256 mm, matrix size = 256 × 256; flip angle = 12°, voxel size = 1 × 1 × 1 mm, 176 slices). During rs-fMRI, participants were instructed to relax and fixate on a cross in the middle of the screen. Functional scans were obtained using a T2*-weighted gradient-echo, echo-planar imaging sequence (repetition time = 2000 ms, echo time = 25 ms, field-of-view = 220 mm, flip angle = 90°, GRAPPA acceleration factor = 2). We collected 32 transverse slices (matrix = 88 × 84, voxel size = 2.5 × 2.5 × 2.5 mm, distance factor = 40%), allowing for 300 volumes.

Statistical analysis

The rs-fMRI data were preprocessed using Statistical Parametric Mapping (SPM12) running in Matlab (v. R2016a; Mathworks, Natick, Massachusetts, USA) and included motion correction with realignment, slice timing correction using the middle slice as the reference slice, coregistration of functional scans to anatomical scans, forward deformation normalization (isotropic voxel size = 3 × 3 × 3 mm), and smoothing using a Gaussian kernel (full-width at half maximum = 5 mm). Preprocessed structural and rs-fMRI data were loaded into the CONN Functional Connectivity Toolbox (v. 17.f; *http://www.nitrc.org/projects/conn/* [22]). Artifact Detection Toolbox (ART; SPM12) was used to identify outlier scans with a global mean signal threshold of 3 SD and movement threshold of 0.5 mm. Single-participant data were denoised using bandpass filters of 0.01–0.1 Hz. Three HCs and two mTBI participants were excluded from further analysis because of excessive head motion (i.e. <20% outlier scans), resulting in a final sample of 14 HCs and 15 with mTBI.

The dorsal DMN was comprised of nine functionally defined regions of interests (ROIs) on the basis of Shirer *et al.* [23] (*http://findlab.stanford.edu/functional_ROIs.html*). Network ROIs included the medial prefrontal cortex (mPFC), posterior cingulate cortex, midcingulate cortex (MCC), right superior frontal gyrus, left and right angular gyri, thalamus, and left and right hippocampi (lHPC, rHPC) (Table 1). A weighted general linear model was used to calculate functional connectivity measures for each participant. Weights for the model were defined as the block-convolved canonical hemodynamic response function and are appropriate for analyzing resting state data [22]. Time courses at each voxel in a ROI were averaged to generate a mean time course specific to that of ROI. Individual bivariate correlation maps (Fisher-transformed) were computed for resting state connectivity between each seed and target ROI time series within the DMN. A group-level approach was used to compare differences in DMN connectivity between the two groups and the association between within-network connectivity and aggression using general linear models, controlling for the effects of depression. Reported results were corrected for multiple comparisons ($P < 0.05$, seed-level false discovery rate correction).

Results

Neuropsychological data

Demographic information and neuropsychological results are presented in Table 2. Significant differences in depression and aggression were previously reported between mTBI and HC groups [6].

Table 1 Functionally defined regions of interest for the default mode network

ROI	Anatomical location	*x* (mm)	*y* (mm)	*z* (mm)	Voxels
1	Medial prefrontal cortex	−4	50	14	5257
2	Left angular gyrus	−48	−66	36	97
3	Superior frontal gyrus	18	40	48	137
4	Posterior cingulate cortex	0	−52	30	1555
5	Midcingulate cortex	2	−14	38	114
6	Right angular gyrus	48	−62	34	38
7	Thalamus	−2	−8	6	220
8	Left hippocampus	−24	−28	−12	393
9	Right hippocampus	26	−22	−16	142

Default mode network regions of interest from Shirer *et al.* [23].
x, *y*, *z*, coordinates correspond to Montreal Neurological Institute cluster centroid in millimeters (mm).
ROI, region of interest.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Default mode network functional connectivity

Connectivity between ROIs comprising the DMN was calculated and compared between the two groups. No significant between-group differences in DMN connectivity were found in any of the ROI-to-ROI comparisons (Fig. 1).

Default mode network connectivity and aggression

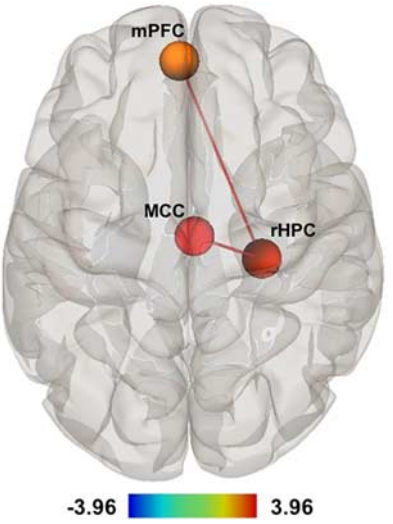
Despite the lack of differences in DMN connectivity between the two groups, we were interested in whether the association between connectivity and aggression differed between groups, given the significantly elevated levels of aggression in those with mTBI. A significant group × aggression interaction was found for functional connectivity [$F(6, 19) = 3.97$, $P = 0.01$]. The groups differed significantly in their association between aggression and ROI-to-ROI connectivity for the rHPC and MCC [$t(24) = 3.96$, $P_{corrected} = 0.01$] and the rHPC and mPFC [$t(24) = 2.89$, $P_{corrected} = 0.03$] (Fig. 2). In the mTBI group, elevated aggression was significantly correlated with increased rHPC–MCC connectivity ($r = 0.68$, $P = 0.01$), but not rHPC–mPFC connectivity ($r = 0.32$, $P = 0.27$). By contrast, in the HC group, aggression was negatively correlated with rHPC–MCC connectivity ($r = -0.58$, $P = 0.04$) and rHPC–mPFC connectivity ($r = -0.63$, $P = 0.02$) (Fig. 3).

Table 2 Demographic and neuropsychological measures by group

	HC	mTBI	*P* value[a]
Age [mean (SD)] (years)	23.88 (3.26)	21.86 (2.79)	0.08
Female/male	10/4	11/4	1.00[b]
BDI [mean (SD)]	1.29 (1.49)	8.47 (7.46)	0.002
BPAQ total [mean (SD)]	44.86 (9.68)	58.33 (10.61)	0.001
TSI (days) [mean (SD)]	NA	290.40 (91.87)	NA
Injury mechanism (%)			
Sport-related	NA	53.3	NA
MVA	NA	20.0	NA
Fall	NA	6.7	NA
Cycling	NA	13.3	NA
Other	NA	6.7	NA

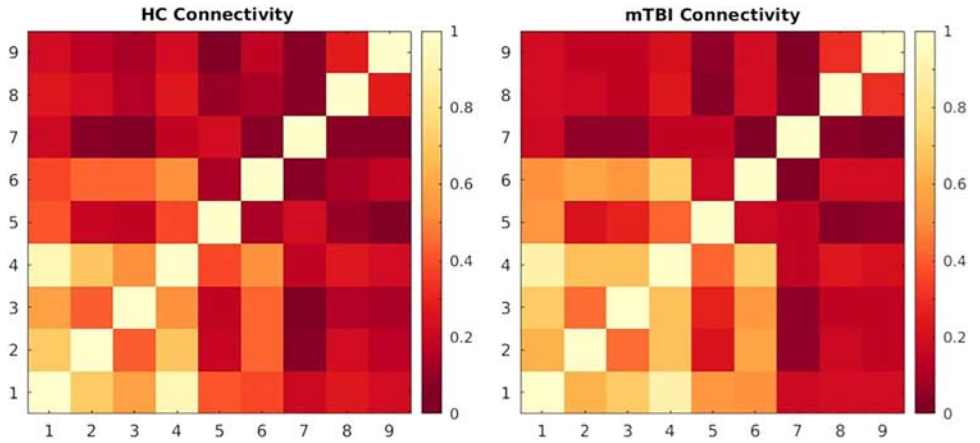
BDI, Beck Depression Inventory; BPAQ total, total aggression on the Buss–Perry Aggression Questionnaire; HC, healthy controls; mTBI, mild traumatic brain injury; MVA, motor vehicle accident; NA, not applicable; TSI, time since injury.
[a]Two-tailed independent-samples *t*-test.
[b]Pearson's χ^2-test.

Fig. 2



Significant between-group differences of ROI-to-ROI connectivity associated with aggression in the default mode network. Color bar indicates *t* scores for mTBI > HC contrast, adjusted for depression ($P < 0.05$, seed-level FDR correction). HC, healthy control; FDR, false discovery rate; MCC, midcingulate cortex; mPFC, medial prefrontal cortex; mTBI, mild traumatic brain injury; rHPC, right hippocampus; ROI, region of interest.

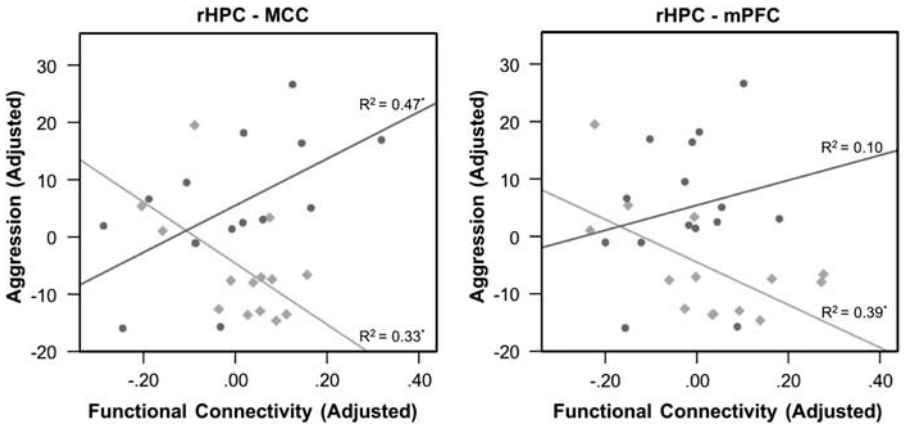
Fig. 1



Matrices showing within-network functional connectivity (mean correlation, *r*) between seed and target regions of the default mode network (DMN) for healthy control (HC) and mild traumatic brain injury (mTBI) groups. Color bars indicate *r* values. 1, medial prefrontal cortex; 2, left angular gyrus; 3, superior frontal gyrus; 4, posterior cingulate gyrus; 5, midcingulate cortex; 6, right angular gyrus; 7, thalamus; 8, left hippocampus; 9, right hippocampus.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Fig. 3



Scatterplots show individual mean Fisher-transformed values for right hippocampal–midcingulate cortex connectivity (rHPC–MCC) and right hippocampal–medial prefrontal cortex connectivity (rHPC–mPFC) in relation to demeaned aggression scores, adjusted for depression. Mild traumatic brain injury group = circle; healthy controls = diamond, $*P < 0.05$.

Discussion

The present study utilized resting state fMRI to examine connectivity within the DMN in relation to long-term postconcussive aggression following mTBI. We found that those recovering from mTBI reported significantly greater aggression than the matched HC group. Moreover, while there were no group differences in overall DMN functional connectivity, increased connectivity between the rHPC and MCC was associated with higher levels of aggression in individuals with mTBI but not in healthy controls. These findings suggest that mTBI-related elevations in aggressive behavior may be associated with altered connectivity within the DMN.

Our results extend previous findings examining behavioral correlates of DMN connectivity following mTBI. In a study by van der Horn *et al.* [15], increased connectivity between posterior cingulate and precuneus regions and medial prefrontal and inferior parietal regions of the DMN positively correlated with persistent cognitive and/or affective complaints at 3 months post-mTBI. In addition to disruptions in connectivity, poor outcomes for individuals with mTBI during the first-year after injury have been associated with morphological alterations of the prefrontal cortex [24]. Our findings of elevated aggression and increased connectivity among regions of the DMN are consistent with the aforementioned studies, and suggest a potential neural mechanism underlying persistent post-mTBI symptomology.

The DMN contributes to recognizing and understanding one's own emotions [8–11], among many other domain-general conceptualization processes [25]. Furthermore, the hippocampus plays an important role in integrating past and present experiences through episodic memory, which is an essential part of the conceptualization process [7]. Differences in emotional awareness have previously been linked to DMN connectivity, and higher emotional awareness has in turn been linked to efficiency of emotion conceptualization [11]. This suggests that altered DMN function could promote aggression through reduced emotional awareness. However, it is important to note that we found increased DMN connectivity with higher aggression. In fact, the relationship we observed within the mTBI group more closely resembles the greater DMN engagement that has been previously associated with depressive rumination [25,26]. Yet, the present findings cannot adequately be explained by post-mTBI depression, as we controlled for depressive symptoms. Thus, another interpretation could be that mTBI promotes greater aggression by increasing the tendency to maladaptively ruminate over negative life events.

Limitations and conclusion

Our study has some limitations that warrant further discussion. First, the sample size of our study was relatively small, which could account for the unexpected absence of group difference in DMN connectivity because of reduced statistical power. Alternatively, these results may be attributable to partial recovery of functional connectivity, as observed in a recent longitudinal study [13]. Second, the analytic approach used a seed-level correction for false discovery rate of post-hoc comparisons. Therefore, type I error cannot be ruled out and ROI-to-ROI findings linking DMN connectivity and aggression should be interpreted with caution. Limitations notwithstanding, our findings align with previous reports of observed associations between DMN connectivity and disrupted emotion processing in mTBI [15].

In summary, higher self-reported aggression in individuals at least 6 months post-mTBI was associated with increased functional connectivity between the right

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

hippocampus and midcingulate cortex. Our results expand current evidence suggesting a link between intrinsic functional network disruptions and the manifestation of postconcussive symptoms within chronic stages of mTBI recovery.

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 Medical Research and Materiel Command (USAMRMC) under Award No. W81XWH-12-0386, to W.D.S. Killgore. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense.

Conflicts of interest

There are no conflicts of interest.

References

1 Faul M, Xu L, Wald MM. *Traumatic brain injury in the United States: Emergency department visits, hospitilizations and deaths 2002–2006*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
2 National Center for Injury Prevention and Control. *Report to congress on mild traumatic brain injury in the united states: steps to prevent a serious public health problem*. Atlanta, GA: Centers for Disease Control and Prevention; 2003.
3 McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, *et al*. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *J Am Med Assoc* 2003; **290**:2556–2563.
4 Epstein DJ, Legarreta M, Bueler E, King J, McGlade E, Yurgelun-Todd D. Orbitofrontal cortical thinning and aggression in mild traumatic brain injury patients. *Brain Behav* 2016; **6**:00581.
5 Roy D, Vaishnavi S, Han D, Rao V. Correlates and prevalence of aggression at six months and one year after first-time traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2017; **29**:334–342.
6 Dailey NS, Smith R, Bajaj S, Alkozei A, Gottschlich MK, Raikes AC, *et al*. Elevated aggression and reduced white matter integrity in mild traumatic brain injury: a DTI study. *Front Behav Neurosci* 2018; **12**:118.
7 Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008; **1124**:1–38.
8 Killgore WDS, Smith R, Olson EA, Weber M, Rauch SL, Nickerson LD. Emotional intelligence is associated with connectivity within and between resting state networks. *Soc Cogn Affect Neurosci* 2017; **12**:1624–1636.
9 Pan J, Zhan L, Hu C, Yang J, Wang C, Gu L, *et al*. Emotion regulation and complex brain networks: association between expressive suppression and efficiency in the fronto-parietal network and default-mode network. *Front Hum Neurosci* 2018; **12**:70.
10 Cui J, Olson EA, Weber M, Schwab ZJ, Rosso IM, Rauch SL, *et al*. Trait emotional suppression is associated with increased activation of the rostral anterior cingulate cortex in response to masked angry faces. *Neuroreport* 2014; **25**:771–776.
11 Smith R, Alkozei A, Bao J, Smith C, Lane RD, Killgore WDS. Resting state functional connectivity correlates of emotional awareness. *Neuroimage* 2017; **159**:99–106.
12 Dall'acqua P, Johannes S, Mica L, Simmen HP, Glaab R, Fandino J, *et al*. Connectomic and surface-based morphometric correlates of acute mild traumatic brain injury. *Front Hum Neurosci* 2016; **10**:127.
13 Dall'acqua P, Johannes S, Mica L, Simmen HP, Glaab R, Fandino J, *et al*. Functional and structural network recovery after mild traumatic brain injury: a 1-year longitudinal study. *Front Hum Neurosci* 2017; **11**:280.
14 Zhu DC, Covassin T, Nogle S, Doyle S, Russell D, Pearson RL, *et al*. A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over thirty days. *J Neurotrauma* 2015; **32**:327–341.
15 van der Horn HJ, Scheenen ME, de Koning ME, Liemburg EJ, Spikman JM, van der Naalt J. The default mode network as a biomarker of persistent complaints after mild traumatic brain injury: a longitudinal functional magnetic resonance imaging study. *J Neurotrauma* 2017; **34**:3262–3269.
16 Palacios EM, Yuh EL, Chang YS, Yue JK, Schnyer DM, Okonkwo DO, *et al*. Resting-state functional connectivity alterations associated with six-month outcomes in mild traumatic brain injury. *J Neurotrauma* 2017; **34**:1546–1557.
17 Sharp DJ, Scott G, Leech R. Network dysfunction after traumatic brain injury. *Nat Rev Neurol* 2014; **10**:156–166.
18 Medicine ACoR. Definition of mild traumatic brain injury. *J Head Trauma Rehab* 1993; **8**:86–87.
19 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**:CP1–CP68.
20 Buss AH, Perry M. The Aggression Questionnaire. *J Pers Soc Psychol* 1992; **63**:452–459.
21 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; **4**:53–63.
22 Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* 2012; **2**:125–141.
23 Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex* 2012; **22**:158–165.
24 Dall'acqua P, Johannes S, Mica L, Simmen HP, Glaab R, Fandino J, *et al*. Prefrontal cortical thickening after mild traumatic brain injury: a one-year magnetic resonance imaging study. *J Neurotrauma* 2017; **34**:3270–3279.
25 Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol* 2012; **8**:49–76.
26 Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, *et al*. The default mode network and self-referential processes in depression. *Proc Natl Acad Sci USA* 2009; **106**:1942–1947.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

frontiers in Neurology

ORIGINAL RESEARCH
published: 20 June 2018
doi: 10.3389/fneur.2018.00468

Diffusion Tensor Imaging (DTI) Correlates of Self-Reported Sleep Quality and Depression Following Mild Traumatic Brain Injury

Adam C. Raikes, Sahil Bajaj, Natalie S. Dailey, Ryan S. Smith, Anna Alkozei, Brieann C. Satterfield and William D. S. Killgore*

Social, Cognitive, and Affective Neuroscience Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States

OPEN ACCESS

Edited by:
Denes V. Agoston, Karolinska Institutet (KI), Sweden

Reviewed by:
Ramon Diaz-Arrastia, University of Pennsylvania, United States
Ralph George Depalma, US Department of Veterans Affairs, United States

****Correspondence:***
Adam C. Raikes
raikes.research@gmail.com

Specialty section:
This article was submitted to Neurotrauma, a section of the journal Frontiers in Neurology

Received: *20 December 2017*
Accepted: *31 May 2018*
Published: *20 June 2018*

Citation:
Raikes AC, Bajaj S, Dailey NS, Smith RS, Alkozei A, Satterfield BC and Killgore WDS (2018) Diffusion Tensor Imaging (DTI) Correlates of Self-Reported Sleep Quality and Depression Following Mild Traumatic Brain Injury. Front. Neurol. 9:468. doi: 10.3389/fneur.2018.00468

Background: Mild traumatic brain injuries (mTBIs) are a significant social, sport, and military health issue. In spite of advances in the clinical management of these injuries, the underlying pathophysiology is not well-understood. There is a critical need to advance objective biomarkers, allowing the identification and tracking of the long-term evolution of changes resulting from mTBI. Diffusion-weighted imaging (DWI) allows for the assessment of white-matter properties in the brain and shows promise as a suitable biomarker of mTBI pathophysiology.

Methods: 34 individuals within a year of an mTBI (age: 24.4 ± 7.4) and 18 individuals with no history of mTBI (age: 23.2 ± 3.4) participated in this study. Participants completed self-report measures related to functional outcomes, psychological health, post-injury symptoms, and sleep, and underwent a neuroimaging session that included DWI. Whole-brain white matter was skeletonized using tract-based spatial statistics (TBSS) and compared between groups as well as correlated within-group with the self-report measures.

Results: There were no statistically significant anatomical differences between the two groups. After controlling for time since injury, fractional anisotropy (FA) demonstrated a negative correlation with sleep quality scores (higher FA was associated with better sleep quality) and increasing depressive symptoms in the mTBI participants. Conversely, mean (MD) and radial diffusivity (RD) demonstrated positive correlations with sleep quality scores (higher RD was associated with worse sleep quality) and increasing depressive symptoms. These correlations were observed bilaterally in the internal capsule (anterior and posterior limbs), corona radiata (anterior and superior), fornix, and superior fronto-occipital fasciculi.

Conclusion: The results of this study indicate that the clinical presentation of mTBI, particularly with respect to depression and sleep, is associated with reduced white-matter integrity in multiple areas of the brain, even after controlling for time since

injury. These areas are generally associated not only with sleep and emotion regulation but also cognition. Consequently, the onset of depression and sleep dysfunction as well as cognitive impairments following mTBI may be closely related to each other and to white-matter integrity throughout the brain.

Keywords: white matter integrity, Pittsburgh sleep quality index, beck depression inventory, fractional anisotropy, radial diffusivity, internal capsule, superior fronto-occipital fasciculus, corona radiata

INTRODUCTION

Concussions and mild traumatic brain injuries (mTBI) represent a significant public and military health crisis. 1.6 to 3.8 million sport-related concussions (SRCs) are reported annually (1, 2), and more than 300,000 mTBIs (hereafter referring to both mTBIs and SRCs) have been documented in military personnel since the year 2000 (3). The actual incidence of these injuries is likely much higher, as estimates reflect only those for which treatment is sought (4). Treatment costs for mTBIs top $22 billion annually in the United States (5). Individuals sustaining an mTBI may exhibit any number of clinical features, including changes in cognitive and motor function as well as post-injury depression, somatic symptoms, and sleep-wake cycle disruption (6). However, these clinical signs and symptoms are not generally associated with visible structural abnormalities when using traditional diagnostic/clinical neuroimaging techniques (e.g., structural magnetic resonance imaging (MRI) or computed tomography (CT) in the emergency department). Furthermore, although many of the clinical signs and symptoms resolve within the first month post-injury (6), many individuals continue to experience symptoms well beyond this clinical timeframe.

Among those persistent symptoms, sleep disruption and depression are among the most common. Estimates of the prevalence of sleep disruption following mTBI ranges from 30 to 80% (7–9), with complaints of insomnia, hypersomnia, and pleiosomnia all reported (8, 10–12). Individuals with prior mTBI also often report and exhibit depressive symptoms, with an estimated 6% per year being clinically diagnosed with depression (13) and many more exhibiting depressive symptoms (14). Notably, depression may additionally cause altered sleep patterns (15). Collectively, both sleep disruption and depression can impair cognitive and physical function (16–20) and may therefore exacerbate the symptoms of and delay the recovery from an mTBI. However, to date, there are have a limited number of studies that have identified the neural correlates of both sleep disruption (21) or depression (22, 23) following mTBI. Consequently, it is needful to identify objective biomarkers of both the pathophysiology and post-injury recovery that underpin the evolution of post-mTBI sleep disruption and depression.

One imaging methodology that is particularly sensitive to altered brain structure is diffusion tensor imaging (DTI). In DTI, water molecule diffusion properties in the brain are quantified, principally by fractional anisotropy (FA) and mean diffusivity (MD). FA quantifies molecular diffusion along three dimensions (FA = 0: diffusion is equally likely in any direction; FA = 1: diffusion occurs along one direction), while MD quantifies the average three-dimensional diffusion rate. Additionally, radial diffusivity (RD) and axial diffusivity (AD) reflect the rates of diffusion perpendicular and parallel to the underlying tissue, respectively. These diffusion metrics, and most prevalently FA, are thought to provide an index of white matter integrity. Mouse models of neural trauma have demonstrated decreased AD concomitant with axonal damage (24, 25) and negative correlations between RD and myelination [e.g., higher RD is associated with reduced myelination; (25, 26)]. MD, the average of AD and RD, is non-specific with respect to the direction of diffusion. Increases in MD and coincident decreases in FA are often associated with neural trauma and neurodegeneration (27, 28), including mTBI (29–31).

Mild traumatic brain injuries may reflect a model of diffuse axonal injury (DAI), characterized by damage to, and subsequently the loss of, axons, myelin, or both (32–34). Demyelination has been observed in animal models of mTBI (35) and may be secondary to axonal loss or loss of oligodendrocytes supplying undamaged axons (36–39). Regardless of mechanism, white matter integrity may be compromised following mTBI. Therefore, DTI metrics may provide a suitable biomarker of both microstructural changes following mTBI as well as clinical presentation.

With respect to mTBI, numerous publications have featured DTI-related findings in civilian, military, and sport populations, spanning timeframes from acute to remote (years) post-injury (40–42). Despite the density of publications, there is little consistency in the findings with respect to directional changes in DTI metrics. While some studies, for instance, report lower FA following mTBI (43–47), this is not always the case (48–51). Such inconsistent patterns are also present with respect to MD, AD, and RD (43, 46, 48, 52). Given the heterogeneous nature of mechanistic/neural changes in mTBI and generally small study sample sizes, such inconsistency is not unexpected and necessitates additional exploration.

Despite the inconsistency in directional findings for DTI diffusion metrics following mTBI, several affected white matter pathways do exhibit some consistency. Changes or differences in FA and MD in the corpus callosum, anterior and posterior corona radiata, anterior and posterior thalamic radiations, superior and inferior longitudinal fasciculi, corticospinal tracts, and internal capsule, are commonly reported (40, 41, 53). Such consistency of reporting suggests that these white matter tracts may be particularly susceptible to the multiple mechanisms (focal injuries, shearing) that may result in an mTBI (40, 41, 53).

Importantly, prior work related to major depressive disorder (54) and insomnia (55, 56), as well as sleep quality (57) and variability (58) in generally healthy populations, has consistently demonstrated correlations with FA, such that more negative outcomes (e.g., greater depressive symptoms, lower sleep quality, and increased variability) are associated with lower FA in these same tracts. Given the overlapping tracts identified on DTI following mTBI and those related to sleep quality and depression from other populations, it is likely that these tracts play an important role in post-mTBI symptom presentation. However, to date, there are no DTI-related findings specific to mTBI and sleep quality or depression.

The purpose of this study was to use DTI to correlate diffusion metrics with self-report indices of sleep quality and depression in individuals with a recent mTBI. This study is part of a larger, on-going project aimed at identifying structural and neural correlates of self-report, neurocognitive, and behavioral outcomes following mTBI. Here, we compared DTI metrics between individuals within a year of an mTBI and individuals with no self-reported history of mTBI. Additionally, we computed within-group correlations between diffusion metrics and self-report outcomes in the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs; http://www.commondataelements.ninds.nih.gov/) psychiatric and psychological status [e.g., depression; (59)] domain and self-reported sleep quality (60). We hypothesized, consistent with the view that mTBI reflects aspects of DAI (32–34), that FA would be lower, and MD, AD, and RD higher in the mTBI group than in the healthy controls. Further we hypothesized that this pattern would extend to symptom presentation, with greater post-mTBI depressive symptoms, and lower sleep quality associated with lower FA and greater MD, AD, and RD.

MATERIALS AND METHODS

Participants

A total of 52 individuals ($n = 34$ with a history of a recent (within 12 months) mTBI; $n = 18$ healthy control individuals with no documented history of head trauma) participated in the present study. Participants were recruited from the Tucson metropolitan area via multiple methods including Internet advertisements, posted flyers, and referral through local emergency departments. The presence of mTBI was defined in agreement with the American Congress of Rehabilitation Medicine guidelines including (1) alteration of mental status related to specific head trauma lasting up to 24 h; (2) loss of consciousness <30 min; (3) post-traumatic amnesia lasting <1 day; and (4) initial Glasgow Coma Scale between 13 and 15 (61). To be eligible, participants were required to provide written documentation from a medical provider or other professional who either witnessed the injury or provided immediate treatment or care as a result of the injury.

All participants were right-handed and reported English as their first language. Individuals were not eligible to participate in this study in the presence of (1) any contraindications for MRI, (2) education <9th grade, (3) history of alcoholism or substance abuse, (4) colorblindness, or (5) lifetime history of DSM-IV Axis I disorder. Healthy control participants were additionally ineligible with any lifetime history of TBI or sport participation in concussion high-risk sports (e.g., football, rugby, boxing, ice hockey, wrestling, soccer, or martial arts) for longer than 1 month. All participants were compensated for their time. All study procedures were approved by The University of Arizona Institutional Review Board and the US Army Human Research Protections Office. All participants provided written informed consent prior to participation. Participant demographics are further summarized in **Table 1.**

Materials and Procedure

As part of a larger, on-going study, individuals in the current sample were evaluated at one of six pre-specified time points relative to their injury date: 2-weeks, 4-weeks, 3-months, 6-months, or 12-months post-injury (see **Table 1**). The purpose of the larger study is to examine structural and neural correlates of neuropsychological, behavioral, and self-reported outcomes over the first year following an mTBI. Individuals are included at only one of six time points and treated as exemplars of recovery at that time. We report here on a subset of the outcomes.

All participants underwent a comprehensive neuropsychological evaluation, including several self-report measures (described below), followed by a neuroimaging session that included diffusion-weighted imaging (DWI). Only a subset of the outcome measures are presented here. In addition to indices of depressive symptoms and sleep quality, we included NINDS CDEs related to global outcomes, post-mTBI symptom presentation, and perceived health-related quality of life, all of which may be impacted by depression and/or lower sleep quality.

Self-Report Outcomes

Glasgow Outcome Scale - Extended (GOS-E)

The GOS-E is a structured interview commonly used to assess overall disability and recovery following TBI (62). It is a core element of the NINDS CDEs for all levels of severity of TBI, including sport-related concussion. Scores on subscales for the GOS-E quantify disability in cognition, independence, employability, and social or community participation. These subscales are cumulatively reported as a single overall outcome, ranging from 1 (death) to 8 (upper good recovery). Reliability for the GOS-E is high [$\kappa = 0.85$; (62)].

Beck Depression Inventory-II (BDI-II)

The BDI-II is a self-administered survey requiring self-appraisal of mood over the preceding 2 weeks (63, 64). Increasing scores on the BDI-II are associated with increasing levels of depression symptoms. The BDI-II has high test-retest reliability ($r > 0.9$), as well as construct (vs. the original BDI) and moderate concurrent (vs. the State-Trait Anxiety Inventory Anxiety and Depression factors) validity ($r > 0.68$; (65, 66)). Previous work has demonstrated that individuals with both recent mTBIs and a history of mTBI report higher levels of depression and increased likelihood for depression by comparison to individuals without mTBI (22, 67–71).

TABLE 1 | Participant demographics and self-report measures.

	Healthy Control Mean (*SD*)	mTBI Mean (*SD*)	Statistic[a]	*p*	Effect Size[b]
n	18	34			
DEMOGRAPHICS					
Age (years)	23.2 (3.4)	24.4 (7.4)	−0.795	0.430	−0.232
Height (in)	67.2 (4.3)	66.4 (4.2)	0.649	0.520	0.189
Weight (lb)	158.4 (41.5)	151.8 (38.1)	0.565	0.576	0.165
Total mTBIs[c]	0 [0]	2 [1]	−12.6	< 0.001	−3.673
Sex (n)			0.272[d]	0.602	0.144
Male	9	13			
Female	9	21			
Race/Ethnicity (n)			4.063[d]	0.540	0.577
Asian/Pacific Islander	2	3			
Black/African American	0	2			
Hispanic/Latino	1	0			
Native American/ American Indian	2	2			
Other	0	1			
White	12	25			
Weeks Post-Injury (n)					
2 weeks		6 (17.6%)			
4 weeks		8 (23.5%)			
12 weeks		7 (20.6%)			
24 weeks		6 (14.7%)			
52 weeks		9 (23.5%)			
Mechanism of Injury (n)					
Sports-related		13 (38.2%)			
Slip and/or fall		7 (20.6%)			
MVA		6 (17.6%)			
Bike related		4 (11.8%)			
Environmental[e]		3 (8.8%)			
Assault		1 (2.9%)			
SELF-REPORT MEASURES					
PSQI Total Score	3.7 (1.8)	6.8 (3.5)	−4.227	< 0.001	−1.232
BDI–II Total Score	2.4 (2.9)	9.6 (8.1)	−4.636	< 0.001	−1.351
RPQ-3	0.2 (0.6)	2.4 (2.5)	−4.771	< 0.001	−1.391
RPQ-13	0.3 (1.0)	10.7 (10.6)	−5.616	< 0.001	−1.637
SWLS Total Score	26.6 (6.0)	26.2 (4.9)	0.230	0.819	0.067
GOS-E Outcome[f] (n)					
Upper Good Recovery		10			
Lower Good Recovery		13			
Upper Moderate Disability		10			
Upper Severe Disability		1			

[a] *Tests are two-tailed t-tests unless otherwise indicated.*
[b] *Cohen's d effect sizes.*
[c] *Data presented as median [interquartile range].*
[d] χ^2 *test.*
[e] *Mechanism of injury is for the most recent mTBI. Environmental accidents include falls from ladders or unanticipated contact with environmental features (ground, structures) unrelated to sports or falls.*
[f] *No GOS-E data were collected on the healthy control participants.*
mTBI, mild traumatic brain injury; MVA, motor vehicle accident; PSQI, Pittsburgh Sleep Quality Index; BDI-II, Beck Depression Inventory – 2; RPQ, Rivermead Post-concussion Symptom Questionnaire; SWLS, Satisfaction with Life Survey; GOS-E, Glasgow Outcome Scale-Extended.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is an 18-item self-report questionnaire yielding information about overall sleep quality, latency, duration, efficiency, disturbances, medication use, and the effects on daytime function (60). Better sleep quality is associated with lower scores, with scores of >5 indicating poor sleep and >8 indicating insomnia. Prior work has indicated good test-retest reliability ($r > 0.80$; (60)) and sensitivity to sleep disruption following mTBI (72, 73).

Satisfaction With Life Survey (SWLS)

The SWLS is a self-administered survey in which individuals assess current life satisfaction based on five questions. Questions are scored "Strongly Disagree" (1) to "Strongly Agree" (7) and summed with a maximum value of 35 (74). Higher scores indicate greater life satisfaction. The SWLS has demonstrated test-retest reliability [$r > 0.80$; (75)]. It is a basic element of the NINDS CDEs for concussion and mTBI (59). Previous research has indicated that individuals with prior mTBIs report greater life dissatisfaction (76, 77).

Rivermead Post-Concussion Symptom Questionnaire (RPCSQ)

The RPCSQ is a common post-mTBI assessment of symptom presentation and is a basic element of the NINDS CDEs for concussion and mTBI (59). Participants self-report the extent to which 16 symptoms currently affect them compared to preinjury-levels. Ratings range from "Not experienced at all" (0) and "No more of a problem" (1) to "A severe problem (4) (78). Previous analyses of the RPCSQ have identified a two-factor structure, such that the first three questions (RPQ3) are sensitive to acute injury symptoms while the final 13 (RPQ13) are sensitive to chronic symptoms. These two scales have good test-retest reliability ($r > 0.70$) and external validity [$\rho > 0.60$; (79)], and the RPQ is a significant predictor of 3-month outcomes (80).

Diffusion-Weighted Imaging

We acquired DWI data using single-shot echo planar imaging (EPI) (TE = 88 ms; TR = 9600 ms; acquisition matrix = 128 × 128; FOV: 256 × 256; slice thickness = 2 mm with no gap) on a Siemens Skyra 3.0 Tesla MRI machine (32-channel head coil; MAGNETO Skyra Siemens Healthcare). Images were acquired following a within-lab standardized process, including cross checks on image acquisition parameters at the time of scanning, with a single MRI technician overseeing all scanning procedures. Diffusion gradients were applied along 72 directions, with b = 1000 s/mm^2 and six non-diffusion weighted images (b_0). Preprocessing followed the standard pipeline available through FMRIB Software Library's [FSL; (81)], including EPI distortion correction using *TOPUP* (82), motion and eddy current distortion correction using *eddy* (83), skull-stripping with the brain extraction tool [*BET*; (84)], and diffusion tensor model fitting using *DTIFIT* (85). Output from *DTIFIT* includes separate images for FA, MD and three eigenvalues (λ_1, λ_2, λ_3). λ_1 is the axial diffusivity and radial diffusivity is the average of λ_2 and λ_3.

The four DTI-metric images (FA, MD, AD, and RD) were then nonlinearly registered to a standard template (FMRIB-58) followed by affine-alignment to standard space (MNI, 1 × 1 × 1 mm) using Tract-Based Spatial Statistics [TBSS; (86)]. A study-specific, averaged whole-brain skeletonized FA mask was created through TBSS (threshold = 0.2). Skeletonizing in this way reduces the number of voxels considered in statistical modeling by only including voxels near the center of white matter tracts.

Whole-brain voxel-wise statistical analysis was conducted via FSL's *randomise* using threshold-free cluster enhancement (87) with 5000 permutations. Significant voxels were identified as those with $p < 0.05$ after family-wise error rate (FWER) adjustment for multiple comparison. We tested between-group differences using a two-sample *T*-test for each of the DTI metrics (FA, MD, AD, RD), controlling for age, sex, and days post-injury. For the self-report measures, we fit within-group GLMs for each combination of measure and metric, controlling for age, sex, and days since injury (mTBI only). Within-group correlations for the relationships between DTI metrics and self-report outcome measures were examined.

A mask of all significant voxels was created for each of the DTI metrics. These masks were then used to compute the mean DTI-metric value for each participant, which was then extracted for *post-hoc* analyses. Mean DTI-metric values and self-report measures were scatter-plotted and the partial correlation coefficient, after controlling for age, sex, and days post-injury, was computed. Significant white matter voxels were anatomically identified using the Johns Hopkins University (JHU) ICBM-DTI-81 White-Matter Labels atlas (88).

Statistical Analyses

Between-group comparisons for continuous demographic characteristics and self-report measures were analyzed using a two-tailed *T*-test in R [v. 3.4.2; (89)]. The between-group gender and ethnicity comparisons were computed using a Chi-square test. Average values over all significant voxels were plotted in R as scatterplots with the relevant self-report outcomes using ggplot2 (90). For the healthy control participants, taking an inverse transformation of the BDI scores [$y = \frac{1}{(x+1)}$)] and a square transformation ($y = x^2$) of the SWLS scores was necessary to reduce skewness. No GOS-E data were collected for the healthy control participants, as this measure is specific to brain injury.

RESULTS

Demographic and Self-Report Measures

Demographic characteristics and self-report outcomes are summarized in **Table 1**. No participants were active duty military; however, we did not query for Veteran status. The groups did not differ in age, height, weight, or gender. Brain injured participants reported a median number of mTBIs, including the one used for referral, of 2 (range: 1–4). Most individuals ($n = 13$) reported a sports-related mechanism of injury for the referring mTBI. The mTBI participants reported significantly more post-concussive symptoms, poorer sleep quality, and greater

depressive symptoms than the healthy control participants. The majority of the mTBI participants ($n = 23$, 68%) reported a good recovery as assessed via the GOS-E.

Given the dynamic nature of post-mTBI recovery and the role that time since injury may play, we additionally report the means and standard deviations for the self-reported outcomes for each of the six distinct time points in **Table 2.** Given the small sample sizes across all of the post-mTBI groups, we do not report any between-group statistical comparisons at this time.

Diffusion Metrics

Whole-Brain Group Differences

After correcting for multiple comparisons, there were no statistically significant differences observed between the healthy control participants and those with a history of mTBI for any of the diffusion metrics at the whole brain level (*a priori* $\alpha = 0.05$). However, there were voxels with a trend toward greater radial diffusivity in the mTBI participants than the healthy control participants (FWER $0.064 \leq p \leq 0.094$; **Supplementary Figures 1**, **5**, top row).

Correlation Between Diffusion Metrics and Self-Report Measures

There were no significant correlations within the healthy control group between any of the DTI metrics and any of the self-report outcomes. However, a positive trend association between AD and SWLS scores was observed ($0.068 \leq$ *corrected* $p \leq 0.099$, **Supplementary Figures 2**, **5,** second row). We found voxels with significant correlations in the mTBI participant group for the BDI-FA (*corrected* $p < 0.05$, **Figures 1**, **6A**), BDI-MD (*corrected* $p < 0.05$, **Figures 2**, **6B**), BDI-RD (*corrected* $p < 0.05$, **Figures 3**, **6C**), PSQI-FA (*corrected* $p < 0.05$, **Figures 4**, **6D**) and PSQI-RD (*corrected* $p < 0.05$, **Figures 5**, **6E**) relationships. Finally, trend associations were observed for RPQ3-AD ($0.093 \leq$ *corrected* $p \leq 0.1$, **Supplementary Figures 3**, **5**, third row) and PSQI-MD ($0.079 \leq$ *corrected* $p \leq 0.1$, **Supplementary Figures 4**, **5**, bottom row). No statistically significant correlations were present in the mTBI group between any diffusion metric and the GOS-E, RPQ13, or SWLS scores.

Anatomical locations of significant correlations were automatically determined using FSL's *atlasquery* function and the JHU ICBM-DTI-81 White-Matter Labels atlas (88). These

TABLE 2 | Participant demographics and self-report measures by weeks post-Mtbi.

n	Uninjured *n* = 18	2 weeks *n* = 6	4 weeks *n* = 8	3 months *n* = 7	6 months *n* = 5	1 year *n* = 8
DEMOGRAPHICS						
Age (years)	23.2 (3.4)	25.1 (10.1)	25.3 (6.7)	26.6 (9.3)	24.9 (8.6)	20.9 (1.4)
Height (in)	67.2 (4.3)	69.3 (6.1)	66.9 (3.5)	65.3 (3.9)	65.2 (2.6)	65.5 (4.3)
Weight (lb)	158.4 (41.5)	169.7 (43.9)	158.9 (36.5)	139.3 (34.6)	157.0 (49.2)	139.0 (32.1)
Total mTBIs[a]	0.0 [0.0]	2.0 [0.8]	2.0 [1.0]	2.0 [2.0]	2.0 [2.0]	2.0 [1.0]
Sex (*n*)						
Male	9 (50%)	4 (66.7%)	4 (50%)	2 (28.6%)	1 (20%)	2 (25%)
Race/Ethnicity (n)						
Asian/Pacific Islander	2	0	0	1	0	2
Black/African American	0	2	0	0	0	0
Hispanic/Latino	1	0	0	0	0	0
Native American/ American Indian	2	0	1	0	1	0
Other	0	0	1	0	0	0
White	12	4	5	6	4	6
SELF-REPORT MEASURES						
PSQI Total Score	3.7 (1.8)	6.7 (4.5)	7.0 (1.4)	6.0 (2.8)	7.2 (3.8)	7.1 (5.0)
BDI-II Total Score	2.1 (2.6)	9.3 (7.2)	9.8 (6.5)	12.6 (10.3)	9.2 (9.8)	5.1 (4.4)
RPQ-3	0.2 (0.6)	2.7 (3.7)	3.8 (2.3)	2.0 (2.3)	1.4 (1.9)	1.9 (2.2)
RPQ-13	0.3 (1.0)	11.7 (9.3)	12.4 (10.0)	9.0 (11.0)	13.2 (16.4)	8.1 (9.8)
SWLS Total Score	26.6 (6.0)	28.2 (2.8)	24.1 (6.2)	25.0 (6.5)	25.6 (4.4)	28.1 (2.8)
GOS-E Outcome[b] (*n*)						
Upper Good Recovery		2	2	3	1	2
Lower Good Recovery		2	1	2	3	5
Upper Moderate Disability		1	5	2	1	1
Upper Severe Disability		1	0	0	0	0

[a] *Data presented as median [interquartile range].*

[b] *No GOS-E data were collected on the healthy control participants. mTBI, mild traumatic brain injury; PSQI, Pittsburgh Sleep Quality Index; BDI-II Beck Depression Inventory – 2; RPQ, Rivermead Post-concussion Symptom Questionnaire; SWLS, Satisfaction with Life Survey; GOS-E, Glasgow Outcome Scale – Extended.*

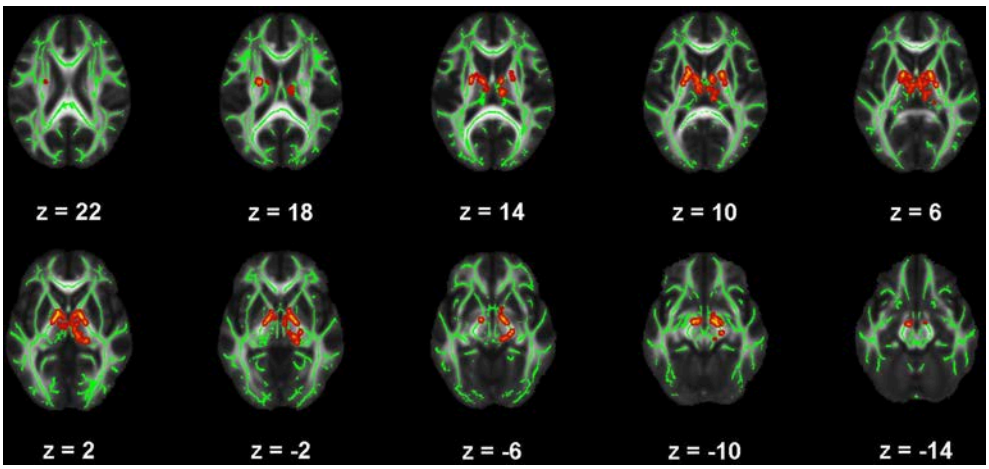


FIGURE 1 | Map of voxels with significant correlations between fractional anisotropy (FA) and Beck Depression Inventory – II (BDI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate significant, negative correlations between FA and BDI total score (family-wise error rate corrected $p < 0.05$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

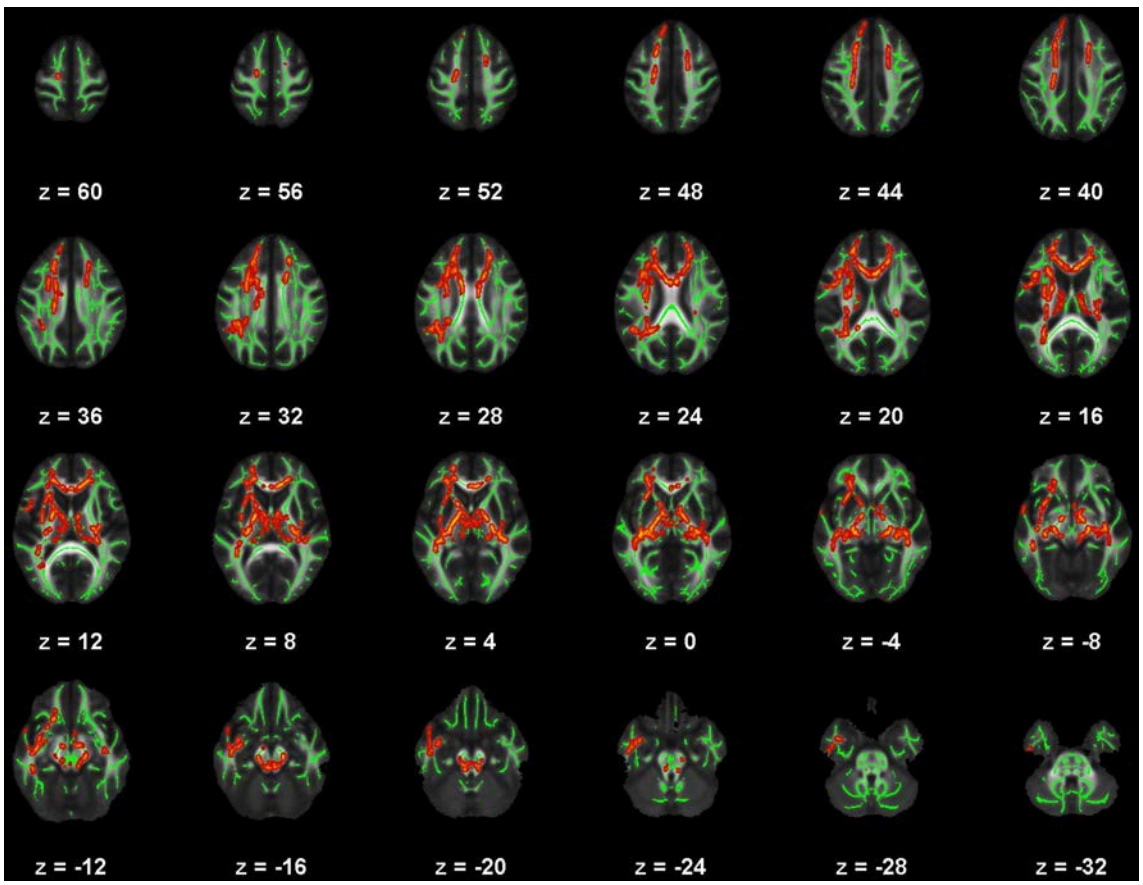


FIGURE 2 | Map of voxels with significant correlations between radial diffusivity (RD) and Beck Depression Inventory – II (BDI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate significant, positive correlations between RD and BDI total score (family-wise error rate corrected $p < 0.05$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

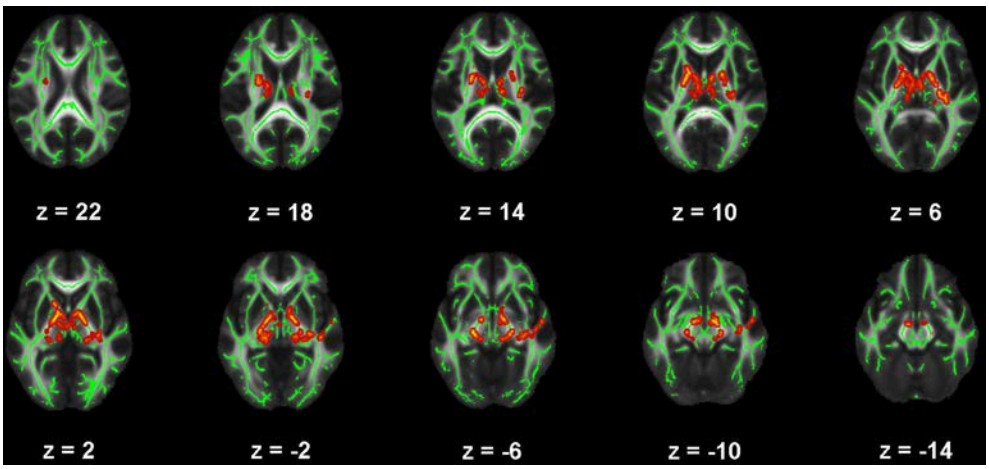


FIGURE 3 | Map of voxels with significant correlations between mean diffusivity (MD) and Beck Depression Inventory – II (BDI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate significant, positive correlations between MD and BDI total score (family-wise error rate corrected $p < 0.05$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

locations are summarized in **Figure 7** and the abbreviations detailed in **Supplementary Table 1**. *Atlasquery* returns the probability (and, in the case of the JHU ICBM-DTI-81 atlas, the proportion) of voxels in a mask belonging to a region identified in a given atlas. The JHU ICBM-DTI-81 atlas does not encompass all white matter, and consequently some voxels remain unclassified. **Figure 7** has been rescaled to reflect only the classified voxels (e.g., 25% = 25% of the classified voxels). Across all five of the significant correlation pairs (BDI-FA, BDI-MD, BDI-RD, PSQI-FA, and PSQI-RD), correlations were consistently observed bilaterally within the internal capsules (anterior and posterior limbs), corona radiata (anterior and superior), fornix, and superior fronto-occipital fasciculi.

Confirmatory *Post-Hoc* Analyses

We performed two additional *post-hoc* analyses to further strengthen these findings. To confirm the lack of PSQI-DTI and BDI-DTI correlation in the healthy controls, we conducted an ROI analysis. Using the significant voxel masks created for the mTBI participants, the healthy control participants' mean DTI-metric values were extracted in the same manner as for the mTBI participants. *Post-hoc* partial correlations for the healthy controls were computed as described above, controlling for age and sex. None of these *post-hoc* correlations were statistically significant, as anticipated based on the results from *randomise*. Additionally, we compared the partial correlation coefficients between the healthy control and mTBI participants (91). These analyses confirmed that the observed correlations in the mTBI participants were significantly different from those in the healthy controls (see **Supplementary Table 2**).

Additionally, the BDI-II includes two questions that specifically address sleep. We observed significant correlations between sleep quality (PSQI) and DTI metrics, as well as depressive symptoms (BDI) and the same DTI metrics (FA and RD). Additionally, there was overlap in the structural areas exhibiting significance. Consequently, it was important to examine whether the BDI-DTI correlations for the mTBI participants depended upon perceived sleep quality. We computed a modified BDI total score that ignored items 16 (changes in sleeping pattern) and 20 (tiredness or fatigue) and re-calculated the partial correlations between BDI and the mean FA, MD, and RD over the previously identified significant voxels, while controlling for age, sex and time since injury. We then compared the two sets of correlation coefficients (91). There were no significant differences between the original and adjusted BDI correlations (see **Supplementary Table 2**), suggesting that the BDI-FA, BDI-MD, and BDI-RD correlations were not necessarily dependent on self-reported sleep characteristics.

DISCUSSION

The focus of this study was to identify neural correlates of clinically-relevant self-report outcomes related to global outcomes, psychiatric and psychological status, perceived health-related quality of life, and post-concussive related symptoms (59) as well as self-reported sleep quality (60). Specifically, the emphasis here was on metrics related to white-matter integrity, including FA as well as MD, AD, and RD. We hypothesized that individuals with a recent mTBI would exhibit lower FA and greater MD and RD than individuals with no prior history of mTBI. Additionally, we hypothesized that within-group correlations would be present such that poorer outcomes (e.g., poorer sleep quality, more depression symptoms) would be associated with lower FA and greater MD and RD. These hypotheses were partially confirmed.

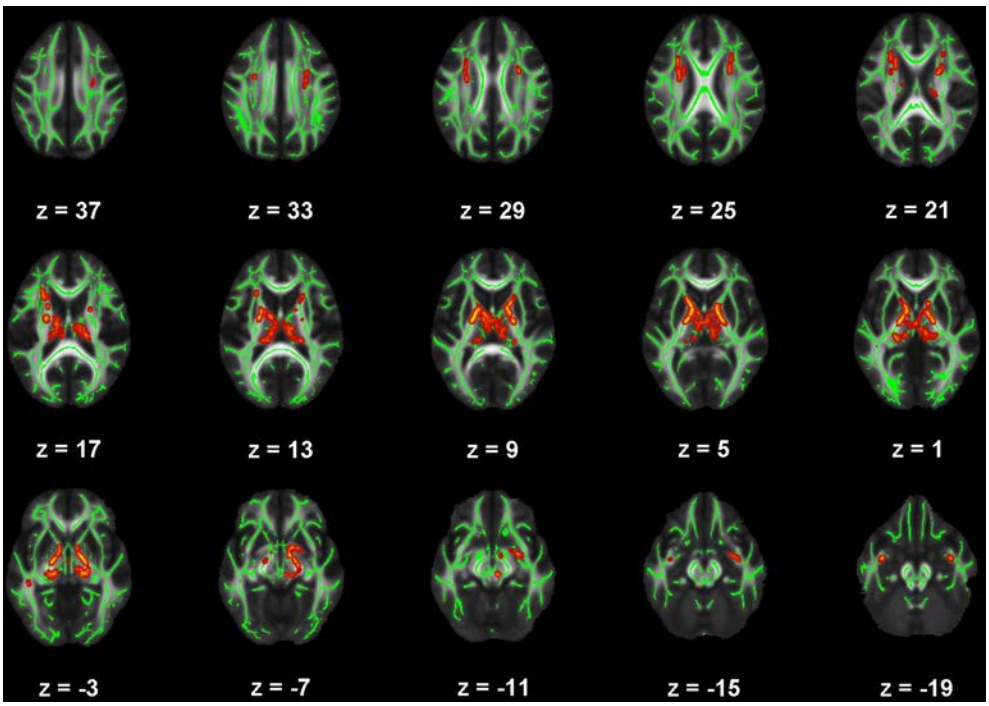


FIGURE 4 | Map of voxels with significant correlations between fractional anisotropy (FA) and Pittsburgh Sleep Quality Index (PSQI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate significant, negative correlations between FA and PSQI total score (family-wise error rate corrected $p < 0.05$). Surrounding voxels are filled in red voxels for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

DTI Sensitivity to mTBI

Contrary to our hypotheses, we did not observe any *statistically significant* differences between the healthy control and mTBI participants for any of the four diffusion metrics. This lack of difference occurred despite participants with mTBI reporting statistically greater sleep disturbances, depression symptoms, and post-concussive symptoms than the healthy controls. Recent systematic reviews and meta-analyses have generally highlighted the sensitivity of FA and MD to mTBI (40, 41, 53), however, the directional difference relative to non-mTBI participants is unclear, with lower, higher, and no differences reported (31, 43, 46, 48, 50–52). Our findings here are consistent with those of "no differences" at a whole brain corrected level, however it is important to note that generalization across DTI studies in mTBI is limited by cross-study heterogeneity in sample sizes, participant ages and populations, imaging protocols, and processing methods (40, 41). Please see **Exploratory trends** for a further discussion of group differences.

Correlations With Self-Report Outcomes

Consistent with our hypotheses, both sleep quality and depressive symptoms in the participants with mTBIs in the present study were correlated with DTI metrics. The relationships with depressive symptoms remained significant after removing sleep-related items from the BDI total score, suggesting that these were not driven by sleep issues *per se*. These measures exhibited negative correlations with FA and positive correlations with RD in projection and association tracts, including the internal capsule (IC), superior and anterior corona radiata (SCR, ACR), anterior and posterior thalamic radiations (ATR, PTR), and superior fronto-occipital fasciculus (SFO). Collectively, these white-matter tracts are integral aspects of neural circuits connecting deep brain structures, specifically the thalamus, parietal, and occipital cortical regions with frontal and prefrontal cortex areas. These connections not only play a critical role in sleep-wake regulation (thalamo-cortical circuits; (92–94), but also facilitate information processing, cognitive control, attention, executive function, and emotion regulation (95–97), all of which may be impaired following mTBI. Recent models of the neural basis of depression have further illustrated how alterations in the information processing supported by these prefrontal-posterior cortical/subcortical pathways (e.g., schema-guided attention, interpretation, and cognitive control processes) may bi-directionally interact with sleep quality to produce/maintain depressive symptoms (98). Consequently, damage in these pathways may precipitate the clinical presentation of mTBI, especially with respect to the correlated sleep and depression-related symptoms we observed in our sample.

There is substantial evidence that prior mTBI is associated with poor sleep quality, both self-reported (8, 12, 99, 100) as well as when measured via actigraphy (11, 101) and/or

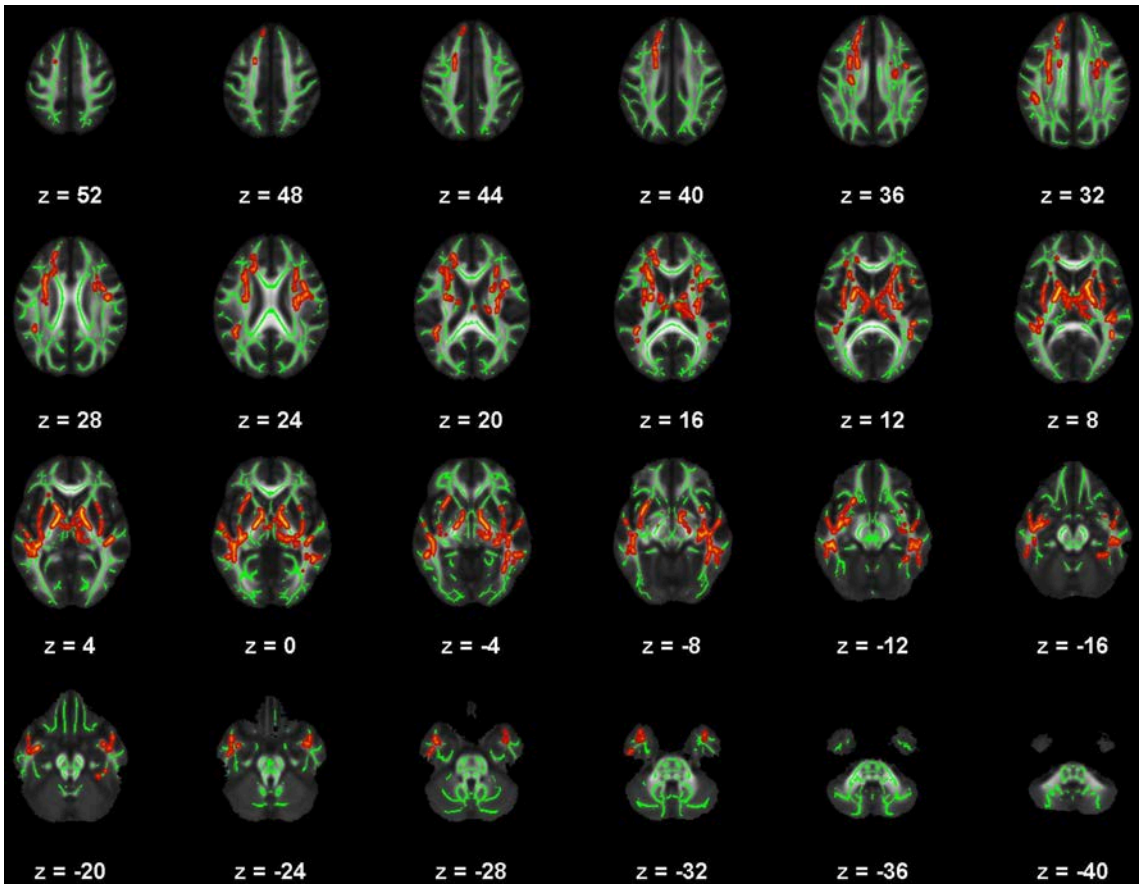


FIGURE 5 | Map of voxels with significant correlations between radial diffusivity (RD) and Pittsburgh Sleep Quality Index (PSQI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate significant, positive correlations between RD and PSQI total score (family-wise error rate corrected $p < 0.05$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

polysomnography (102). Poor sleep quality may manifest in numerous ways, including insomnia (8, 12), hypersomnia (10), pleiosomnia (11), and increased night-to-night sleep variability (101). Proposed mechanisms for sleep-wake disturbances following mTBI include reduced sleep-wake regulation neurotransmitter availability, specifically low hypocretin/orexin, and lower counts of wake-promoting neurons in the hypothalamus (103–105). To our knowledge, the findings here are the first to link sleep quality with white-matter integrity following mTBI, and suggest that there are likely overlapping relationships between these mechanisms.

The results reported here are consistent with findings from both depression- and sleep-related studies apart from mTBI [i.e., where sleep disturbance is thought to both promote, and be promoted by, underlying neural processing abnormalities in depression; (98)]. Lower FA in the SLF, IC, and corpus callosum are frequently observed in major depressive disorder (54). Additionally, individuals with poor sleep quality (57), increased sleep variability (58), and insomnia (55, 56) all exhibit lower FA, particularly in the IC, SLF, and thalamic radiations. Importantly, previous work has indicated that poor sleep quality is associated with lower FA and increased RD even in healthy individuals and can cause reduced myelination and limit oligodendrocyte precursor proliferation (57, 58). In light of mouse models indicating that mTBI can directly result in loss of myelination (35–38), it is unclear to what extent post-mTBI sleep quality leads to white-matter damage vs. trauma-induced white-matter damage leading to poor sleep. Regardless, white-matter damage in these pathways may explain overlapping presentations of poor sleep quality, psychological distress, and cognitive impairment typically associated with mTBI. Identifying the independent contributions of traumatic insult vs. sleep loss-induced alterations in white-matter remains an open area of investigation in this population.

Exploratory Trends

Surprisingly, and generally contrary to the bulk of the literature on mTBI and DTI, there were no statistically significant differences (at a whole brain FWER *corrected* $p < 0.05$ level) between the mTBI participants and healthy controls. We did, however, observe a trend toward greater RD in the mTBI

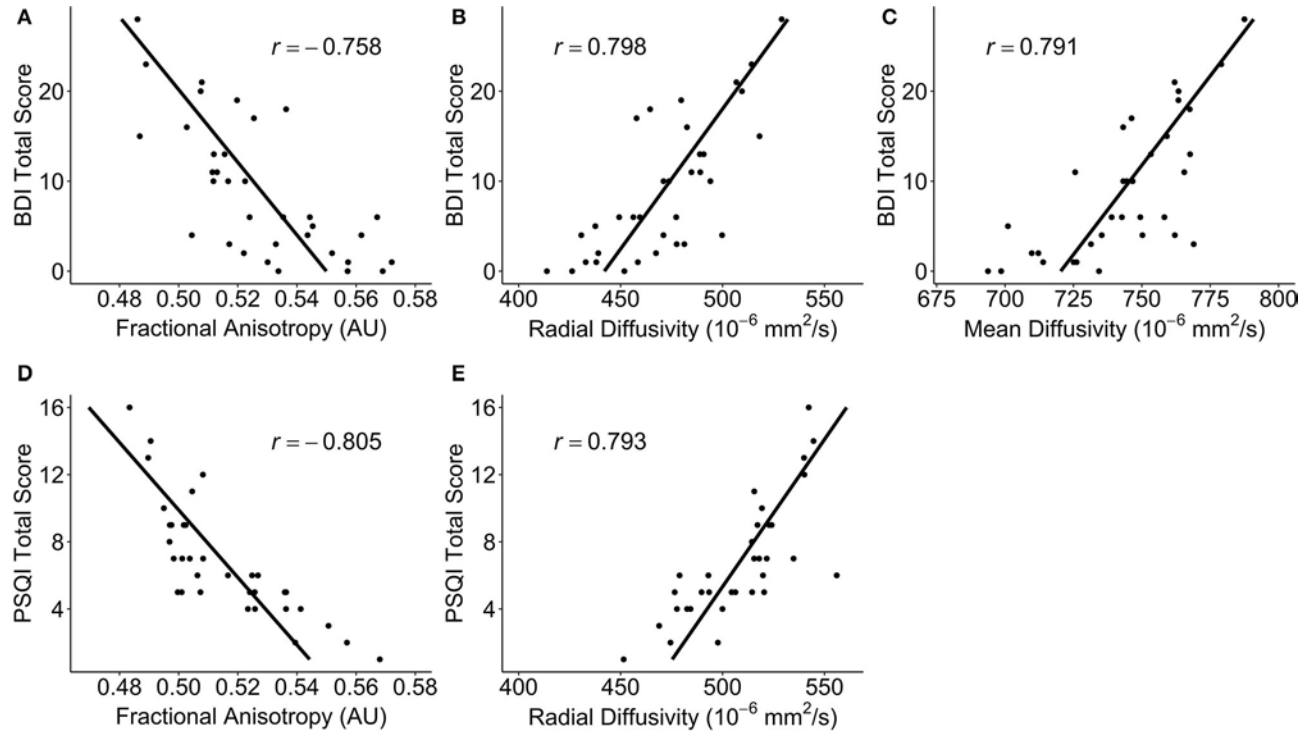


FIGURE 6 | Scatterplots of *post-hoc* partial correlations between diffusivity measures and self-reported outcomes for participants with a mild traumatic brain injury. The points in each plot are the average DTI measure over all of the significant voxels. The black line is a regression line predicting the self-report outcomes from the diffusivity measures, controlling for age, sex, and days post-injury. Correlation coefficients are noted as *r*. **(A)** The Beck Depression Inventory – II (BDI) total score vs. fractional anisotropy (FA); (**B)** BDI total score vs. radial diffusivity (RD); **(C)** BDI total score vs. mean diffusivity (MD); **(D)** Pittsburgh Sleep Quality Index (PSQI) total score vs. FA; **(E)** PSQI total score vs. RD.

participants (at a FWER *corrected* $p < 0.1$), primarily in the right hemisphere. While areas did not overlap exactly with the significant voxels from the mTBI group correlations, they do exist within the same pathways, particularly the corona radiata, longitudinal fasciculi, and the corpus callosum. While these differences do not meet the conventional level of significance, they do point to the possibility of myelin-related damage following mTBI.

Similarly, despite the observed relationships between FA/RD and both sleep quality and depressive symptoms, there were no statistically significant correlations (at a FWER *corrected* $p < 0.05$ level) between diffusion measures and post-concussive symptom presentation on the Rivermead Post-concussion Symptom Questionnaire. However, a negative *trend* did exist between AD and post-concussive symptoms on the RPQ3 (which identifies somatic symptoms; i.e., headaches, dizziness, nausea), such that lower AD was associated with greater symptom presentation. This result is in line with other recent findings (106), suggesting that somatic symptom presentation may be related to axonal damage.

Limitations

The present study indicates an association between diffusion metrics and self-report outcomes subsequent to mTBI, particularly with regard to sleep and depressive symptoms. However, a number of challenges remain. First, our overall sample was relatively small, which may contribute to the lack of statistically significant differences observed between healthy control participants and mTBI participants. Secondly, despite significant correlations between diffusion metrics and both sleep quality and depressive symptoms, the findings here present only a cross-sectional view of post-mTBI outcomes. Consequently, we cannot make any assertions about causation with respect to either the white matter integrity or self-report outcomes.

Third, our group had considerable heterogeneity of time since injury, ranging from 2-weeks to 12-months post injury. There is reasonable evidence that diffusion-related metrics may change over the weeks to months following an mTBI (40). Given the exclusively cross-sectional nature of our data, we addressed this potential limitation in the following ways. First, both our between-group and within-group models controlled for days since injury. Second, a *post-hoc* mTBI participant within-group correlation between the mean significant voxel values for PSQI and BDI-II scores reported earlier and time since injury revealed a non-significant correlation ($r = 0.026$, $p = 0.146$). Therefore, while intra-individual DTI-metrics may typically change over the course of mTBI recovery (40), the relationships between DTI measures, sleep quality, and depression we observed in the present sample appear independent of time since injury.

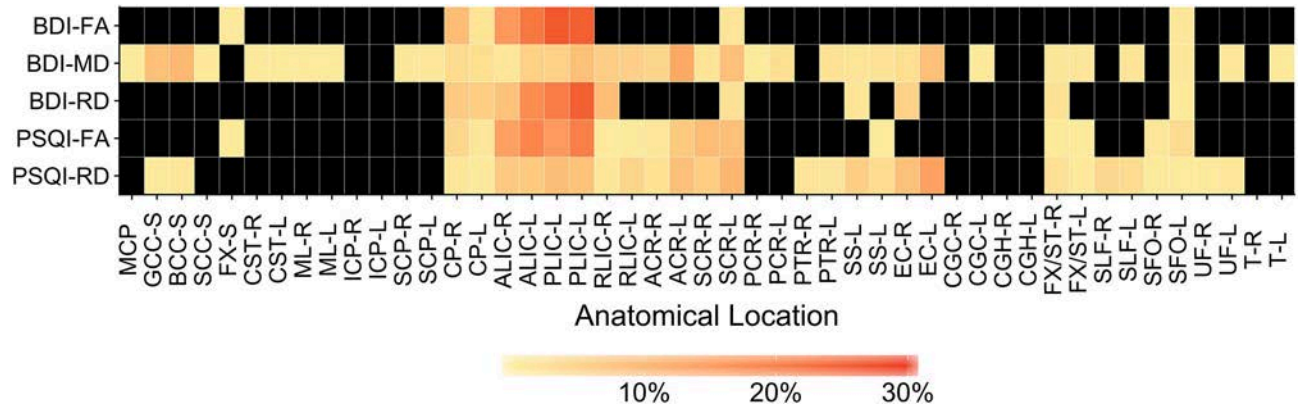


FIGURE 7 | Heatmap showing distribution of labeled, significantly correlated voxels (family-wise error rate corrected $p < 0.05$) for each correlation pair. Anatomical labels are drawn from the JHU ICBM-DTI-81 White-Matter Labels atlas and retrieved using the FMRIB Software Library (FSL) *atlasquery* function. *Atlasquery* returns the probability (and, in the case of the JHU ICBM-DTI-81 atlas, the proportion) of voxels in a mask belonging to a region identified in a given atlas. The JHU ICBM-DTI-81 atlas does not encompass all white matter, and consequently some voxels remain unclassified. Colors reflect the percentage of labeled voxels identified within each anatomical location ($\frac{localized\ voxels}{\sum(classified\ voxels)}$. Black boxes indicate no voxels with a significant correlation were present in that anatomical location. BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; FA, Fractional Anisotropy; MD, Mean Diffusivity; RD, Radial Diffusivity. Anatomical location abbreviations are summarized in **Supplementary Table 1**.

Finally, the white matter skeleton created during TBSS is based upon FA local maxima, generally near the midline of the white-matter tract (107). Thus, group differences between controls and mTBI participants may be present in non-maxima areas of the tracts, but these potential differences would not be detectable using the methods employed here. Finally, there are no established cutoffs, or reliable change indices, for DTI metrics after mTBI to identify whether the observed relationships reflect clinically meaningful changes in diffusion. Future work should address longitudinal outcomes, ideally with pre-injury DTI (though we recognize the inherent challenge in that), as well as machine-learning-based modeling methods (e.g., cross-validated logistic regression, classification trees) to identify discriminative post-mTBI changes in DTI metrics.

CONCLUSION

The results of this study contribute to a growing body of literature indicating that there are correlations between white-matter structure and clinical measures related to sleep quality and depression following mTBI. We have identified that the self-reported presentation of poor sleep quality and depressive symptoms following mTBI correlates with lower white-matter integrity in multiple areas of the brain involved in sleep-wake cycle and emotion regulation, in addition to information processing, cognitive control, attention, and executive function. Finally, trends in our data suggest that there may be alterations in white-matter structure that distinguish individuals with a history of mTBI from those without. Future work should emphasize identifying cutoff values in DTI metrics that provide clinically meaningful distinctions between individuals. Such findings will help not only to continue to increase what is known about mTBI pathophysiology and recovery, but will also help to guide best practices for the diagnosis and treatment of mTBI.

AUTHOR CONTRIBUTIONS

AR conducted the MRI data processing, statistical analyses, and drafted the initial manuscript. SB, ND, RS, and AA assisted with data interpretation and manuscript revisions. BS assisted with manuscript revisions. WK designed the study, assisted with data interpretation and critique, as well as manuscript review and revisions.

FUNDING

This work was supported by a grant to WK from 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 Medical Research and Materiel Command (USAMRMC, Award #W81XWH-12-0386). The opinions, interpretations, conclusions and recommendations in this paper 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.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00468/full#supplementary-material

Supplementary Figure 1 | Map of voxels with greater radial diffusivity (RD; family-wise error rate corrected $0.064 \leq p \leq 0.094$) in mild traumatic brain injury (mTBI) participants compared to healthy control participants. The average white-matter skeleton is presented in green. Yellow voxels indicate voxels with a trend toward statistical significance. Surrounding voxels are filled with red for visual

purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

Supplementary Figure 2 | Map of voxels indicating a positive trend between axial diffusivity (AD) and Satisfaction with Life Scale (SWLS) total scores in the healthy control participants. The average white-matter skeleton is presented in green. Yellow voxels indicate positive correlations between AD and SWLS total score (family-wise error rate corrected $0.068 \leq p \leq 0.099$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

Supplementary Figure 3 | Map of voxels indicating a positive trend between mean diffusivity (MD) and Pittsburgh Sleep Quality Index (PSQI) total scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate positive correlations between MD and PSQI total score (family-wise error rate corrected $0.079 \leq p \leq 0.1$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

Supplementary Figure 4 | Map of voxels indicating a positive trend between axial diffusivity (AD) and Rivermead Post-concussion Symptom Questionnaire − 3 (RPQ3) scores in the mild traumatic brain injury (mTBI) participants. The average white-matter skeleton is presented in green. Yellow voxels indicate negative correlations between AD and RPQ3 total score (family-wise error rate corrected $0.093 \leq p \leq 0.1$). Surrounding voxels are filled in red for visual purposes only. Images are in neurological orientation and Z-coordinates are presented in MNI standard space.

Supplementary Figure 5 | Heatmap showing the distribution of labeled voxels (family-wise error rate corrected $0.05 < p \leq 0.1$). Anatomical labels are drawn from the JHU ICBM-DTI-81 White-Matter Labels atlas and retrieved using the FMRIB Software Library (FSL) *atlasquery* function. *Atlasquery* returns the probability (and, in the case of the JHU ICBM-DTI-81 atlas, the proportion) of voxels in a mask belonging to a region identified in a given atlas. The JHU ICBM-DTI-81 atlas does not encompass all white matter, and consequently some voxels remain unclassified. Colors reflect the percentage of labeled voxels identified within each anatomical location ($\frac{localized\ voxels}{\sum(classified\ voxels)}$. Black boxes indicate no voxels with a trend (family-wise error rate corrected $0.05 < p \leq 0.1$) were present in that anatomical location. BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; FA, Fractional Anisotropy; MD, Mean Diffusivity; RD, Radial Diffusivity. Anatomical location abbreviations are summarized in **Supplementary Table 1**.

Supplementary Table 1 | JHU ICBM-DTI-81 White-Matter Labels atlas abbreviations.

Supplementary Table 2 | Confirmatory *post-hoc* correlations.

REFERENCES

1. 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
2. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil.* (2006) 21:375–8. doi: 10.1097/00001199-200609000-00001
3. *Defense Veterans Brain Injury Center DoD Worldwide Numbers for TBI*. Available online at: http://dvbic.dcoe.mil/files/tbi-numbers/worldwide-totals-2000-2017_feb-14-2018_v1.0_2018-03-08.pdf (Accessed October 6, 2017).
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.* (2016) 44:220–5. doi: 10.1177/0363546515612082
5. Finkelstein EA, Corso PS, Miller TR. *Incidence and Economic Burden of Injuries in the United States*. New York, NY: Oxford University Press (2006).
6. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, 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.* (2017) 51:838–47. doi: 10.1136/bjsports-2017-097699
7. Beetar JT, Guilmette TJ, Sparadeo FR. Sleep and pain complaints in symptomatic traumatic brain injury and neurologic populations. *Arch Phys Med Rehabil.* (1996) 77:1298–302. doi: 10.1016/S0003-9993(96)90196-3
8. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. *Brain Inj.* (2002) 16:197–206. doi: 10.1080/02699050110103940
9. Ouellet, MC., 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
10. Billiard M, Podesta C. Recurrent hypersomnia following traumatic brain injury. *Sleep Med.* (2013) 14:462–5. doi: 10.1016/j.sleep.2013.01.009
11. Imbach LL, Valko PO, Li T, Maric A, Symeonidou, ER., Stover JF, et al. Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. *Brain* (2015) 138:726–35. doi: 10.1093/brain/awu391
12. Ouellet, MC., Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. *Sleep Med.* (2006) 7:486–97. doi: 10.1016/j.sleep.2006.03.017
13. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *NeuroRehabilitation* (2002) 17:311–24. doi: 10.1080/09540260310001606700
14. Kreutzer JS, Seel RT, Gourley E. The prevalence and symptom rates of depression after traumatic brain injury: A comprehensive examination. *Brain Inj.* (2001) 15:563–76. doi: 10.1080/02699050010009108
15. Riemann D, Berger M, Voderholzer U. Sleep and depression — results from psychobiological studies: an overview. *Biol Psychol.* (2001) 57:67–103. doi: 10.1016/S0301-0511(01)00090-4
16. 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.* (2012) 93:1751–6. doi: 10.1016/j.apmr.2012.03.032
17. Rapoport MJ, McCullagh S, Shammi P, Feinstein A. Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* (2005) 17:61–5. doi: 10.1176/jnp.17.1.61
18. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med.* (2014) 44:2029–40. doi: 10.1017/S0033291713002535
19. Sufrinko A, Johnson EW, Henry LC. The influence of sleep duration and sleep-related symptoms on baseline neurocognitive performance among male and female high school athletes. *Neuropsychology* (2015) 30:484–91. doi: 10.1037/neu0000250
20. Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res.* (2000) 9:335–52. doi: 10.1046/j.1365-2869.2000.00225.x
21. Datta SGS, Pillai SV, Rao SL, Kovoor JME, Chandramouli BA. Post-concussion syndrome: Correlation of neuropsychological deficits, structural lesions on magnetic resonance imaging and symptoms. *Neurol India* (2009) 57:594–8. doi: 10.4103/0028-3886.57810
22. Chen, JK., Johnston KM, Petrides M, Ptito A. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. *Arch Gen Psychiatry* (2008) 65:81–9. doi: 10.1001/archgenpsychiatry.2007.8
23. Matthews SC, Strigo IA, Simmons AN, O'Connell RM, Reinhardt LE, Moseley SA. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. *NeuroImage* (2011) 54:S69–75. doi: 10.1016/j.neuroimage.2010.04.269

24. Budde MD, Xie M, Cross AH, Song, SK. Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: A quantitative pixelwise analysis. *J Neurosci.* (2009) 29:2805–13. doi: 10.1523/JNEUROSCI.4605-08.2009
25. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage* (2003) 20:1714–22. doi: 10.1016/j.neuroimage.2003.07.005
26. Song, SK., Yoshino J, Le TQ, Lin, SJ., Sun, SW., Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage* (2005) 26:132–40. doi: 10.1016/j.neuroimage.2005.01.028
27. Kasper E, Schuster C, Machts J, Kaufmann J, Bittner D, Vielhaber S, et al. Microstructural white matter changes underlying cognitive and behavioural impairment in ALS - An *in vivo* study using DTI. *PLoS ONE* (2014) 9:e114543. doi: 10.1371/journal.pone.0114543
28. Longoni G, Brown RA, MomayyezSiahkal P, Elliott C, Narayanan S, Bar-Or A, et al. White matter changes in paediatric multiple sclerosis and monophasic demyelinating disorders. *Brain* (2017) 140:1300–15. doi: 10.1093/brain/awx041
29. Ryan NP, Genc S, Beauchamp MH, Yeates KO, Hearps S, Catroppa C, et al. White matter microstructure predicts longitudinal social cognitive outcomes after paediatric traumatic brain injury: A diffusion tensor imaging study. *Psychol Med.* (2017) 48:679–91. doi: 10.1017/S0033291717002057
30. Ting WKC, Schweizer TA, Topolovec-Vranic J, Cusimano MD. Antisaccadic eye movements are correlated with corpus callosum white matter mean diffusivity, Stroop performance, and symptom burden in mild traumatic brain injury and concussion. *Front Neurol.* (2016) 6:271. doi: 10.3389/fneur.2015.00271
31. Wilde EA, Li X, Hunter JV, Narayana PA, Hasan K, Biekman B, et al. Loss of consciousness is related to white matter injury in mild traumatic brain injury. *J Neurotrauma* (2016) 33:2000–10. doi: 10.1089/neu.2015.4212
32. Browne KD, Chen, XH., Meaney DF, Smith DH. Mild traumatic brain injury and diffuse axonal injury in swine. *J Neurotrauma* (2011) 28:1747–55. doi: 10.1089/neu.2011.1913
33. Kirov I, Tal A, Babb J, Lui Y, Grossman R, Gonen O. Diffuse axonal injury in mild traumatic brain injury: a 3D multivoxel proton MR spectroscopy study. *J Neurol.* (2013) 260:242–52. doi: 10.1007/s00415-012-6626-z
34. Lipton ML, Kim N, Park YK, Hulkower MB, Gardin TM, Shifteh K, et al. Robust detection of traumatic axonal injury in individual mild traumatic brain injury patients: Intersubject variation, change over time and bidirectional changes in anisotropy. *Brain Imaging Behav.* (2012) 6:329–42. doi: 10.1007/s11682-012-9175-2
35. Taib T, Leconte C, Steenwinckel JV, Cho AH, Palmier B, Torsello E, et al. Neuroinflammation, myelin and behavior: temporal patterns following mild traumatic brain injury in mice. *PLoS ONE* (2017) 12:e0184811. doi: 10.1371/journal.pone.0184811
36. Hall ED, Sullivan PG, Gibson TR, Pavel KM, Thompson BM, Scheff SW. Spatial and temporal characteristics of neurodegeneration after controlled cortical impact in mice: More than a focal brain injury. *J Neurotrauma* (2005) 22:252–65. doi: 10.1089/neu.2005.22.252
37. Hall ED, Bryant YD, Cho W, Sullivan PG. Evolution of post-traumatic neurodegeneration after controlled cortical impact traumatic brain injury in mice and rats as assessed by the de Olmos silver and fluorojade staining methods. *J Neurotrauma* (2008) 25:235–47. doi: 10.1089/neu.2007.0383
38. Mouzon B, Chaytow H, Crynen G, Bachmeier C, Stewart J, Mullan M, et al. Repetitive mild traumatic brain injury in a mouse model produces learning and memory deficits accompanied by histological changes. *J Neurotrauma* (2012) 29:2761–73. doi: 10.1089/neu.2012.2498
39. Mouzon BC, Bachmeier C, Ferro A, Ojo, JO, Crynen G, Acker CM, et al. Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. *Ann Neurol.* (2014) 75:241–54. doi: 10.1002/ana.24064
40. Asken BM, DeKosky ST, Clugston JR, Jaffee MS, Bauer RM. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): A systematic critical review. *Brain Imaging Behav.* (2017) 12:585–612. doi: 10.1007/s11682-017-9708-9
41. Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, et al. Neuroimaging after mild traumatic brain injury: review and meta-analysis. *NeuroImage Clin.* (2014) 4:283–94. doi: 10.1016/j.nicl.2013.12.009
42. Hulkower MB, Poliak DB, Rosenbaum SB, Zimmerman ME, Lipton ML. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *Am J Neuroradiol.* (2013) 34:2064–74. doi: 10.3174/ajnr.A3395
43. Bazarian JJ, Zhu T, Blyth B, Borrino A, Zhong J. Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. *Magn Reson Imaging* (2012) 30:171–80. doi: 10.1016/j.mri.2011.10.001
44. 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) 103:298–303. doi: 10.3171/jns.2005.103.2.0298
45. 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) 252:816–24. doi: 10.1148/radiol.2523081584
46. Meier TB, Bergamino M, Bellgowan PSF, Teague TK, Ling JM, Jeromin A, et al. Longitudinal assessment of white matter abnormalities following sports-related concussion. *Hum Brain Mapp.* (2016) 37:833–45. doi: 10.1002/hbm.23072
47. Messé A, Caplain S, Pélégrini-Issac M, Blancho S, Montreuil M, Lévy R, et al. Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging Behav.* (2012) 6:283–92. doi: 10.1007/s11682-012-9159-2
48. Bazarian JJ, Zhong J, Blyth B, Zhu T, Kavcic V, Peterson D. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J. Neurotrauma* (2007) 24:1447–59. doi: 10.1089/neu.2007.0241
49. Dretsch MN, Lange RT, Katz JS, Goodman A, Daniel TA, Deshpande G, et al. Examining microstructural white matter in active duty soldiers with a history of mild traumatic brain injury and traumatic stress. *Open Neuroimaging J.* (2017) 11:46–57. doi: 10.2174/1874440001711010046
50. Veeramuthu V, Narayanan V, Kuo TL, Delano-Wood L, Chinna K, Bondi MW, et al. Diffusion tensor imaging parameters in mild traumatic brain injury and its correlation with early neuropsychological impairment: a longitudinal study. *J Neurotrauma* (2015) 32:1497–509. doi: 10.1089/neu.2014.3750
51. Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology* (2008) 70:948–55. doi: 10.1212/01.wnl.0000305961.68029.54
52. Lancaster MA, Olson DV, McCrea MA, Nelson LD, LaRoche AA, Muftuler LT. Acute white matter changes following sport-related concussion: A serial diffusion tensor and diffusion kurtosis tensor imaging study. *Hum Brain Mapp.* (2016) 37:3821–34. doi: 10.1002/hbm.23278
53. Shenton ME, Hamoda HM, Schneiderman JS, Bouix S, Pasternak O, Rathi Y, et al. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav.* (2012) 6:137–92. doi: 10.1007/s11682-012-9156-5
54. Murphy ML, Frodl T. Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biol Mood Anxiety Disord.* (2011) 1:3. doi: 10.1186/2045-5380-1-3
55. Li S, Tian J, Bauer A, Huang R, Wen H, Li M, et al. Reduced integrity of right lateralized white matter in patients with primary insomnia: A diffusion-tensor imaging study. *Radiology* (2016) 280:520–8. doi: 10.1148/radiol.2016152038
56. Spiegelhalder K, Regen W, Prem M, Baglioni C, Nissen C, Feige B, et al. Reduced anterior internal capsule white matter integrity in primary insomnia. *Hum Brain Mapp.* (2014) 35:3431–8. doi: 10.1002/hbm.22412
57. Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A, et al. Associations between self-reported sleep quality and white matter in community-dwelling older adults: a prospective cohort study. *Hum Brain Mapp.* (2017) 38:5465–73. doi: 10.1002/hbm.23739
58. Telzer EH, Goldenberg D, Fuligni AJ, Lieberman MD, Gálvan A. Sleep variability in adolescence is associated with altered brain development. *Dev Cogn Neurosci.* (2015) 14:16–22. doi: 10.1016/j.dcn.2015.05.007

59. Grinnon ST, Miller K, Marler JR, Lu Y, Stout A, Odenkirchen J, et al. National institute of neurological disorders and stroke common data element project – approach and methods. *Clin Trials* (2012) 9:322–9. doi: 10.1177/1740774512438980
60. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
61. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* (1993) 8:86–87. doi: 10.1097/00001199-199309000-00010
62. Wilson JTL, Pettigrew LEK, Teasdale GM. Structured interviews for the glasgow outcome scale and the extended glasgow outcome scale: guidelines for their use. *J Neurotrauma* (1998) 15:573–85. doi: 10.1089/neu.1998.15.573
63. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol.* (1988) 56:893. doi: 10.1037/0022-006X.56.6.893
64. Beck AT, Steer R, Brown G. *Manual for The Beck Depression Inventory Second Edition (BDI-II)*. San Antonio, TX: Psycholoigcal Corporation (1996).
65. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of beck depression inventories-ia and-ii in psychiatric outpatients. *J Pers Assess.* (1996) 67:588–97. doi: 10.1207/s15327752jpa670313
66. Storch EA, Roberti JW, Roth DA. Factor structure, concurrent validity, and internal consistency of the beck depression inventory—second edition in a sample of college students. *Depress Anxiety* (2004) 19:187–9. doi: 10.1002/da.20002
67. Chrisman SPD, Richardson LP. Prevalence of diagnosed depression in adolescents with history of concussion. *J Adolesc Health* (2014) 54:582–6. doi: 10.1016/j.jadohealth.2013.10.006
68. Covassin T, Elbin RJ, Larson E, Kontos AP. Sex and age differences in depression and baseline sport-related concussion neurocognitive performance and symptoms. *Clin J Sport Med.* (2012) 22:98–104. doi: 10.1097/JSM.0b013e31823403d2
69. Strain J, Didehbani N, Cullum CM, Mansinghani S, Conover H, Kraut MA, et al. Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology* (2013) 81:25–32. doi: 10.1212/WNL.0b013e318299ccf8
70. Vanderploeg RD, Curtiss G, Luis CA, Salazar AM. Long-term morbidities following self-reported mild traumatic brain injury. *J Clin Exp Neuropsychol.* (2007) 29:585–98. doi: 10.1080/13803390600826587
71. Yang J, Peek-Asa C, Covassin T, Torner JC. Post-concussion symptoms of depression and anxiety in Division I collegiate athletes. *Dev Neuropsychol.* (2015) 40:18–23. doi: 10.1080/87565641.2014.973499
72. 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) 3:93–6. doi: 10.1177/1545968315619697
73. Theadom A, Cropley M, Parmar P, Barker-Collo S, Starkey N, Jones K, et al. Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med.* (2015) 16:926–32. doi: 10.1016/j.sleep.2015.04.013
74. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. *J Pers Assess.* (1985) 49:71–5. doi: 10.1207/s15327752jpa490113
75. Pavot W, Diener E. Review of the satisfaction with life scale. *Psychol Assess.* (1993) 5:164–72. doi: 10.1037/1040-3590.5.2.164
76. Dams-O'Connor K, Spielman L, Singh A, Gordon WA, Lingsma HF, Maas AIR, et al. The impact of previous traumatic brain injury on health and functioning: A TRACK-TBI study. *J. Neurotrauma* (2013) 30:2014–20. doi: 10.1089/neu.2013.3049
77. McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, et al. Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. *J Neurotrauma* (2014) 31:26–33. doi: 10.1089/neu.2013.2984
78. King NS, Crawford S, Wenden FJ, Moss NEG, Wade DT. The rivermead post concussion symptoms questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol.* (1995) 242:587–92. doi: 10.1007/BF00868811
79. Eyres S, Carey A, Gilworth G, Neumann V, Tennant A. Construct validity and reliability of the rivermead post-concussion symptoms questionnaire. *Clin Rehabil.* (2005) 19:878–87. doi: 10.1191/0269215505cr905oa
80. Guise E, de, Bélanger S, Tinawi S, Anderson K, LeBlanc J, Lamoureux J, et al. Usefulness of the rivermead postconcussion symptoms questionnaire and the trail-making test for outcome prediction in patients with mild traumatic brain injury. *Appl Neuropsychol Adult* (2016) 23:213–22. doi: 10.1080/23279095.2015.1038747
81. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* (2004) 23:S208–19. doi: 10.1016/j.neuroimage.2004.07.051
82. Andersson JLR, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage* (2003) 20:870–88. doi: 10.1016/S1053-8119(03)00336-7
83. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage* (2016) 125:1063–78. doi: 10.1016/j.neuroimage.2015.10.019
84. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp.* (2002) 17:143–55. doi: 10.1002/hbm.10062
85. Behrens TEJ, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med.* (2003) 50:1077–88. doi: 10.1002/mrm.10609
86. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* (2006) 31:1487–05. doi: 10.1016/j.neuroimage.2006.02.024
87. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061
88. Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, et al. Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. *NeuroImage* (2008) 43:447–57. doi: 10.1016/j.neuroimage.2008.07.009
89. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2016). Available online at: https://www.R-project.org/
90. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag (2009).
91. Diedenhofen B, Musch J. cocor: A Comprehensive Solution for the Statistical Comparison of Correlations. *PLoS ONE* (2015) 10:e0121945. doi: 10.1371/journal.pone.0121945
92. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. *Physiol Rev.* (2012) 92:1087–187. doi: 10.1152/physrev.00032.2011
93. Larson-Prior LJ, Ju, YE., Galvin JE. Cortical–subcortical interactions in hypersomnia disorders: mechanisms underlying cognitive and behavioral aspects of the sleep–wake cycle. *Front Neurol.* (2014) 5:165. doi: 10.3389/fneur.2014.00165
94. Steriade M. Corticothalamic resonance, states of vigilance and mentation. *Neuroscience* (2000) 101:243–76. doi: 10.1016/S0306-4522(00)00353-5
95. Asato MR, Terwilliger R, Woo J, Luna B. White matter development in adolescence: A DTI study. *Cereb Cortex* (2010) 20:2122–131. doi: 10.1093/cercor/bhp282
96. Schmahmann J, Pandya D. *Fiber Pathways of the Brain*. New York, NY: Oxford University Press (2009).
97. Sherman SM, Guillery RW. The role of the thalamus in the flow of information to the cortex. *Philos Trans R Soc B Biol Sci.* (2002) 357:1695–708. doi: 10.1098/rstb.2002.1161
98. Smith R, Alkozei A, Killgore WDS, Lane RD. Nested positive feedback loops in the maintenance of major depression: an integration and extension of previous models. *Brain Behav Immun.* (2018) 67:374–97. doi: 10.1016/j.bbi.2017.09.011
99. 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

100. Kaufman Y, Tzischinsky O, Epstein R, Etzioni A, Lavie P, Pillar G. Long-term sleep disturbances in adolescents after minor head injury. *Pediatr Neurol.* (2001) 24:129–34. doi: 10.1016/S0887-8994(00)00254-X
101. Raikes AC, Schaefer SY. Sleep quantity and quality during acute concussion: A pilot study. *SLEEP* (2016) 39:2141–7. doi: 10.5665/slee p.6314
102. Imbach LL, Büchele F, Valko PO, Li T, Maric A, Stover JF, et al. Sleep–wake disorders persist 18 months after traumatic brain injury but remain underrecognized. *Neurology* (2016) 86:1945–9. doi: 10.1212/WNL.0000000000002697
103. Baumann CR, Stocker R, Imhof H, Trentz O, Hersberger M, Mignot E, et al. Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology* (2005) 65:147–9. doi: 10.1212/01.wnl.0000167605.02541.f2
104. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: A prospective study. *Brain* (2007) 130:1873–83. doi: 10.1093/brain/awm109
105. Baumann CR, Bassetti CL, Valko PO, Haybaeck J, Keller M, Clark E, et al. Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann Neurol.* (2009) 66:555–9. doi: 10.1002/ana.21836
106. Mustafi SM, Harezlak J, Koch KM, Nencka AS, Meier T, West JD, et al. Acute white-matter abnormalities in sports-related concussion: a diffusion tensor imaging study from the NCAA-DoD CARE Consortium. *J Neurotrauma.* (2017). doi: 10.1089/neu.2017.5158. [Epub ahead of print].
107. Edden RA, Jones DK. Spatial and orientational heterogeneity in the statistical sensitivity of skeleton-based analyses of diffusion tensor MR imaging data. *J Neurosci Methods* (2011) 201:213–9. doi: 10.1016/j.jneumeth.2011.07.025

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Raikes, Bajaj, Dailey, Smith, Alkozei, Satterfield and Killgore. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Neuroscience Letters 612 (2016) 238–244

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury

William D.S. Killgore[a,b,*], Prabhjyot Singh[a], Maia Kipman[c], Derek Pisner[a], Andrew Fridman[a], Mareen Weber[d]

[a] Social, Cognitive and Affective Neuroscience Lab, University of Arizona College of Medicine, United States
[b] McLean Hospital, Harvard Medical School, United States
[c] Tufts University School of Medicine, United States
[d] Stanford Concussion and Brain Performance Center, Stanford University School of Medicine, United States

HIGHLIGHTS

- A voxel based morphometric study in people with mild traumatic brain injury.
- Longer duration of time since injury was associated with larger gray matter volume.
- Particularly in ventromedial prefrontal cortex and fusiform gyrus regions.
- Compensatory remodeling of cortical regions might be the reason for these findings.

ARTICLE INFO

Article history:
Received 13 November 2015
Received in revised form
14 December 2015
Accepted 15 December 2015
Available online 19 December 2015

Keywords:
mTBI
Mild traumatic brain injury
Concussion
VBM
Voxel-based morphometry
SPM8
Gray matter
Emotion regulation
Motor speed
Psychomotor vigilance

ABSTRACT

Most people who sustain a mild traumatic brain injury (mTBI) will recover to baseline functioning within a period of several days to weeks. A substantial minority of patients, however, will show persistent symptoms and mild cognitive complaints for much longer. To more clearly delineate how the duration of time since injury (TSI) is associated with neuroplastic cortical volume changes and cognitive recovery, we employed voxel-based morphometry (VBM) and select neuropsychological measures in a cross-sectional sample of 26 patients with mTBI assessed at either two-weeks, one-month, three-months, six-months, or one-year post injury, and a sample of 12 healthy controls. Longer duration of TSI was associated with larger gray matter volume (GMV) within the ventromedial prefrontal cortex (vmPFC) and right fusiform gyrus, and better neurocognitive performance on measures of visuospatial design fluency and emotional functioning. In particular, volume within the vmPFC was positively correlated with design fluency and negatively correlated with symptoms of anxiety, whereas GMV of the fusiform gyrus was associated with greater design fluency and sustained visual psychomotor vigilance performance. Moreover, the larger GMV seen among the more chronic individuals was significantly greater than healthy controls, suggesting possible enlargement of these regions with time since injury. These findings are interpreted in light of burgeoning evidence suggesting that cortical regions often exhibit structural changes following experience or practice, and suggest that with greater time since an mTBI, the brain displays compensatory remodeling of cortical regions involved in emotional regulation, which may reduce distractibility during attention demanding visuo-motor tasks.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Traumatic brain injury (TBI) affects approximately 1.5 million individuals each year [27]. While TBI can be classified as mild, moderate, or severe, the vast majority of these injuries are in the mild range [33]. In contrast to moderate or severe TBI, mild traumatic brain injury (mTBI) is diagnosed following a blow or other insult to the head that leads to transient alterations in cognitive, sensory, or motor functioning, and may or may not involve brief loss of consciousness (i.e., no more than 30 min), and is usually not associated with identifiable abnormalities on standard clinical neuroimaging [2]. Common post-concussive symptoms include reduced attention, memory, and information processing speed [4,21]. Psychiatric

* Corresponding author at: Social, Cognitive, and Affective Neuroscience Lab Department of Psychiatry University of Arizona College of Medicine 1501N Campbell Ave Tucson, AZ 85724, United States. Fax: +1 520 626 6050.
E-mail address: killgore@psychiatry.arizona.edu (W.D.S. Killgore).

http://dx.doi.org/10.1016/j.neulet.2015.12.033
0304-3940/© 2015 Elsevier Ireland Ltd. All rights reserved.

mood disturbances, including anxiety, depression, post-traumatic stress, and phobic symptoms, are often elevated among those with mTBI compared to healthy controls [3]. For most individuals who have sustained an mTBI, the associated cognitive and affective symptoms reduce with longer time since injury (TSI), typically resolving to baseline levels within the first few days or weeks post-injury [21] and full recovery within 90 days [14]. However, some evidence suggests that nearly 50% of patients with mTBI show some persistent deficits at three months [26], and a smaller proportion will continue to have chronic post-concussive symptoms or cognitive deficits that persist for at least a year or longer [29]. Despite the rapid advancement of powerful neuroimaging techniques, little is known about the structural brain changes that are associated with the recovery process.

Voxel-based morphometry (VBM) is a neuroimaging technique that enables quantification of regional gray matter volume (GMV) throughout the cortex. A number of studies suggest that GMV may be reduced in patients with mTBI compared to healthy controls in the semi-acute to post-acute stages [12,19]. Others have shown that GMV often remains decreased in various areas of the cortex when assessed for up to a year after injury [11,39]. The research to date, however, has not examined whether and how GMV differs at various time-points following an injury nor investigated whether there are regions of increased GMV with longer recovery time, and whether this correlates with possible recovery of cognitive capacities. This latter question is important, as numerous studies have suggested that regional GMV can be increased through training or practice in particular cognitive and motor domains [20,32]. This remodeling process is known as experience-dependent cortical plasticity [15], and involves increases in dendritic arborization or neuronal spine density as a result of frequent neuronal stimulation or use (i.e., practice) [5,16]. This raises the possibility that individuals who repeatedly engage in particular cognitive or emotional strategies to compensate for their deficits might show increased experience-dependent cortical remodeling of relevant cortical structures, which over time, might be expressed as increased GMV within those structures.

The goal of the present study was to examine regional GMV within individuals following mTBI at various time-points post-injury and correlate GMV with neuropsychological and emotional functioning. Based on the aforementioned rationale of compensation through experience-dependent cortical plasticity, we hypothesized that greater TSI would be associated with increased GMV within prefrontal regions involved in regulating attention, emotion, and behavior (e.g., dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial/ventromedial prefrontal cortex), and that greater volume in such regions would correlate with better speed of information processing, greater vigilance, and reduced neuropsychiatric symptom expression.

2. Methods

2.1. Participants

Twenty-six right-handed, native English speaking, individuals (age range 20–45 years, mean age 23.38 ± 5.23, 11 males, 15 females) with a history of mTBI experienced within the preceding 12 months took part in this study (two-weeks [$n = 2$], one-month [$n = 6$], three-months [$n = 5$], six-months [$n = 10$], one-year [$n = 3$]). All participants were recruited from the Boston metropolitan area using advertisements on the Internet, public transportation billboards, newspaper, radio, and posted flyers. Eligible participants were required to have sustained a documented injury involving head impact, followed by some alteration in mental status (e.g., confusion, “seeing stars”, disorientation, post-traumatic amnesia not more than 24 h) or loss of consciousness lasting no more than 30 min. To be eligible, participants had to provide written documentation from an impartial but professionally responsible witness to the head injury (e.g., coach, sports trainer, police officer) or its immediate medical aftermath (e.g., physician, nurse, ambulance driver, medical record, neuropsychologist). In addition, 12 healthy control participants (age range 20–43 years, mean age 25.00 ± 6.55, 4 males, 8 females), without history of head injury or loss of consciousness were also recruited for comparison. Participants were compensated for their time. All study procedures were conducted in accordance with the 1964 declaration of Helsinki and were approved by the McLean Hospital Institutional Review Board. Furthermore, because the study was funded by the US Army Medical Research and Materiel Command (USMRMC), all procedures were also approved by the US Army Human Research Protections Office.

2.2. Materials and procedure

Based on the timing of their injury, mTBI participants were scheduled for an evaluation at one of six different time-points following their mTBI: 2-weeks, 1-month, 3-months, 6-months, or 12-months post injury (all sessions were scheduled within 3 days of the respective anniversary date). Participants underwent a morning assessment session that involved completing several questionnaires and cognitive tasks, followed by a series of neuroimaging scans. Healthy control participants underwent the same structural scanning sequence.

2.3. Neuropsychological assessments

2.3.1. Delis–Kaplan Executive Function System (D–KEFS)

Participants with mTBI were administered the Delis–Kaplan Executive Function System (D–KEFS), a widely used metric of higher order executive functions with established psychometric properties [6,34]. The D–KEFS provides methods for delineating underlying cognitive processes that may contribute to executive functioning. For the present analyses, we focused on two ‘matched fluency’ subtasks of the D–KEFS, (1) the verbal fluency (VF) subtest to measure verbally mediated executive control, and (2) the Design Fluency (DF) subtest to measure visuospatial executive control. For VF, four subtests were collected, including VF1 (letter fluency: number of items correct), VF2 (category fluency: number of items correct), VF3 (switching: number of items correct regardless of whether switching rule was correct), and VF3-A (switching accuracy: number of correct category switches). VF1 required the examinee to say as many words that they could think of in 60 s that began with a particular letter. VF2 required the examinee to name as many animals that they could think of in 60 s. VF3 required the examinee to name as many fruits and furniture as possible in 60 s, alternating between categories for each item. VF3-A is derived from the number of correct across-category switches from the VF3 trial. This procedure allows determination of whether deficits are due to more fundamental executive processes (VF1 and VF2) or higher level executive processes involved in switching (VF3 and VF3-A). For DF, a task that requires the examinee to connect pre-printed circles together using straight lines to make as many uniquely different designs as possible in 60 s, the following three related subtests were evaluated: DF1 (filled dots: number of correctly connected black circles), DF2 (empty dots: number of correctly connected empty circles), and DF3 (switching: number of correct designs where the examinee alternated between filled and empty circles). DF1 required the examinee to generate as many different designs as possible by connecting sets comprised of filled black circles using only 4 straight lines per design. DF2 is nearly identical to DF1, except that the pre-printed sets include both empty and filled circles, requiring the examinee to inhibit the prepotent response

from the previous trial (i.e., connecting filled circles). DF3 required the examinee to create designs such that each line has a filled circle at one end point and an empty circle at the other.

2.3.2. Psychomotor vigilance test (PVT)

Participants with mTBI were administered a 10-min version of the psychomotor vigilance test (PVT), a well-validated metric for the assessment of sustained vigilance and response time [9]. During this computerized task, participants pressed a response key as quickly as possible each time a pseudo-randomly presented stimulus (time interval ranged from 2 to 10 s) appeared on the screen. For the present study, mean simple reaction time derived from the entire duration of the task was used as the metric of interest.

2.3.3. Wechsler abbreviated scale of intelligence (WASI-II)

All participants were also administered the Wechsler Abbreviated Scale of Intelligence (WASI-II) [36] by a trained research technician to provide an estimate of general cognitive ability. For this study, the full-scale intelligence quotient (FSIQ) was calculated from the four-subtest version of the WASI-II.

2.3.4. Personality assessment inventory (PAI)

Finally, as in index of potential clinical anxiety problems, mTBI participants also completed the anxiety related disorders (ARD) scale of the Personality Assessment Inventory (PAI) [22]. This scale measures the general behavioral expression of anxiety and maladaptive attempts to control anxiety, particularly as they relate to intrusive thoughts, common phobic fears, and prior traumatic experiences. For the present analysis, normalized *T*-scores based on the standard community sample were used [22].

2.4. Magnetic resonance imaging parameters

2.4.1. Data acquisition

A 3.0 T magnetic resonance imaging scanner (Siemens Tim Trio, Erlangen, Germany) with a 32-channel head coil was used for the study. For this analysis, a T-1 weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) was used to obtain 176 sagittal slices (256 × 256 matrix) with a slice thickness of 1 mm and a voxel size of 1 × 1 × 1 mm. Participants also completed several other neuroimaging sequences, including diffusion tensor imaging and a resting state functional scan, but these were not relevant to the present analysis and will not be discussed further.

2.4.2. Voxel based morphometry (VBM) image processing

T-1 weighted structural images were preprocessed using the VBM8 toolbox in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Images were realigned to the anterior–posterior commissure axis in SPM8. After realignment, images were segmented into gray matter, white matter, and cerebrospinal fluid using VBM8, a fully automated algorithm in SPM8. 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.

2.5. Statistical analysis

Statistical analyses were conducted in two stages. First, GMV was regressed against days since injury. In this stage, the normalized, smoothed gray matter images were entered into a whole-brain general linear model (GLM) in SPM8. We used a cluster-extent based thresholding, following the recommended approach suggested by Woo, Krishnan, and Wager [38], 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 false discovery rate (FDR) maintained at $p < 0.05$. Based on the present data, this threshold was k = 894 voxels. Additionally, age, gender, and intracranial volume (ICV) were included as nuisance covariates in the regression equation.

In the second stage of analysis, estimates of GMV were extracted for each distinct cluster exceeding our significance threshold. For this analysis, the total cluster eigenvariate was extracted for each participant and then exported into IBM SPSS Statistics 22 for correlational analysis with neuropsychological test scores. It was predicted that GMV would correlate positively with better neuropsychological performance among the patients with mTBI. Partial correlations between GMV of each regional cluster and neuropsychological scores were calculated, controlling for FSIQ and education level ($\alpha = 0.05$, 1-tailed). For the ARD, analyses were also controlled for the positive and negative impression validity index scores.

Finally, the GMV findings for the mTBI sample were compared to a group of 12 healthy control participants to determine if the changes in GMV over time differed from the normal pattern in non-injured individuals. For this analysis, the mTBI sample was divided into the "post-acute" stage (i.e., 0–99 days post injury; $n = 13$) and the chronic stage (i.e., 100–367 days post injury; $n = 13$), and compared to a third group of healthy controls ($n = 12$) using a one-way analysis of variance in SPM12, with age, sex, and ICV entered as nuisance covariates. Contrast estimates were extracted from the same locations identified in the first stage of analysis and compared across groups using SPSS 22, with $p < 0.05$, and post-hoc group comparisons evaluated at a Bonferroni corrected threshold of $p < 0.05$.

3. Results

All scans were initially evaluated by a clinical neuroradiologist blind to diagnostic status to identify possible clinically relevant abnormalities. None of the scans showed clinically significant abnormalities, although there was evidence of minimal to mild ventricular prominence ($n = 8$) and mild white matter hyperintensity/hypointensity in some participants ($n = 3$).

As evident in Fig. 1, two regions of the cortex showed significant positive correlations between GMV and TSI, even after whole brain correction for multiple comparisons. Table 1 presents the stereotaxic coordinates for the maximally correlated voxels, cluster volumes, and statistics for these two regions. The most strongly correlated of these regions was a cluster within the right fusiform gyrus. As shown in the left scatterplot of Fig. 1, greater TSI accounted for approximately 66% of the variance in the GMV (1st eigenvariate) of this region after controlling for nuisance covariates, including age, gender, and ICV. The second cluster that correlated positively with TSI was located in the posterior vmPFC, primarily within the gyrus rectus and olfactory cortex regions. In this case, TSI accounted for approximately 57% of the variance in GMV of this region (see Fig. 1). There were no regions showing significant negative correlations with TSI.

To examine the association between the GMV and neuropsychological test performance, the extracted cluster values for these two regions were then correlated with VF, DF, and PVT mean reaction time (RT) scores. As shown in Table 2, after controlling for FSIQ and years of education, none of the four VF indices were significantly associated with either TSI or GMV in either of the extracted clusters. On the other hand, DF1 and DF2 were both positively correlated with TSI as well as GMV in the right fusiform gyrus and bilateral vmPFC clusters (see Table 2 for a complete Table of partial correlations). DF3, however, was not significantly correlated with TSI or GMV. On the PVT, faster RT was associated with greater

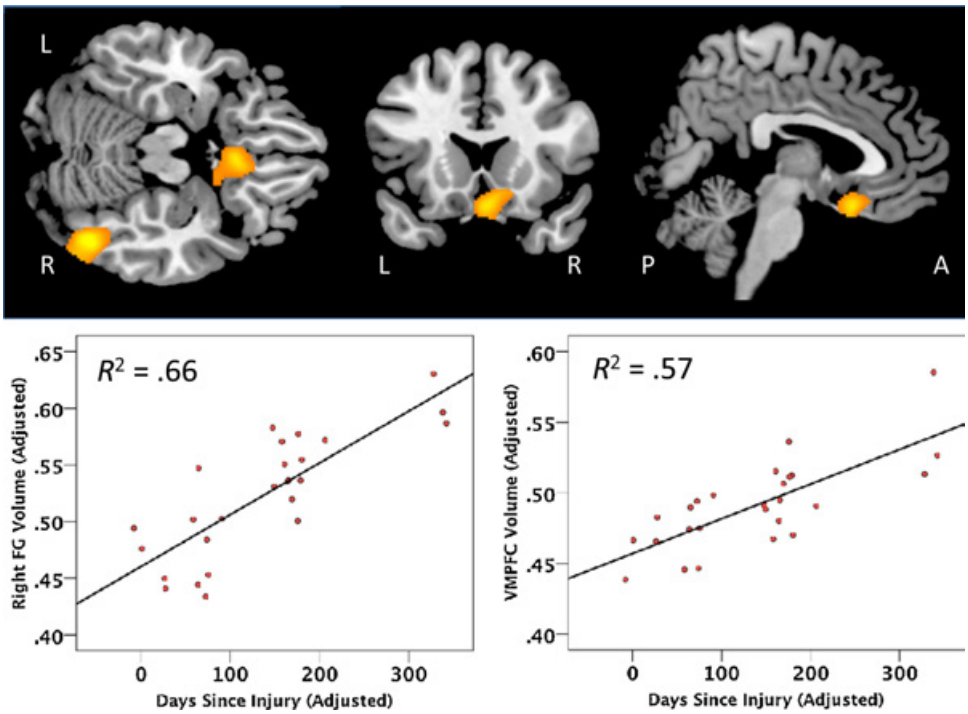


Fig. 1. Time since injury (TSI) was positively correlated ($p < .05$, FWE cluster extent corrected) with gray matter volume (GMV) in the right fusiform gyrus (FG) and ventromedial prefrontal cortex (VMPFC; Top Panel; L = left; R = right; A = anterior; P = posterior). The partial correlation scatterplots show the linear association between the adjusted (i.e., residuals re-scaled to raw data) number of days since injury and the adjusted (i.e., residuals re-scaled to raw data) volume of the right fusiform gyrus (bottom left panel) and the ventromedial prefrontal cortex (bottom right panel).

Table 1
Cortical voxel clusters significant positive volume correlations with time since injury.

Target region	Cluster size	MNI coordinates			Pearson	
		x	*y*	*z*	*r*	*T*
Right FG (BA 37)	1766	46	−61	−17	.817	6.50
Bilateral vmPFC/GR (BA 25)	894	3	18	−18	.773	5.59

All voxels significant at $p < 0.001$ (height) and cluster extent corrected at $p < .05$ (FWE).
BA = brodmann area; FG = fusiform gyrus; GR = gyrus rectus; vmPFC = ventromedial prefrontal cortex.

Table 2
Partial correlations (controlling for years of education and full scale intelligence) between time since injury, significant gray matter clusters, and neuropsychological variables.

Neuropsychological Test	Time Since Injury	Right FG (BA 17)	Bilateral vmPFC/GR (BA 25)
D–KEFS verbal fluency 1 (letter fluency correct)	−0.175	−0.199	−0.101
D–KEFS verbal fluency 2 (category fluency correct)	−0.057	−0.299	−0.164
D–KEFS verbal fluency 3 (switching correct)	0.141	−0.134	−0.256
D–KEFS verbal fluency 3 (switching accuracy)	0.094	−0.160	−0.306
D–KEFS design fluency 1 (filled dots correct)	0.443*	0.422*	0.417*
D–KEFS design fluency 2 (empty dots correct)	0.415*	0.358*	0.418*
D–KEFS design fluency 3 (switching correct)	−0.064	−0.087	0.175
PVT mean RT	−0.278	−0.359*	−0.273
PAI ARD	−0.481*	−0.325	−0.406*

*$p < 0.05$ (1-tailed). BA = brodmann area; FG = fusiform gyrus; GR = gyrus rectus; vmPFC = ventromedial prefrontal cortex; D–KEFS = Delis–Kaplan Executive Function System; PVT = 10-minute psychomotor vigilance test; RT = reaction time; PAI = personality assessment inventory; ARD = anxiety related disorders scale

GMV of the right fusiform gyrus, but not with TSI or vmPFC volume. Finally, there was a significant reduction in anxiety symptoms in association with longer TSI and larger GMV within the vmPFC.

Finally, to determine if the increase in GMV reflected a divergence from normal levels, we compared the post-acute, chronic, and healthy control groups using a one-way ANOVA in SPM12. As evident in Fig. 2 Fig., there was a significant effect of group for both the previously identified fusiform gyrus region, $F(2,32) = 72.93$, $p < 0.000001$, and the vmPFC region, $F(2,32) = 39.61$, $p < .000001$. Bonferroni corrected post-hoc comparisons showed that for the fusiform gyrus, GMV differed significantly ($p < .05$) for all three groups, with the chronic group greater than the healthy controls, which were in turn greater than the post-acute group. For the vmPFC, the chronic group showed greater GMV than both the

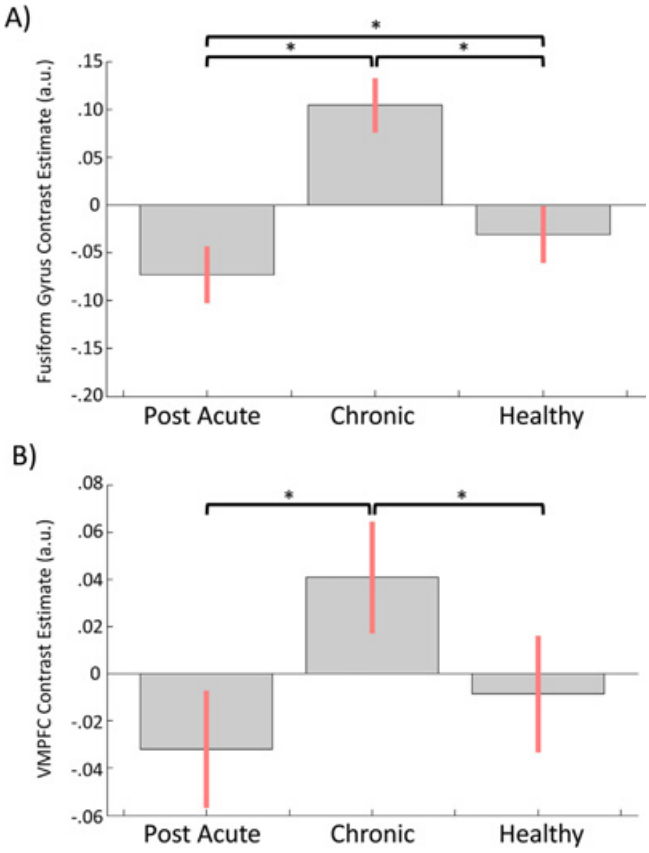


Fig. 2. A comparison of mTBI participants in the post-acute (0 to 99 days post injury) or chronic (100–367 days) stage versus healthy controls showed that the chronic stage group had higher gray matter volume within the (A) fusiform gyrus [$x = 46, y = -61, z = -17$] and (B) ventromedial prefrontal cortex (vmPFC) [$x = 3, y = 18, z = -18$] compared to the other groups. Error bars reflect 90% confidence interval. *Comparison is significant at $p < .05$ (Bonferonni corrected).

healthy and post-acute groups, which did not differ from each other.

4. Discussion

Several key findings emerged from this study. First, longer TSI was associated with better visual attention, visuo-motor speed, and emotional functioning. Consistent with prior evidence [23], these findings suggest that individuals improve in some visuospatially-mediated neurocognitive abilities and emotional functioning with a longer time window following an mTBI. Moreover, consistent with our hypothesis, we found that greater TSI was associated with larger GMV within the prefrontal cortex, specifically the posterior vmPFC, and also within a region that was not hypothesized—the right fusiform gyrus. Moreover, those with the longest TSI showed increased GMV in these regions that was significantly greater than that observed in healthy controls, suggesting potential focal volume increases beyond normal. Extracted GMV estimates from both of the aforementioned regions correlated positively with several neurocognitive abilities, including visual attention, visuo-motor speed, and nonverbal creativity, suggesting that larger cortical volume of these regions was associated with better visuospatially mediated neurocognitive performance. Finally, there were also regionally-specific neurocognitive correlations, with greater GMV of the fusiform gyrus associated with greater visual psychomotor vigilance performance, while greater GMV of the vmPFC was associated with reduced anxiety related concerns on a self-report measure of psychopathology. Additionally, neither TSI nor its correlated GMV clusters were associated with any aspect of verbal fluency. Together, these findings are generally consistent with our hypothesis that during the first 12 months of recovery from mTBI there is significant remodeling within regions of the cortex that are involved in visual attention, information processing, psychomotor speed, and emotional regulation, and that these GMV structural changes relate to improved performance.

The present findings are correlational and taken from a cross-sectional sample of participants assessed at a single assessment session, so it is impossible to assert a causal mechanism from these preliminary data. However, the associations between larger regional GMV, longer TSI, and improved functioning are consistent with the hypothesis of cortical remodeling over time due to experience-dependent cortical plasticity [15], and the finding that the increases are significantly greater than normal further bolsters this argument. Common complaints of people with persistent post-concussive syndrome include vague difficulties with attention, fatigue, slowed responsiveness, and mood dysregulation [24,28,30]. Evidence suggests that TBI patients expend greater psychophysiological resources to sustain stable cognitive performance over time, which can lead to excessive fatigue [41]. We speculate that as individuals exert effort to overcome these diffuse neurocognitive and emotional regulation problems, they may consistently engage specific brain systems, such as the vmPFC and fusiform gyrus, to *compensate* for their deficits. Through repeated engagement of these cortical regions over many weeks and months post-injury, there may be increased dendritic arborization and spine density within the most utilized areas of the cortex [16], which may ultimately manifest as greater GMV of these structures and contribute to the improvement of some aspects of cognitive and affective functioning. This interpretation does not imply, however, that the regions of increased GMV would necessarily be related to the locus of injury or the particular networks that were damaged. Brain repair and experience-dependent remodeling are likely to involve very different neuroplastic processes, with the former involving heterogeneous regions that differ from one patient to the next, whereas the latter may involve relatively specific regions that are consistently engaged to compensate for common deficits, such as attention or emotion regulation. We therefore suggest that the changes in GMV over time may simply reflect the *compensatory* increase in cortical volume within (potentially non-injured) brain regions that independently contribute to the sustainment of attention, psychomotor speed, and affective regulation, irrespective of the particular location of damage.

The present findings are consistent with evidence suggesting that regular practice of specific motor or cognitive activities can be associated with increased regional GMV [20,32]. For example, recent VBM research with animals suggests that GMV can be increased in a matter of days to weeks in accordance with specific levels of activity or training [25,35]. In humans, similar neuroplastic changes in the cortex have been observed following unilateral eye surgery [20] and even after 12 weeks of self-regulation therapy [32], suggesting use-dependent plasticity. Numerous quasi-experimental and correlational studies show a similar pattern of cortical remodeling with experience. For example, compared to those with less experience, well-trained professional musicians [31], academic mathematicians [1], long-term meditators [18], and people with strong emotional conflict resolution skills [8] exhibit correspondingly larger GMV in specific task-relevant regions, consistent with the hypothesis of experience-dependent plasticity. Our data are consistent with the notion that this process may also play a role during recovery from mTBI.

Our primary hypothesis focused on the prefrontal cortex, because this region is central to most aspects of self-regulation,

including sustaining vigilant attention [13], behavior [7], and emotional control [10], all of which are commonly impaired in patients with mTBI [17,21]. Interestingly, TSI was only associated with larger volume of the posterior vmPFC and not other regions of the prefrontal cortex. The vmPFC has been shown to be particularly important for emotional processing and regulation [37], and GMV of this region was directly associated with lower anxiety related clinical complaints in the present sample. However, this region has not been directly associated with psychomotor vigilance or visuo-motor speed, suggesting that the neurocognitive findings observed here may be related to greater vmPFC mediated self-regulation of anxiety or other aspect of emotional control, which secondarily yielded improved performance on these processing speed-related cognitive tasks.

While not hypothesized, we also found that a cluster within the right fusiform gyrus was significantly larger with greater TSI and correlated with visuo-motor speed and sustained visual psychomotor vigilance. Among the chronic mTBI participants, this region significantly exceeded the volume of normal healthy controls. Recent evidence suggests that the fusiform gyrus plays an important role in protecting cognition from emotional distraction [40]. While speculative, it is therefore possible that this region may show adaptive plasticity to reduce the impairing effects of emotional distraction or frustration that often occur among individuals with persistent post-concussive symptoms. Hence, larger GMV of this region may be associated with greater performance on tasks requiring sustained focus and vigilance. However, as this region was not hypothesized a priori, this possibility remains speculative.

5. Conclusion

Among individuals with an mTBI in the preceding year, longer TSI was associated with larger GMV within the vmPFC and right fusiform gyrus. Among those whose injuries were more than three months old, these volumes exceeded those of healthy controls. Functionally, we found that larger GMV of the vmPFC was associated with greater visuo-motor performance and reduced symptoms of anxiety. Larger GMV of the fusiform gyrus was similarly associated with greater visuo-motor speed, creativity, and sustained visual psychomotor vigilance performance. These findings corroborate existing research on compensatory brain mechanisms following mTBI by suggesting that as time elapses following an mTBI, there may be greater compensatory remodeling of distinct cortical regions and particularly those involved in emotional regulation, which in turn may reduce attentional distractibility during timed visuo-motor tasks.

Conflicts of interests

None declared.

Funding

This research was supported by a USAMRAA grant to WDSK (W81XWH-12-1-0386).

References

[1] K. Aydin, A. Ucar, K.K. Oguz, O.O. Okur, A. Agayev, Z. Unal, S. Yilmaz, C. Ozturk, Increased gray matter density in the parietal cortex of mathematicians: a voxel-based morphometry study, AJNR Am. J. Neuroradiol. 28 (2007) 1859–1864.
[2] E.D. Bigler, Neuropsychology and clinical neuroscience of persistent post-concussive syndrome, J. Int. Neuropsychol. Soc. 14 (2008) 1–22.
[3] R.A. Bryant, M.L. O'Donnell, M. Creamer, A.C. McFarlane, C.R. Clark, D. Silove, The psychiatric sequelae of traumatic injury, Am. J. Psychiatry 167 (2010) 312–320.
[4] L.J. Carroll, J.D. Cassidy, P.M. Peloso, J. Borg, H. von Holst, L. Holm, C. Paniak, M. Pepin, WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury, Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury, J. Rehabil. Med. (2004) 84–105.
[5] W.L. Comeau, R.J. McDonald, B.E. Kolb, Learning-induced alterations in prefrontal cortical dendritic morphology, Behav. Brain Res. 214 (2010) 91–101.
[6] J.R. Crawford, D. Sutherland, P.H. Garthwaite, On the reliability and standard errors of measurement of contrast measures from the D–KEFS, J. Int. Neuropsychol. Soc. 14 (2008) 1069–1073.
[7] F. Dambacher, A.T. Sack, J. Lobbestael, A. Arntz, S. Brugmann, T. Schuhmann, The role of right prefrontal and medial cortex in response inhibition: interfering with action restraint and action cancellation using transcranial magnetic brain stimulation, J. Cogn. Neurosci. 26 (2014) 1775–1784.
[8] Z. Deng, D. Wei, S. Xue, X. Du, G. Hitchman, J. Qiu, Regional gray matter density associated with emotional conflict resolution: evidence from voxel-based morphometry, Neuroscience 275 (2014) 500–507.
[9] D.F. Dinges, J.W. Powell, Microcomputer analyses of performance on a portable, simple, visual RT task during sustained operations, Behav. Res. Methods Instrum. Comput. 17 (1985) 652–655.
[10] D. Dorfel, J.P. Lamke, F. Hummel, U. Wagner, S. Erk, H. Walter, Common and differential neural networks of emotion regulation by detachment, reinterpretation, distraction, and expressive suppression: a comparative fMRI investigation, Neuroimage 101 (2014) 298–309.
[11] S.D. Gale, L. Baxter, N. Roundy, S.C. Johnson, Traumatic brain injury and grey matter concentration: a preliminary voxel based morphometry study, J. Neurol. Neurosurg. Psychiatry 76 (2005) 984–988.
[12] K.M. Hasan, E.A. Wilde, E.R. Miller, V. Kumar Patel, T.D. Staewen, M.L. Frisby, H.M. Garza, J.J. McCarthy, J.V. Hunter, H.S. Levin, C.S. Robertson, P.A. Narayana, Serial atlas-based diffusion tensor imaging study of uncomplicated mild traumatic brain injury in adults, J. Neurotrauma 31 (2014) 466–475.
[13] O. Hinds, T.W. Thompson, S. Ghosh, J.J. Yoo, S. Whitfield-Gabrieli, C. Triantafyllou, J.D. Gabrieli, Roles of default-mode network and supplementary motor area in human vigilance performance: evidence from real-time fMRI, J. Neurophysiol. 109 (2013) 1250–1258.
[14] J.E. Karr, C.N. Areshenkoff, M.A. Garcia-Barrera, The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury, Neuropsychology 28 (2014) 321–336.
[15] A.L. Kerr, S.Y. Cheng, T.A. Jones, Experience-dependent neural plasticity in the adult damaged brain, J. Commun. Disord. 44 (2011) 538–548.
[16] B. Kolb, R. Gibb, Plasticity in the prefrontal cortex of adult rats, Front. Cell. Neurosci. 9 (15) (2015).
[17] C. Konrad, A.J. Geburek, F. Rist, H. Blumenroth, B. Fischer, I. Husstedt, V. Arolt, H. Schiffbauer, H. Lohmann, Long-term cognitive and emotional consequences of mild traumatic brain injury, Psychol. Med. 41 (2011) 1197–1211.
[18] M.K. Leung, C.C. Chan, J. Yin, C.F. Lee, K.F. So, T.M. Lee, Increased gray matter volume in the right angular and posterior parahippocampal gyri in loving-kindness meditators, Soc. Cogn. Affect. Neurosci. 8 (2013) 34–39.
[19] J. List, S. Ott, M. Bukowski, R. Lindenberg, A. Floel, Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults, Front. Hum. Neurosci. 9 (2015) 228.
[20] A.R. Lou, K.H. Madsen, H.O. Julian, P.B. Toft, T.W. Kjaer, O.B. Paulson, J.U. Prause, H.R. Siebner, Postoperative increase in grey matter volume in visual cortex after unilateral cataract surgery, Acta Opthalmol. 91 (2013) 58–65.
[21] M. McCrea, K.M. Guskiewicz, S.W. Marshall, W. Barr, C. Randolph, R.C. Cantu, J.A. Onate, J. Yang, J.P. Kelly, Acute effects and recovery time following concussion in collegiate football players: the NCAA concussion study, JAMA 290 (2003) 2556–2563.
[22] L.C. Morey, Personality Assessment Inventory, Psychological Assessment Resources, Inc., Lutz, FL, 2007.
[23] K. Muller, T. Ingebrigtsen, T. Wilsgaard, G. Wikran, T. Fagerheim, B. Romner, K. Waterloo, Prediction of time trends in recovery of cognitive function after mild head injury, Neurosurgery 64 (2009) 698–704, discussion 704.
[24] J.L. Ponsford, C. Ziino, D.L. Parcell, J.A. Shekleton, M. Roper, J.R. Redman, J. Phipps-Nelson, S.M. Rajaratnam, Fatigue and sleep disturbance following traumatic brain injury-their nature, causes, and potential treatments, J. Head Trauma Rehabil. 27 (2012) 224–233.
[25] M.M. Quallo, C.J. Price, K. Ueno, T. Asamizuya, K. Cheng, R.N. Lemon, A. Iriki, Gray and white matter changes associated with tool-use learning in macaque monkeys, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 18379–18384.
[26] A.R. Rabinowitz, X. Li, S.R. McCauley, E.A. Wilde, A. Barnes, G. Hanten, D. Mendez, J.J. McCarthy, H.S. Levin, Prevalence and predictors of poor recovery from mild traumatic brain injury, J. Neurotrauma 32 (2015) 1488–1496.
[27] W. Rutland-Brown, J.A. Langlois, K.E. Thomas, Y.L. Xi, Incidence of traumatic brain injury in the United States, 2003, J. Head Trauma Rehabil. 21 (2006) 544–548.
[28] L.M. Ryan, D.L. Warden, Post concussion syndrome, Int. Rev. Psychiatry 15 (2003) 310–316.
[29] P.S. Satz, M.S. Alfano, R.F. Light, H.F. Morgenstern, K.F. Zaucha, R.F. Asarnow, S. Newton, Persistent post-concussive syndrome: a proposed methodology and literature review to determine the effects, if any, of mild head and other bodily injury, J. Clin. Exp. Neuropsychol. 21 (1999) 620–628.

[30] J.M. Silver, T.W. McAllister, D.B. Arciniegas, Depression and cognitive complaints following mild traumatic brain injury, Am. J. Psychiatry 166 (2009) 653–661.
[31] V. Sluming, T. Barrick, M. Howard, E. Cezayirli, A. Mayes, N. Roberts, Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians, Neuroimage 17 (2002) 1613–1622.
[32] D.W. Soh, J. Skocic, K. Nash, S. Stevens, G.R. Turner, J. Rovet, Self-regulation therapy increases frontal gray matter in children with fetal alcohol spectrum disorder: evaluation by voxel-based morphometry, Front. Hum. Neurosci. 9 (108) (2015).
[33] D.M. Sosin, J.E. Sniezek, D.J. Thurman, Incidence of mild and moderate brain injury in the United States, 1991, Brain Inj. 10 (1996) 47–54.
[34] C.A. Strong, D. Tiesma, J. Donders, Criterion validity of the Delis–Kaplan Executive Function System (D–KEFS) fluency subtests after traumatic brain injury, J. Int. Neuropsychol. Soc. 17 (2011) 230–237.
[35] A. Sumiyoshi, Y. Taki, H. Nonaka, H. Takeuchi, R. Kawashima, Regional gray matter volume increases following 7 days of voluntary wheel running exercise: a longitudinal VBM study in rats, Neuroimage 98 (2014) 82–90.
[36] D. Wechsler, WASI: Wechsler abbreviated scale of intelligence, The Psychological Corp., San Antonio, TX, 1999.
[37] B.L. Welborn, X. Papademetris, D.L. Reis, N. Rajeevan, S.M. Bloise, J.R. Gray, Variation in orbitofrontal cortex volume: relation to sex, emotion regulation and affect, Soc. Cogn. Affect. Neurosci. 4 (2009) 328–339.
[38] C.W. Woo, A. Krishnan, T.D. Wager, Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations, Neuroimage 91 (2014) 412–419.
[39] Y. Zhou, A. Kierans, D. Kenul, Y. Ge, J. Rath, J. Reaume, R.I. Grossman, Y.W. Lui, Mild traumatic brain injury: longitudinal regional brain volume changes, Radiology 267 (2013) 880–890.
[40] M. Ziaei, N. Peira, J. Persson, Brain systems underlying attentional control and emotional distraction during working memory encoding, Neuroimage 87 (2014) 276–286.
[41] C. Ziino, J. Ponsford, Vigilance and fatigue following traumatic brain injury, J. Int. Neuropsychol. Soc. 12 (2006) 100–110.

PERSPECTIVE

Time dependent differences in gray matter volume post mild traumatic brain injury

When the brain is subjected to excessive physical forces, including blunt impact, high-speed rotation, or blast overpressure waves, its tissue structure and function can be compromised, leading to traumatic brain injury (TBI). Based on the level of structural and functional damage, these injuries can be classified as mild, moderate, or severe, with mild TBI (mTBI) being by far the most common. Also known as concussion, mTBI frequently occurs in a wide variety of activities, including accidental falls, sports injuries, moving vehicle accidents, military training, and combat related events such as blast exposure. mTBI can lead to various cognitive, sensory and motor complaints like reduced memory, attention, and information processing speed, and emotional dysregulation (Carroll et al., 2004). Most individuals with mTBI will recover from these symptoms within 90 days post injury (Karr et al., 2014), but for some individuals, the symptoms may be protracted, persisting up to a year or longer (Satz et al., 1999). For a small minority of individuals, these cognitive and emotional symptoms are severe enough to significantly affect social and occupational functioning.

In contrast to moderate and severe injuries, one of the defining features of an mTBI is the absence of detectible structural lesions on a standard clinical imaging scan. While individual lesions may not be present, there is emerging evidence that, as a group, patients with mTBI may actually be differentiated from non-injured controls based on brain volume data. For instance, previous studies have shown decreased gray matter volume (GMV) post mTBI, suggesting a loss of cortical neurons (List et al., 2015). Very few studies, however, have explored differences in GMV at different time intervals post mTBI and their relationship with neuropsychological performance. Such research is crucial to understanding the recovery process because the brain is not static and neuroplastic remodeling may continue for some time after an injury. Understanding this relationship can facilitate better-targeted intervention strategies to aid in rehabilitation following mTBI.

We recently reported findings suggesting that mTBI may not simply be associated with reduced cortical volume, but instead may show specific increases in gray matter volume (GMV) as well (Killgore et al., 2016). In that project we studied the cortical volume changes and their association with neuropsychological task performance at various time intervals up to a year following injury. We used a 3.0 Tesla magnetic resonance imaging scanner (Siemens Trim Trio, Erlangen, Germany) with a 32-channel head coil for our study. A T1 weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) was used to acquire 176 sagittal slices (256 × 256 matrix) with a 1-mm slice thickness, yielding a voxel size of 1 × 1 × 1 mm^3. The VBM8 toolbox in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used to process the T-1 weighted structural images. All images were spatially realigned to the anterior-posterior commissure axis and then segmented into GM, WM, and CSF using VBM8. A custom DARTEL template was created using the segmented images and then the images were normalized to Montreal Neurological institute (MNI) space. Images were then smoothed with a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

The study participants included 26 right-handed adults (age range 20–45 years, mean age 23.38 ± 5.23, 11 males, 15 females), with English as their primary language. All participants had a history of sports-related mTBI experienced within the 12 months prior to participation this study (2 weeks [n = 2], 1 month [n = 6], 3 months [n = 5], 6 months [n = 10], 1 year [n = 3]). All of these participants sustained mTBI while engaging in sports activities such as rugby (n = 7), basketball (n = 3), softball (n = 1), ultimate frisbee (n = 1), soccer (n = 1), ice hockey (n = 2), lacrosse (n = 1), martial arts (n = 2), weight lifting/gym (n = 4) and track and field (n = 4). The participants were initially screened over the telephone for the details of their head injury, medical and psychiatric history. Participants were ruled out for any serious chronic medical, neurological or psychiatric condition like hypertension, diabetes, epilepsy, bipolar disorder, attention deficit hyperactivity disorder *etc.* The only exception was depression and anxiety developing after the concussion. Also, they were required to provide official documentation of head injury signed by an impartial but professionally responsible witness to the head injury or its immediate consequences (*e.g.*, physician, nurse, ambulance driver, medical records, neuropsychologist). Additionally, 12 healthy control participants (age range 20–43 years, mean age 25.00 ± 6.55, 4 males, 8 females), with no history of head injury or loss of consciousness were recruited as a comparison group. On the day of visit, the healthy and mTBI individuals underwent same series of neuropsychological assessments and MRI sequences.

Remarkably, in contrast to the general finding of reduced GMV following mTBI found in other studies, our results did not show such reductions, but instead showed that longer time since injury (TSI) was associated with increased GMV in two brain regions (see **Figure 1**), including the cortex of the right fusiform gyrus (RFG) and bilateral ventromedial prefrontal cortex (VMPFC). In other words, the cortex of these regions appeared to be larger among those whose injuries were most

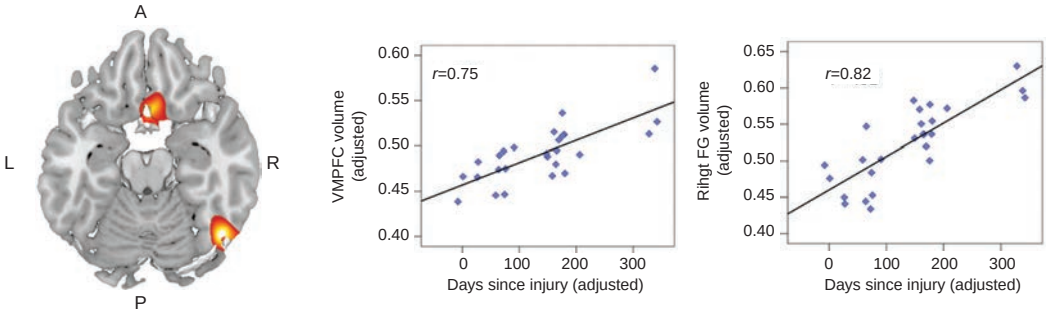


Figure 1 Regions where larger gray matter volume was significantly correlated with time since injury, including the ventromedial prefrontal cortex and the right fusiform gyrus.
L: Left; R: right; A: anterior; P: posterior; VMPFC: ventromedial prefrontal cortex; FG: fusiform gyrus.

distal in time. Moreover, larger GMV was associated with better performance for visual motor, visual attention, and emotional functioning tasks, suggesting that greater cortical volume in specific regions was associated with better functional outcome. We speculate that these data point toward significant cortical remodeling occurring in the months following injury. To further evaluate that possibility, we divided our sample roughly in half so that we could compare those in the post-acute stage (0–99 days post-injury) to those in the chronic stage (100–365 days post-injury), and further compared them to a separate sample of healthy individuals with no reported history of head injury. Consistent with our hypothesis, the chronic group showed significantly greater GMV in both regions compared to the post-acute group, confirming that gray matter was increased with longer TSI. Moreover, the chronic group also showed significantly greater GMV compared to the healthy controls, suggesting that not only was the GMV returning to normal with greater TSI, it was actually exceeding the volume seen in healthy normals. Thus, for these individuals, the later stages of recovery were associated with exaggerated GMV in specific regions that are involved in regulating emotion as well as sustaining visual attention and information processing speed.

We interpreted these findings as evidence of experience dependent cortical plasticity. In other words, we propose that for many individuals, mTBI leads to a host of subtle core cognitive impairments and emotional regulation deficits post-injury, which over time, lead the injured individual to draw upon these other cortical regions to compensate. For example, reduced frustration tolerance and emotional dysregulation are common experiences after mTBI and are not specific to a particular lesion site (Ryan and Warden, 2003). It is conceivable that individuals with these emotional difficulties may more routinely activate the ventromedial prefrontal cortical regions, which play an important role in emotional and visceromotor regulation, in an attempt to maintain emotional control. Similarly, many people experience slowed processing speed and attentional difficulties following a concussion (Levin et al., 1987). This may cause such individuals to draw more heavily upon regions such as the fusiform gyrus and other visual attention regions in order to compensate. With sustained and exaggerated use, it is conceivable that these highly exercised regions may begin to develop larger cortical volume through more extensive dendritic arborization. It is well established that repeated practice with certain motor or cognitive skills can lead to an increase in specific cortical regions supporting that skill (Quallo et al., 2009). The preliminary findings from our study are encouraging, suggesting that mTBI is not uniformly defined by decreased cortical volumes. On the contrary, regional increases in volume are possible within this population and these volume changes are associated with improved cognitive and emotional functioning. The fact that we identified specific regions of volume increases is remarkable given the fact that mTBI is an extremely heterogeneous injury, with multiple potential causes and diffuse locations of damage (Bigler, 2008). The fact that these areas of increased volume were consistent and focal suggests that they are likely independent of lesion location—rather they likely reflect common pathways for compensation that are relatively independent of the site of impact or location of damage.

Previous studies have shown that behavioral experience interacts with regenerative and degenerative changes in the brain to induce structural and motor plasticity (Kerr et al., 2011). Compensatory remodeling is one of the ways neuroplasticity works and may undergird the mechanisms behind rehabilitative training, which forms one the mainstays of treatment post mTBI. On the basis of our findings we suggest that rehabilitative training might be even more beneficial if it can capitalize on this aspect of neuroplasticity. Perhaps by focusing rehabilitation efforts toward exercising existing compensatory skills that draw upon these regions (*e.g.*, emotional regulation; regulating attention from distraction), patients can further develop the cortical volume of those regions and, over time, gain greater functional capacity. This would be encouraging and suggest that there is more that could be done for patients recovering from concussions than merely to "wait and see." Clearly this is speculative at this point, but further research should examine whether the cortical volume, structural and functional connectivity, and functional capacity of these same regions can be voluntarily enhanced in patients recovering from mTBI *via* focused training. Finally, it will be important for future work to focus efforts toward using functional neuroimaging. This will enable linkage among the cognitive tasks and identified deficits caused by an injury and the regions of increased gray matter volume identified in our study.

The present study was supported by a USAMRAA grant to WDSK (W81XWH-12-1-0386).

Prabhjyot Singh, William D. S. Killgore*

Department of Psychiatry, University of Arizona, Tucson, AZ, USA

***Correspondence to:** *William D. S. Killgore, Ph.D.*
Killgore@psychiatry.arizona.edu.
***Accepted:** 2016-05-17*
***orcid:** 0000-0002-5328-0208 (William D. S. Killgore)*
***doi:** 10.4103/1673-5374.184487*
***How to cite this article:** Singh P, Killgore WDS (2016) Time dependent differences in gray matter volume post mild traumatic brain injury. Neural Regen Res 11(6):920-921.*

References

Bigler ED (2008) Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. J Int Neuropsychol Soc 14:1-22.

Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, Paniak C, Pepin M, Injury WHOCCTFoMTB (2004) Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med:84-105.

Karr JE, Areshenkoff CN, Garcia-Barrera MA (2014) The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. Neuropsychology 28:321-336.

Kerr AL, Cheng SY, Jones TA (2011) Experience-dependent neural plasticity in the adult damaged brain. J Commun Disord 44:538-548.

Killgore WD, 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. Neurosci Lett 612:238-244.

Levin HS, Mattis S, Ruff RM, Eisenberg HM, Marshall LF, Tabaddor K, High WM, Jr., Frankowski RF (1987) Neurobehavioral outcome following minor head injury: a three-center study. J Neurosurg 66:234-243.

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 Human Neurosci 9:228.

Quallo MM, Price CJ, Ueno K, Asamizuya T, Cheng K, Lemon RN, Iriki A (2009) Gray and white matter changes associated with tool-use learning in macaque monkeys. Proc Natl Acad Sci U S A 106:18379-18384.

Ryan LM, Warden DL (2003) Post concussion syndrome. Int Rev Psychiatry 15:310-316.

Satz PS, Alfano MS, Light RF, Morgenstern HF, Zaucha KF, Asarnow RF, Newton S (1999) Persistent post-concussive syndrome: a proposed methodology and literature review to determine the effects, if any, of mild head and other bodily injury. J Clin Exp Neuropsychol 21:620-628.

Frontal Cortical Surface Area is Associated with Lexical-Semantic Knowledge in Adults with Mild Traumatic Brain Injury

Natalie S. Dailey, Adam C. Raikes, Sahil Bajaj, Anna Alkozei, Sarah Sanasac, & William D. S. Killgore

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective
Verbal fluency (VF), a task sensitive to mTBI deficits, requires accurate search and retrieval of lexical-semantic knowledge, thereby utilizing vocabulary, attention, working memory, and self-monitoring. Prior research on a two-component model of VF has been used to indirectly associate lexical-semantic knowledge to cortical damage in patients with mTBI. This study, however, aims to directly link VF components to frontal and temporal cortical surface area (CSA). We hypothesized that patients with mTBI would exhibit fewer clusters and more switches compared to healthy controls. We further hypothesized that clusters would be associated with temporal, while switches would be associated with frontal CSA.

Participants and Methods
Sixty young adults participated (M_{age}=23.49; SD=5.34), including 20 healthy controls (HCs), 22 sub-acute mTBI patients (2-4 weeks post-injury), and 18 chronic mTBI patients (6-12 months post-injury). Participants were administered the D-KEFS semantic VF task, and responses were coded for total clusters and switches. T1-weighted anatomical images were acquired and FreeSurfer was used to measure CSA.

Results
The three groups differed significantly on total switches ($F(2,53)=3.34$, $p=.04$, $\eta^2=.11$), where the chronic mTBI group produced more switches compared to HCs. The three groups showed no significant difference in semantic clusters ($F(2,53)=6.38$, $p=.10$, $\eta^2=.08$). Switching was significantly correlated with CSA in the left caudal middle frontal region (r=.27, p=.04) and left parsopercularis (r=-0.29, p=.03), whereas clustering was significantly correlated with CSA in the left parahippocampus (r=-0.27, p=.04).[WDK1]

Conclusions
These findings provide direct evidence for cortical characteristics associated with VF deficits often observed in patients with mTBI. Switching was directly linked to frontal regions[WDK2], which play a critical role in attention and task maintenance. The increased use of switching in patients 6-12 months post-injury may be indicative of long-lasting disruptions to frontal brain regions, and further highlight the clinical importance of targeting executive function skills in treatment approaches for patients with mTBI.

Exploring Verbal Recall Throughout Mild Traumatic Brain Injury Recovery

Simon Esbit, Daisy Raygoza, Corinne Meinhausen, Natalie S. Dailey and William D. S. Killgore

Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA

Objective
Impaired memory is often reported after a mild traumatic brain injury (mTBI). However, little is known about the memory deficits across the recovery timeline. This study explores the efficacy of semantic and serial recall strategies in acute (2-12 weeks) and chronic (6-12 months) stages of mTBI recovery. Semantic clustering involves recalling words based on their meaning; whereas, serial clustering involves recalling words in the order they were presented. We predicted all participants would exhibit a positive relationship between total verbal recall and semantic clustering and a positive relationship between total verbal recall and serial clustering.

Participants and Methods
One hundred and nine adults completed this study, including 29 HCs (M_{age}=2.83; SD=3.73), 39 in the acute group (M_{age}=24.93; SD=7.34) and 41 in the chronic group (M_{age}=23.08; SD=5.74). The California Verbal Learning Test, 2nd Edition (CVLT) assessed episodic verbal recall and recall strategies with an orally presented wordlist. We explored the relationship between recall strategy and total verbal recall using Pearson's Correlation.

Results
There were significant positive relationships between total verbal recall and semantic clustering for all three groups (HC, r=0.56; acute, r=0.74; and chronic, r=0.41: all p<0.01). Whereas, there was only a significant relationship between total verbal recall and serial clustering for the acute group (r=-0.35, p=0.02).

Conclusions
All groups displayed significant relationships between total verbal recall and the use of semantic clustering. This finding is consistent with previous literature, and supports the advantage of strong lexical-semantic networks during verbal recall. Furthermore, the acute group had a negative relationship between total verbal recall and the use of serial clustering. Our findings suggest that people in the acute stage of mTBI recovery might benefit from avoiding serial clustering in favor of semantic clustering to perform optimally in verbal recall.

The Compounding Impact of Daytime Sleepiness and Brain Injury on Sustained Vigilance

Dailey, N. S.·Raikes, A. C.·Wager, M. E.·Grandner, M. A.·Alkozei, A.·Killgore, W. D.
University of Arizona
Tucson, AZ.

Introduction: Daytime sleepiness is among the most frequent self-reported complaints by individuals who have sustained a mild traumatic brain injury (mTBI). Previous research demonstrates reduced vigilance and processing speed following mTBI. It has yet to be determined, however, if sustaining a mTBI alone, or the combination of daytime sleepiness and brain injury more greatly impacts cognitive function. The goal of this preliminary analysis was to determine the association between vigilance, daytime sleepiness, and mTBI.
Methods: A total of 137 adults (M_{age} = 24.89±7.2; 83 females) participated in the study, including 33 healthy controls (HCs) and 104 individuals with a documented mTBI within the preceding 12 months. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), while daytime vigilance was measured using the Psychomotor Vigilance Task (PVT). To assess the effect of mTBI and daytime sleepiness on vigilance, we fit a Poisson regression to the number of lapses on the PVT, with group and ESS scores as predictors.
Results: ESS scores were significantly higher ($p<.001$) and there were significantly more PVT lapses ($p=.03$) in those with a recent mTBI, compared to HCs. For those with mTBI, the rate of lapses increased by 7.5% for every 1-point increase in ESS score ($p< .001$). Furthermore, when compared to HCs, the PVT lapse rate was 1.8x higher for individuals with a history of mTBI ($p< 0.001$), after controlling for ESS scores.
Conclusion: Daytime sleepiness was negatively associated with sustained vigilance for all participants. However, the magnitude of this association was roughly twice as high in individuals who had sustained a mTBI in the previous year. These findings provide evidence of a significant compounding effect of daytime sleepiness and brain injury on sustained vigilant attention. Clinical evaluation of mTBI would benefit from routine assessment of daytime sleepiness.
Support: USAMRMC grant (W81XWH-12-0386).

Reduced Cortical Thickness as a Biomarker of Daytime Sleepiness in Mild Traumatic Brain Injury

Dailey, N. S.·Raikes, A. C.·Alkozei, A.·Grandner, M. A.·Killgore, W. D.
University of Arizona
Tucson, AZ.

Introduction: Sleep disruptions, including the increase of daytime sleepiness, are reported in roughly 70% of all individuals who have suffered a mild traumatic brain injury (mTBI). Prior research using magnetic resonance imaging (MRI) has identified associations between functional brain changes and daytime sleepiness following mTBI. In the present study, we aimed to identify whether structural differences in cortical thickness are associated with increased daytime sleepiness in adults with mTBI.

Methods: A total of 58 adults between 18 and 45 years of age (M=23.58±5.31) participated in the study, including 19 healthy controls and 39 individuals with a documented mTBI. Individuals with mTBI were further divided based on time-since-injury into a sub-acute (n=22) or chronic (n=17) group. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and cortical thickness was measured using high-resolution T1-weighted structural MRI. Whole-brain vertex-wise estimations of cortical thickness were calculated using FreeSurfer (v.6.0) and entered into a GLM to identify between-group differences in cortical thickness and the association with ESS.

Results: Significant differences in cortical thickness were found between the two mTBI groups (cluster-forming threshold $p<.01$; cluster-wise threshold $p<.05$; two-tailed; FWE-corrected). Specifically, lower cortical thickness in the left hemisphere was found in the inferior parietal lobule ($p=.01$), precuneus ($p=.03$), and pars triangularis ($p=.04$) for the sub-acute, compared to chronic group. Furthermore, a significant negative correlation was found between ESS and cortical thickness in the inferior parietal lobule ($r=-.55$, $p=.009$) for the sub-acute mTBI group.

Conclusion: More daytime sleepiness was associated with reduced inferior parietal cortical thickness in those 2 to 12-weeks post-injury, an association not observed in those 6 to 12-months post-injury or healthy controls. The inferior parietal lobule is part of the frontoparietal attention network and has been associated with vulnerability to sleep loss. Our findings suggest structural damage to the attention network following mTBI may be one factor affecting daytime sleepiness in mTBI. These findings may reflect a potential biomarker of sleep disturbances in mTBI.

Support: USAMRMC grant (W81XWH-12-0386).

Reading Fluency in Mild Traumatic Brain Injury

Natalie S. Dailey[1] and William D. S. Killgore[1]

[1]Social, Cognitive, and Affective Neuroscience (SCAN) Lab, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ.

BACKGROUND

A growing number of young adults enrolled in postsecondary education have a history of brain injury [1]. Mild traumatic brain injury (mTBI) can result in impaired cognitive functions including slowed processing speed and attention deficits [2,3]. Furthermore, reading fluency, or the ability to quickly and accurately process linguistic information, relies heavily on processing speed. However, reading fluency following mild traumatic brain injury has yet to be fully investigated. The current study aimed to identify reading ability at acute and chronic recovery stages of mTBI. We hypothesized that individuals with an acute mTBI would exhibit deficits in reading fluency, compared to those with a chronic mTBI.

METHODS

Preliminary data was collected on 10 individuals with mTBI between 18 and 40 years of age. All participants were native English speakers with no history of psychiatric disorder or alcohol/substance abuse. Participants provided head injury documentation prior to study enrollment. The acute mTBI group (n=3) included individuals who were either 2-weeks or 4-weeks post injury. The chronic mTBI group (n=7) included individuals who were either 6-moths or 12-months post injury. The study was approved by the Institutional Review Board (IRB) at the University of Arizona and the U.S. Army Human Research Protections Office, and all participants provided written informed consent prior to their participation.

Reading Fluency

Participants completed the Sentence Reading Fluency subtest of the Woodcock-Johnson Test of Achievement – IV [4]. This subtest measures reading speed, as well as comprehension accuracy. Participants silently read sentences (i.e. ‘A cow is an animal) and decide if the answer is ‘Yes’ or ‘No’. Participants are given 3minutes to complete as many of the 110-items as possible. The primary outcome measures included the number correct, the number incorrect, and total number completed.

RESULTS

A multivariate analysis of variance (MANOVA) was calculated to determine whether the two groups differed on the 3 outcome variables of reading fluency. We found that individuals in the chronic mTBI group had significantly more items correct ($F(1,7) = 6.10$, $p < .05$) and more completed items ($F(1,7) = 5.98$, $p < .05$), compared to individuals in the acute mTBI group.

CONCLUSIONS

As predicted, individuals who recently experienced a mTBI (i.e. within 1-month of the injury) exhibited deficits in reading fluency compared to individuals who are in the chronic recovery stage (i.e. 6-months to a year of the injury. These findings provide preliminary support for

cognitive deficits that impact reading fluency following mTBI. Furthermore, our findings suggest that deficits in reading fluency recover within 6-months of the injury.

References/Citations

1. Krug, H. and L.S. Turkstra, Assessment of Cognitive-Communication Disorders in Adults with Mild Traumatic Brain Injury. Perspectives on Neurophysiology and Neurogenic Speech and Language Disorders, 2015. 25(1).
2. Silver, J.M., T.W. McAllister, and S.C. Yudofsky, Textbook of Traumatic Brain Injury. 2nd Edition ed. 2011: American Psychiatric Publishing.
3. McInnes, K., et al., Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. PLoS One, 2017. 12(4): p. e0174847.
4. Mather, N. and B.J. Wendling, Examiner's Manual. Wodcock-Johnson IV Tests of of Achievement. 2014, Rolling Meadows, IL: Riverside.

Self-Initiated Recall Strategies in Mild Traumatic Brain Injury: Identifying the Neural Correlates

Natalie S. Dailey[1], Corinne Meinhausen[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective

In memory tasks, serial and semantic clustering are self-initiated recall strategies that can improve performance. Emerging evidence suggests adults with acute mild traumatic brain injury (mTBI) are more likely to use semantic clustering compared to adults with chronic mTBI. However, the neural mechanisms associated with recall strategies remain unknown. We hypothesized that white matter integrity and time since injury predict the use recall strategies.

Participants and Methods

Fifty-six adults participated, including 20 controls, 22 adults with acute mTBI (2-12weeks post-injury), and 15 adults with chronic mTBI (6-12months post-injury). Serial and semantic clustering was measured using the California Verbal Learning Test. The superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF) were targeted using diffusion weighted imaging and measured by fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. Separate stepwise linear regressions were calculated to determine the relationship between white matter integrity and time since injury on the use of serial and semantic clustering.

Results

Fractional anisotropy in the left SLF (β=-.28, p=.03) and axial diffusivity in the right UF (β=.25, p=.05) significantly predicted serial clustering, accounting for 16% of the total variance (p<.05). In contrast, fractional anisotropy in the left UF (β=.30, p=.03) significantly predicted semantic clustering, accounting for 9% of the total variance (p<.05). Finally, contrary to our hypothesis, time since injury was not a significant predictor of recall strategy.

Conclusions

Serial clustering is associated with reduced white matter integrity in the left SLF, and increased integrity in the right UF, whereas semantic clustering is associated with increased integrity in the left UF. Adults who utilize serial clustering may exhibit disrupted axonal integrity within left-lateralized language pathways, impeding their ability to use a higher-level recall strategy, such as semantic clustering.

Making a List and Checking it Twice: Episodic Verbal Recall in Mild Traumatic Brain Injury

Simon Esbit[1], Natalie S. Dailey[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective

Mild traumatic brain injury (mTBI) can subtly change brain structure resulting in symptoms, such as memory deficits. Impaired cognitive functioning is frequently reported after a mTBI; however, little is known about the timeline for recovery. This study aims to assess recall strategies in acute and chronic stages of mTBI recovery. We predicted poor verbal recall for those with mTBI relative to healthy controls (HCs). We hypothesized that adults in the acute recovery stage (i.e. 1-month or less post-injury) would exhibit greater verbal recall, compared to adults in the chronic recovery stage (i.e., 6-months to 1-year post-injury).

Participants and Methods

Sixty adults completed the study, including 22 HCs (M_{age} = 22.97; SD = 3.38), 18 adults in the acute mTBI group (M_{age}=24.43; SD=7.59) and 20 adults in the chronic mTBI group (M_{age}=23.37; SD=5.25). Trials 1-5 of the California Verbal Learning Test (CVLT) were used to assess episodic verbal recall strategies. Percentage of correct words recalled from the beginning (RfP), middle (RfM), and end (RfR) of the list was measured for each group.

Results

The three groups did not significantly differ on age, gender, or IQ. There was a significant main effect of group on RfM (F(2,59)=4.87; p=0.011; η^2 =0.15), but not RfP (F(2,59)=2.69; p=0.076; η^2 =0.09) or RfR (F(2,59)=1.939; p=0.153; η^2 =0.06). Post-hoc analyses showed that RfM was significantly reduced in chronic mTBI (M=42.10, SD=5.88), compared to acute mTBI (M=47.00; SD=4.34) ($p < .05$). RfM was not significant between adults in the acute compared to HCs nor between the chronic mTBI and HC groups.

Conclusions

Our results show that adults in the chronic recovery phase displayed lower RfM relative to those in the acute recovery. Contrary to our hypotheses, none of the groups differed in terms of RfP or RfR. Proactive and retroactive interference can impede consolidation of words from the middle of the list, suggesting adults in the chronic recovery stage may be more vulnerable to inference effects.

Identifying Memory Retrieval Strategies Following a Mild Traumatic Brain Injury Using the CVLT-II

Corinne Meinhausen[1], Natalie S. Dailey[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective:
Mounting evidence suggests learning, memory and attentional deficits occur in the acute stage of mild traumatic brain injury (mTBI). However, the extent to which these deficits remain longer than 12 weeks is unclear. This study aimed to identify memory retrieval strategies used in the acute and chronic stages post-mTBI. It was predicted that the use of serial and semantic clustering would differ in the acute stage (2-12 weeks) compared to adults the chronic stage (6-12 months) and healthy controls.

Participants and Methods:
A total of 69 adults participated in the study and included 20 HCs, 26 adults in the acute phase, and 23 adults in the chronic phase. The California Verbal Learning Test, 2nd Edition (CVLT-II) was administered to identify the use of memory retrieval strategies including serial and semantic clustering. Serial clustering involves recalling words in the order in which they were heard and semantic clustering is a secondary memory strategy in which words are grouped by meaning.

Results:
Raw semantic and serial clustering scores were compared between the acute, chronic and HC groups using one-way ANOVAs. There was a main effect of group on serial clustering ($F(2,66)=3.142$, $p=0.05$, partial eta-squared=0.87). Post-hoc comparisons showed the acute group had significantly fewer serial clusters than HCs ($p=0.03$) and the chronic group ($p=0.04$). There was also an observed tendency in the acute group to perform semantic clustering over the HCs and the chronic group.

Conclusions:
Our findings show that serial recall was reduced in the acute group relative to the chronic and HC groups, suggesting the use of different memory retrieval strategies. These findings, in addition to an increased tendency to use semantic clustering may indicate a compensatory effect during early mTBI recovery in response to deficits in the memory process.

Excessive Daytime Sleepiness and mTBI:
Determining Factors Leading to Decreased Cognitive Function

Mark E. Wager[1], Natalie S. Dailey[1], & William D. S. Killgore[1]

[1]Social, Cognitive, and Affective Neuroscience Laboratory (SCAN LAB), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective:

Ample research suggests excessive daytime sleepiness results in impaired cognitive and motor function. Similar conclusions can be drawn for those who have suffered a mild traumatic brain injury (mTBI). It is yet to be determined the extent to which the combined effects of daytime sleepiness and mTBI impair cognitive and motor function. We explored the relationship between these two factors on cognitive function. We hypothesized that the combination of excessive daytime sleepiness and mTBI show slower reaction time (RT) and response lapses (i.e., RTs > 500 ms) on a vigilance task relative to the presence of either factor alone or healthy controls.

Participants and Methods:

Participants totaled 57 adults, including 19 healthy controls (HC) (8 male, 11 female; M_{age}= 23.56, *SD*= 3.48 years; $M_{ed.}$=13.89, *SD*= 1.49 years; M_{IQ}= 226.84, *SD*= 18.94) and 38 subjects who experienced an mTBI (12 male, 26 female; M_{age}= 23.06, *SD*= 4.86 years; $M_{ed.}$=13.63, *SD*= 1.67 years; M_{IQ}= 225.18, *SD*= 19.71). Participants in the mTBI group were up to 1-year post-injury (M_{TSI}= 159.95, *SD*= 141.95 days). Daytime sleepiness was self-assessed using the Epworth Sleepiness Scale (ESS; Johns, 1991). Total scores ranged from 0 (would never doze off) to 24 (high chance of dozing off). Participants then completed a psychomotor vigilance task (PVT) to measure cognitive and motor function. Separate independent samples t-tests were calculated to determine if there were significant differences between the HC and mTBI groups on daytime sleepiness and reaction time. Lapses in responses on the PVT were compared between the groups using a Mann-Whitney U-Test, due to non-normality. Post-hoc comparisons were used to determine which of these three groups from the Kruskal Wallis H-Test differed significantly, comparing two of the three groups at a time using the Mann-Whitney U-Test.

Results:

The mTBI group was significantly sleepier during the daytime than HCs ($t(55)=-5.06$, $p < 0.001$). No significant difference in reaction time was found between the groups ($t(52)= -1.43$, $p=0.159$). There was, however, a significant difference in the number of lapses, with the mTBI group exhibiting more lapses ($M_{mTBI\ lapses}$=5.71, *SD*=6.26) on the PVT than HCs ($M_{HC\ lapses}$=2.37, *SD*=2.27) (*U*= 133.5, *p*= 0.001). Based on the previous finding of increased sleepiness in those with mTBI, we wanted to determine whether those with mTBI *and* excessive daytime sleepiness would exhibit greater lapses compared to HCs, and individuals with mTBI *without* excessive daytime sleepiness. Individuals with mTBI were therefore divided into two groups, those with excessive daytime sleepiness (ESS score $\geq$ 10) and those without excessive daytime sleepiness (ESS score < 9). Lapses from mTBI individuals who reported excessive daytime sleepiness were compared to that of HCs and individuals with mTBI without excessive daytime sleepiness, using a Kruskal Wallis H-Test for three groups. There was a significant difference in lapses between the three groups (*H*= 10.7, *p*= 0.005). Post-hoc showed that HCs had fewer lapses than an mTBI with low ESS ($M_{low\ mTBI\ ESS}$= 5.30, *SD*= 4.88) (*U*= 78.5, *p*= 0.008) and mTBI with high ESS

($M_{high\ mTBI\ ESS}$= 6.17, *SD*= 7.63) (*U*=55.0, *p*=0.002). No difference was found between the mTBI with low ESS group and mTBI with high ESS group (*U*= 177.5, *p*= 0.942).

Conclusions:

Our results demonstrate individuals with mTBI experience excessive daytime sleepiness and reduced cognitive function, compared to HCs. Those with mTBI showed significantly more lapses than HCs, however no significant difference was found in reaction time between the two groups. Cognitive function was further compared within the mTBI group, to assess whether those with an mTBI *and* excessive daytime sleepiness would exhibit significantly reduced function. Lapses within the mTBI groups comparing high ESS to low ESS were not significantly different. It can thus be inferred that the increase in number of lapses is not significantly affected by excessive daytime sleepiness, but instead by sustaining an mTBI. Increased daytime sleepiness may be the result of decreased nighttime sleep, a factor which research suggests is a symptom of decreased psychomotor function (Wickwire et al., 2018). Additional studies can be performed to determine if other factors play a role in excessive daytime sleepiness and cognitive function, such reporting how much sleep the participant received the night prior to the exam.

References:

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *sleep*, *14*(6), 540-545

Wickwire, Emerson M., et al. “Sleep, Sleep Disorders, and Circadian Health Following Mild Traumatic Brain Injury in Adults: Review and Research Agenda.” Journal of Neurotrauma, vol. 35, 15 Nov. 2018, p. 2619.

Neural Correlates of Aggression in the Chronic and Post-Acute Stages of Recovery from Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study

Natalie S. Dailey[1], Sahil Bajaj[1], Anna Alkozei[1], Ryan Smith[1], Sara A. Knight[1] & William D. S. Killgore[1]

[1]Social, Cognitive, and Affective Neuroscience (SCAN) Lab, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ.

Objective
Aggression is a commonly reported symptom associated with mild traumatic brain injury (mTBI). However, the neural basis of mTBI-related aggression is poorly understood. Here we sought to characterize aggression in adults at different stages of recovery from mTBI, and its relation to axonal integrity, using diffusion tensor imaging (DTI).

Participants and Methods
Participants included 37 age-matched adults, including 16 healthy controls, 11 adults with post-acute mTBI (≤ 1-month post-injury), and 10 with chronic mTBI (≥ 6-months post-injury). Overall aggression, physical aggression, verbal aggression, anger, and hostility were measured using the Buss-Perry Aggression Questionnaire. FMRIB Software Library (FSL) was used to preprocess DTI data and calculate fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). Tracts of interest that are particularly susceptible to injury in mTBI included the corpus callosum (CC), anterior thalamic radiation (ATR), cingulum (Cg), and uncinate fasciculus (UF).

Results
Significant group-differences were found for physical aggression ($F(2,32)=5.83$, $p<.05$, d=1.22), anger ($F(2,32)=4.06$, $p<.05$, $d=1.00$), and total aggression ($F(2,32)=5.52$, $p<.05$, $d=1.19$), with the chronic mTBI group reporting higher levels of physical ($p<.01$) and total aggression ($p<.01$), compared to healthy controls. No significant differences were found for the post-acute mTBI group. In the chronic mTBI group, physical aggression was negatively correlated with AD in the left ATR ($p<.05$), and total aggression was negatively correlated with FA and AD in the right ATR ($p<.05$).

Conclusions
The present study provides preliminary evidence supporting an association between reduced white matter integrity in the ATR and persistent and elevated levels of self-reported aggression in adults with chronic mTBI. In addition, the inverse relationship between AD and aggression is consistent with axonal damage, a characteristic of mTBI.

The Executive Control Network after Mild Traumatic Brain Injury: Associations between Functional Connectivity and Aggression

Natalie S. Dailey[1], Adam C. Raikes[1], Ryan Smith[1], Anna Alkozei[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

*_E-mail_: ndailey@email.arizona.edu

Background:
Emotional disturbances, including increased aggression, are commonly reported following mild traumatic brain injury (mTBI). Recent evidence suggests damage to interconnected large-scale neural networks, such as the executive control network (ECN) are believed to subserve cognitive processes involved in emotional regulation. The ECN supports a range of domain-general cognitive functions including working memory, selective attention, stimulus-response mapping, and performance monitoring, all of which play an important role in reappraising and regulating emotional responses. Advancements in neuroimaging techniques, including resting-state functional connectivity may prove valuable in the examination of large-scale neural networks that contribute to emotional regulation and the possible dysfunction of such networks following mTBI. In the present study, we hypothesized that ECN functional connectivity (FC) would differ between individuals with mTBI and healthy controls (HCs), and this FC would correlate with aggression.

Methods:
Thirty-four individuals (n = 17 mTBI, 10 females, mean age = 23.49 ± 3.36 years; n = 17 HC, 13 females, mean age = 22.88 ± 5.14 years) participated in the study. All individuals in the mTBI group were at least 6-months post-injury. All participants completed a battery of neuropsychological assessments followed by the collection of neuroimaging data. The Buss-Perry Aggression Questionnaire (BPAQ) was used to quantify physical and verbal aggression, anger, hostility, and total aggression. Depression was measured by the Beck Depression Inventory and used as a covariate in subsequent analyses. Resting-state functional connectivity magnetic resonance imaging data was collected using a 3.0 Tesla Siemens Skyra with a 32-channel head coil. Six functionally defined ROIs in the ECN were based on previous literature and targeted in the left and right hemispheres separately. Between-group ROI-to-ROI connectivity within the ECN was calculated using the *CONN* toolbox, while controlling for age, sex, and depression (FDR-analysis-level corrected at $p < .05$). Partial correlations between connectivity and aggression were calculated.

Results: Adults with mTBI reported significantly elevated levels of physical aggression ($F = 12.34$, $p = .001$), anger ($F = 12.54$, $p = .001$), and hostility ($F = 6.37$, $p = .02$) compared to HCs. The two groups did not differ on levels of verbal aggression. There were no significant between-group differences for FC in the right ECN. In the left ECN, individuals with mTBI exhibited lower FC between the thalamus (xyz = -14, -28, 2) and middle temporal gyrus (MTG; xzy = -59, -42, -12) than HCs ($t = -3.64$, $p = .02$). Furthermore, thalamic-MTG FC was inversely related to physical aggression ($r = -.50$, $p = .016$, corrected for multiple comparisons).

Conclusions: Elevated physical aggression, as observed in individuals at least 6-months post-mTBI, was associated with lower thalamic-MTG FC. As these ECN regions are implicated in voluntary emotion regulation processes, our novel findings indicate mTBI may disrupt large-scale network connections important for regulating anger/aggression. Furthermore, our results expand current evidence suggesting a link between neuroanatomical disruptions and the manifestation of post-concussive symptoms, identifying the ECN as a potentially critical network for emotional regulation.

Funding Source: USAMRMC W81XWH-12-0386 awarded to WSK.

	Healthy Contols Mean (SD)	mTBI Mean (SD)	Statistic
Age, in years	23.49 (3.36)	22.88 (5.14)	t (1, 32) = .41
Sex (female, male)	10, 7	13, 4	x^2 (1) = 1.21
BDI	2.24 (3.09)	7.59 (7.42)	t (1, 32) = -2.75*

ROI	Anatomical Location of Functionally Defined ROIs	MNI Coordinates (cluster centroid)	Cluster Size
1	Superior and Inferior Parietal Gyrus, Percuneus, Angular Gyrus	-42, -63, 46	19651
2	Middle and Superior Frontal Gyrus	-31, 24, 49	14826
3	Inferior Frontal Gyrus, Orbitofrontal Gyrus	-40, 48, -1	4666
4	Inferior and Middle Temporal Gyrus	-59, -42, -12	3640
5	Cerebellum	36, -68, -43	3253
6	Thalamus	-15, -27, 2	128

Reduced Functional Connectivity in the Executive Control Network Following Mild Traumatic Brain Injury: Implications for Emotional Regulation

Natalie S. Dailey[1], Ryan Smith[1], Adam C. Raikes[1], Anna Alkozei[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

**E-mail*: ndailey@email.arizona.edu

Background: Emotional disturbances are common following mild traumatic brain injury (mTBI). Recent evidence suggests diffuse damage to large-scale neural networks, such as the executive control network (ECN), may account for these mood changes. The ECN supports a range of domain-general cognitive control functions and play an important role in regulating emotional responses. We hypothesized that ECN functional connectivity (FC) would differ between individuals with mTBI and healthy controls (HCs), and this FC would correlate with aggression.

Methods: Thirty-four individuals (n=17 mTBI, 10 females, age=23.49±3.36 years; n=17 HC, 13 females, age=22.88±5.14 years) completed the Buss-Perry Aggression Questionnaire, which quantifies physical and verbal aggression, anger, hostility, and total aggression. Resting-state FC data were collected. Between-group ROI-to-ROI connectivity in the ECN was calculated using the *CONN* toolbox, while controlling for age, sex, and depression (FDR-analysis-level corrected at $p<.05$). Partial correlations between connectivity and aggression were calculated.

Results: Adults with mTBI reported significantly elevated levels of physical aggression ($F=12.34$, $p=.001$), anger ($F=12.54$, $p=.001$), and hostility ($F=6.37$, $p=.02$) compared to HCs. In the left ECN, individuals with mTBI exhibited lower FC between the thalamus (xyz=-14, -28, 2) and middle temporal gyrus (MTG; xzy=-59, -42, -12) than HCs ($t=-3.64$, $p=.02$). Thalamic-MTG FC was inversely related to physical aggression ($r=-.50$, $p=.004$) and hostility ($r=-.38$, $p=.03$).

Conclusions: Lower post-mTBI thalamic-MTG FC is associated with increased aggression. As these ECN regions are implicated in voluntary emotion regulation processes, these novel findings indicate mTBI may disrupt large-scale network connections important for regulating anger/aggression.

Disrupted Functional Connectivity and Elevated Aggression in Yound Adults with Mild Traumatic Brain Injury

Natalie S. Dailey[1], Sahil Bajaj[1], Ryan Smith[1], Adam C. Raikes[1], Anna Alkozei[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

**E-mail*: ndailey@email.arizona.edu

Background:
Emotional disturbances, including increased aggression, are commonly reported following mild traumatic brain injury (mTBI) [Epstein 2016]. Furthermore, aggressive attitutues and behavior can interfere with clinical intervention and is, therefore, an important factor to consider when designing and implementing treatment approaches for those who have experienced an mTBI. Recent evidence suggests interconnected large-scale neural networks, such as the executive control network (ECN), are believed to subserve cognitive processes involved in emotional regulation[1]. The ECN supports a range of domain-general functions including working memory, selective attention, stimulus-response mapping, and performance monitoring[2], all of which play an important role in reappraisal and regulation of emotional responses. Advancements in neuroimaging techniques, including resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) may prove valuable in the examination of large-scale neural networks that contribute to emotional regulation and the possible dysfunction of such networks following mTBI. In the present study, we hypothesized that functional connectivity (FC) within the ECN would differ between individuals with mTBI and healthy controls (HCs), and this FC would correlate with aggression.

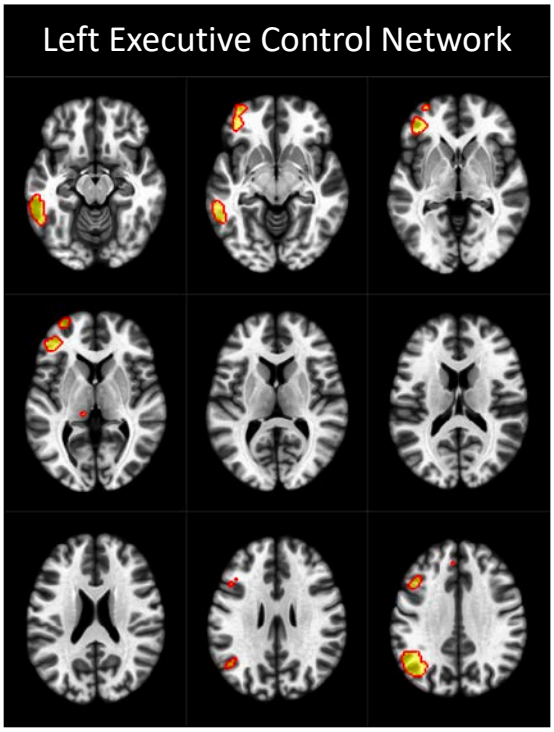
Methods:
Thirty-four individuals (n = 17 mTBI, 10 females, mean age = 23.49 ± 3.36 years; n = 17 HC, 13 females, mean age = 22.88 ± 5.14 years) participated in the study. All individuals in the mTBI group were at least 6-months post-injury. All participants completed a battery of neuropsychological assessments followed by the collection of neuroimaging data. The Buss-Perry Aggression Questionnaire (BPAQ)[3] was used to quantify physical and verbal aggression, anger, hostility, and total aggression. Depression was measured by the Beck Depression Inventory and used as a covariate in subsequent analyses. Resting-state fMRI data was collected using a 3.0 Tesla Siemens Skyra with a 32-channel head coil. The ECN was divided into six functionally defined ROIs[4], including the 1) middle and superior frontal gyri, 2) inferior frontal and orbital frontal gyri, 3) superior parietal, inferior parietal, precuneus, and angular gyri, 4) inferior temporal and middle temporal gyri, 5) lobule V11 of the cerebellum, and 6) thalamus. Between-group ROI-to-ROI connectivity within the ECN was calculated for the left and right hemispheres separately using the *CONN* toolbox (www.nitrc.org/projects/conn), controlling for the effects of age, sex, and depression (FDR-analysis-level corrected at $p < .05$). Partial correlations (controlling for age, sex, and depression) were calculated between FC and BPAQ aggression subscales.

Results: Adults with mTBI reported significantly elevated levels of physical aggression ($F(1, 29) = 12.34$, $p = .001$), anger ($F(1,29) = 12.54$, $p = .001$), and hostility ($F(1,29) = 6.37$, $p = .02$) compared to HCs. The two groups did not differ on levels of verbal aggression. There were no significant between-group differences for FC in the right ECN. In the left ECN, individuals with mTBI exhibited lower FC between the thalamus and inferior/middle temporal gyrus (ITG/MTG) compared to HCs ($t = -3.64$, $p = .02$). Furthermore, FC between the thalamus and inferior/middle temporal gyrus was inversely related to physical aggression ($r = -.50$, $p = .016$, corrected for multiple comparisons).

Conclusions: Significantly elevated Elevated physical aggression, as observed in individuals at least 6-months post-mTBI, was associated with lower thalamic-ITG/MTG FC. As these ECN regions are implicated in voluntary emotion regulation processes, our novel findings indicate mTBI may disrupt large-scale network connections important for regulating anger/aggression. Furthermore, our results expand current evidence suggesting a link between functional disruptions and the manifestation of post-concussive symptoms, identifying the ECN as a potentially critical network for emotional regulation.

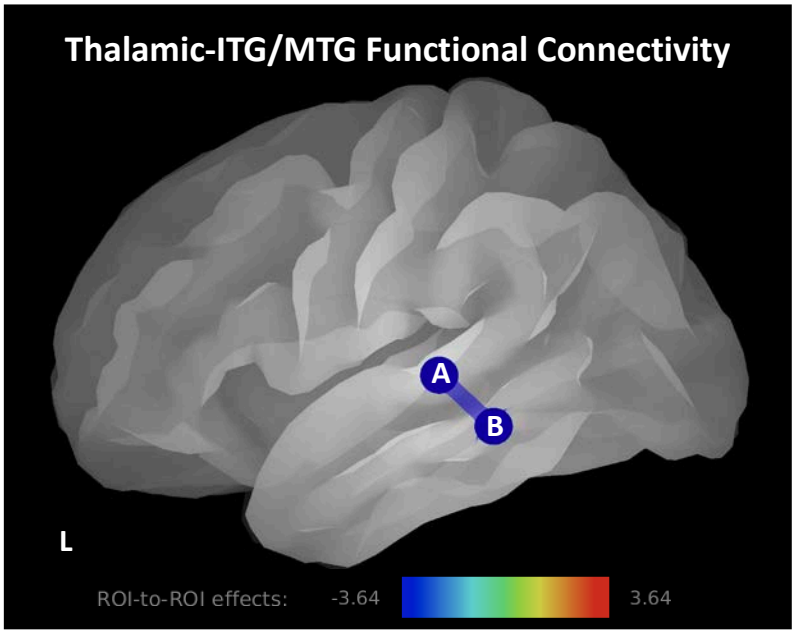
Funding Source: USAMRMC W81XWH-12-0386 awarded to William. D.S. Killgore.

Figure 1.



Note: Functionally defined regions of interest (ROIs) within the Executive Control Network (ECN) outlined in red. Voxels included in each ROI are shown in yellow.

Figure 2.



Note: Functional connectivity between the thalamus and inferior/middle temporal gyrus was significantly lower in mTBI compared to HC participants. A = thalamus; B = inferior/middle temporal gyrus (ITG/MTG) ; L = left hemisphere; ROI = region of interest.

1. Lindquist, K.A., et al., *The brain basis of emotion: a meta-analytic review.* Behav Brain Sci, 2012. **35**(3): p. 121-43.
2. Niendam, T.A., et al., *Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions.* Cogn Affect Behav Neurosci, 2012. **12**(2): p. 241-68.
3. Buss, A.H. and M. Perry, *The Aggression Questionnaire.* Journal of Personality and Social Psychology, 1992. **63**(3): p. 452-459.
4. Shirer, W.R., et al., *Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns.* Cerebral Cortex, 2012. **22**(1): p. 158 - 165.

White Matter Correlates of Self-Reported Sleep Quality after a Mild Traumatic Brain Injury: A DTI Study

Adam C. Raikes[1], Sahil Bajaj[1], Natalie S. Dailey[1], Brieann C. Satterfield[1], Anna Alkozei[1], Ryan Smith[1], William D.S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Background: Mild traumatic brain injuries (mTBIs) often result in lingering post-concussive symptoms, lasting months to years after the initial injury. Sleep difficulties, especially self-reported insomnia and poor sleep quality, are among the most common persistent post-concussive symptoms. Despite the prevalence of post-mTBI sleep-related complaints, the neurophysiological causes are not well understood. While the clinical presentation of mTBI is thought to reflect diffuse axonal injuries (i.e., damage to the axons and myelin sheaths), supporting findings are inconsistent. There is, therefore, the need for further clarification as to both the overall effects of mTBI on neural structures as well as the specific implications for self-reported sleep quality. Here, we examined whole-brain white-matter differences following mTBI as well as post-mTBI correlates of self-reported sleep quality.

Methods: 52 individuals (n = 34 post-mTBI, 21 females, age: 24.4 ± 7.4 years; n = 18 healthy controls, 9 females, age: 23.2 ± 3.4 years) completed the Pittsburgh Sleep Quality Index (PSQI) as part of a comprehensive neuropsychological battery. All individuals additionally underwent diffusion-weighted imaging (DWI). Imaging data were analyzed using Tract-Based Spatial Statistics, resulting in four diffusion tensor (DTI) metrics: fractional anisotropy (FA; a measure of white-matter fiber coherence), mean diffusivity (MD; average 3-dimensional water molecule diffusion rate), axial diffusivity (AD; water molecule diffusion rate parallel to underlying tissue), and radial diffusivity (RD; water diffusion rate perpendicular to underlying tissue). We computed voxel-wise whole-brain differences between the groups for each DWI metric, controlling for age and sex (family-wise error corrected at $\alpha < 0.05$). To understand the relationship between post-mTBI white-matter integrity and self-reported sleep quality, we fit within-group whole-brain correlations between the DTI metrics and PSQI total scores, controlling for age, sex, and days post-injury (mTBI only; family-wise error corrected at $\alpha < 0.05$).

Results: There were no whole-brain differences between the mTBI and healthy participants or correlations with PSQI total scores for the healthy participants for any DTI outcome. We observed a significant negative correlation ($r = -0.805$, $p < 0.001$) and positive correlation ($r = 0.793$, $p < 0.001$) between PSQI total scores and FA and RD, respectively, in the mTBI participants. These correlations were observed bilaterally, primarily in the anterior and posterior limbs of the internal capsules, anterior and superior corona radiata, and superior fronto-occipital fasciculi.

Conclusions: Poor sleep quality, evidenced by increasing PSQI total scores, and lower white-matter fiber coherence (lower FA) as well as faster perpendicular water diffusion (higher RD). Increasing RD is an indicator of axon, and particularly myelin, damage were linearly associated in our sample. Thus, poor sleep quality here was associated with indicators of damage in white-

matter tracts that are utilized in cognitive tasks (information processing, attentional maintenance, executive function), emotion processing, and sleep regulation. Damage to these association and projection white-matter tracts may explain inter-related and overlapping post-mTBI sleep-related, emotional, and cognitive complaints. Additionally, these findings support existing hypotheses that symptom manifestation following mTBI results from altered white-matter integrity, consistent with diffuse axonal injury models. Finally, these findings extend the currently available evidence for mTBI-related changes in white-matter integrity and pathways associated with clinically-relevant outcomes.

Self-Reported Sleep Quality is Related to Cerebellar Grey Matter Volume After Mild Traumatic Brain Injury

Adam C. Raikes[1], Brieann C. Satterfield[1], Natalie S. Dailey[1], Sahil Bajaj[1], William D.S. Killgore[1]

[1]Social, Cognition, Affect Neuroscience Lab, Department of Psychiatry, University of Arizona

Introduction: Among the observed symptoms following a mild traumatic brain injury (mTBI), sleep disruption is common. Individuals self-report a range of symptoms, including poor sleep quality and insomnia. These often persist beyond the general time course for clinical recovery. However, the neurological correlates of these self-perceptions remain poorly understood. Appropriate intervention for sleep-related complaints requires greater clarity as to the pathophysiology. In this study, we explored the relationship between Pittsburgh Sleep Quality Index (PSQI) total scores and grey matter volume in post-mTBI participants.

Methods: 39 right-handed individuals with a self-reported history of mTBI within the past year (25 females; mean age: 24.17 ± 7.11y) completed a comprehensive neuropsychological assessment, including the PSQI, followed by a neuroimaging session. High-resolution, T1-weighted, structural magnetic resonance imaging scans were processed using voxel-based morphometry following a standard pipeline (CAT12/SPM12). We fit a GLM to whole-brain grey matter volume (GMV) with PSQI total scores as the predictor, controlling for age, sex, total intracranial volume, and days post-injury. We additionally correlated GMV with psychomotor vigilance task (PVT; a sustained attention task sensitive to sleep deprivation) performance metrics.

Results: A significant positive correlation was observed in one cluster for GMV and PSQI total score (family-wise error corrected, $p = 0.019$). This cluster was located in the left cerebellar hemisphere, spanning lobules 7 and 8. Post-hoc analyses of the GMV in this cluster revealed a significant negative correlation with psychomotor vigilance task (PVT) mean reaction time (e.g., larger GMV associated with faster PVT mean reaction time; $r = -0.320$) and a positive correlation with PVT reaction time coefficient of variation ($r = 0.367$). PSQI total scores and PVT outcomes exhibited no significant correlations.

Conclusion: Cerebellar GMV was larger for individuals reporting poorer sleep quality in this post-mTBI sample. GMV was also associated with more variable yet better overall PVT reaction time. PVT performance metrics and total PSQI scores were uncorrelated. This indicates that cerebellar GMV may help maintain PVT performance despite self-reported poor sleep following mTBI.

Grey Matter Volumetric Differences with Increasing Numbers of Previous Mild Traumatic Brain Injuries: A Voxel-Based Morphometric Study

Adam C. Raikes[1], Brieann C. Satterfield[1], Sara A. Knight[1], William DS Killgore[1]

[1]Social, Cognition, Affect Neuroscience Lab, Department of Psychiatry, University of Arizona

Objective: Mild traumatic brain injury (mTBI) is a functional injury without evidence of structural abnormality. While there is mounting evidence that mTBI may be associated with changes in grey matter (GM) volume, the direction, timing, and extent of these changes remain unclear. Few studies have investigated the relationship between the number of past mTBIs and GM volume changes. The purpose of this study was to quantify differences in GM volume with respect to the number of prior head injuries.

Participants and Methods: The T1 high-resolution structural scans of 39 right-handed individuals with a self-reported history of mTBI (14 males; mean age: 24.17 ± 7.11y) were used for volume-based morphometric analysis (CAT12). Images were segmented and normalized following an automated procedure in CAT12 and smoothed prior to analysis. GM volume was correlated with the total number of self-reported past mTBIs, after controlling for age, sex, total intracranial volume, and time since most recent mTBI. Volumetric data from the single surviving cluster were exported for additional analyses.

Results: GM volume in a single cluster encompassing areas of the left superior temporal and supramarginal gyri (proximal to Wernicke's Area) positively correlated with total number of mTBIs (FWE corrected, $p = 0.035$). GM volume in this cluster was additionally significantly positively correlated with Delis-Kaplan executive function system (DKEFS) tasks, including letter fluency ($R2 = 0.102$) and category switching ($R2 = 0.106$).

Conclusions: In individuals with a history of mTBI, GM volume in the left superior temporal and supramarginal gyri was greater with increasing numbers of mTBIs. This increase in volume may reflect an adaptive neuroplastic response to increasing numbers of mTBIs that preserves aspects of language-based executive function. Longitudinal studies are needed to identify a causal relationship between mTBI and adaptive neuroplastic processes in the grey matter.

Self-Reported Sleep Quality is Associated with Reductions in White-Matter Integrity Following Recent Mild Traumatic Brain Injury

Adam C. Raikes[1], Natalie S. Dailey, Brieann C. Satterfield[1], Sahil Bajaj[1], William D.S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Background: Individuals with a history of mild traumatic brain injury (mTBI) often report post-injury sleep disruption that may persist for months up to years after the initial injury. These disruptions include insomnia, hypersomnia, pleiosomnia, as well as subjectively reported poor sleep quality. While the associations between mTBI and sleep disruption are known, there is little research supporting these observations from a neurophysiological perspective. The purpose of this study was to examine white-matter correlates of sleep quality in mTBI.

Methods: As part of a larger Department of Defense funded study, 34 individuals with a recent mTBI (<12 months post-injury) completed a comprehensive neuropsychological battery, including the Pittsburgh Sleep Quality Index (PSQI), and neuroimaging protocol, including diffusion-weighted imaging (DWI). Diffusion-weighted images were analyzed using a standardized processing pipeline, yielding four diffusion-related metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Whole-brain correlations were computed between the DWI metrics and PSQI total scores, controlling for age, sex, and days post-injury. Post-hoc correlation values were computed as the mean DWI-metric value over all significant voxels.

Results: PSQI total scores were significantly negatively correlated with FA (r = -0.805, p < 0.001) and positively correlated with RD (r = 0.793, p < 0.001). Correlations were primarily observed in the bilateral internal capsules, corona radiata, and superior fronto-occipital fasciculi.

Conclusions: Increasingly poor sleep quality, evidenced by increasing PSQI total scores, in post-mTBI individuals was linearly associated with lower white-matter fiber coherence (lower FA) and potentially reduced myelination and/or axonal density (higher RD). These findings are consistent with the hypothesis that the clinical presentation and pathophysiology following mTBI result from diffuse axonal injuries, affecting both projection and association white-matter tracts. Furthermore, the identified tracts are integrally involved in sleep regulation, information processing, attention, and executive function. Damage to these white-matter tracts may explain often comorbid presentations of both sleep-related and cognitive complaints following mTBI. These findings extend the current evidence for mTBI-related changes in white-matter integrity and pathways associated with clinically-relevant outcomes.

Support: This work was supported by a grant to WDSK from 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 Medical Research and Material Command (USAMRMC, Award #W81XWH-12-0386). The opinions, interpretations, conclusions and recommendations in this paper are solely those of the authors and are not necessarily endorsed by the Department of Defense or the U.S. Army Medical Research and Material Command.

Subjectively Poor Sleep Quality is Associated with Increased Cerebellar Grey Matter Volume Following Mild Traumatic Brain Injury

Adam C. Raikes[1], Brieann C. Satterfield[1], Natalie S. Dailey[1], Sahil Bajaj[1], William DS Killgore[1]

[1]Social, Cognition, Affect Neuroscience Lab, Department of Psychiatry, University of Arizona

Introduction: Sleep-related disruptions are a common feature of the symptoms following a mild traumatic brain injury (mTBI). Individuals self-report a range of symptoms, including poor sleep quality and insomnia, persisting well beyond the typical clinical recovery timeframe. However, the neurological underpinnings of these self-perceptions remain poorly understood. Appropriate intervention for sleep-related complaints requires a more clear understanding of related pathophysiology. In this study, we explored the relationship between Pittsburgh Sleep Quality Index (PSQI) total scores and grey matter volume in post-mTBI participants.

Methods: 39 right-handed individuals with a self-reported history of mTBI within the past year (25 females; mean age: 24.17±7.11y) completed a comprehensive neuropsychological assessment, including the PSQI followed by a neuroimaging session. High-resolution, T1-weighted, structural magnetic resonance imaging scans were processed using voxel-based morphometry following a standard pipeline (CAT12/SPM12). We fit a GLM to whole-brain grey matter volume (GMV) with PSQI total scores as the predictor, controlling for age, sex, total intracranial volume, and days post-injury.

Results: A single cluster exhibited a significant positive correlation between GMV and PSQI total score (family-wise error corrected, p=0.019). This cluster was located in the left cerebellar hemisphere, spanning lobules 7 and 8. Post-hoc analyses of the GMV in this cluster revealed a significant negative correlation with psychomotor vigilance task (PVT) mean reaction time (e.g., larger GMV associated with faster PVT mean reaction time; r=-0.320) and a positive correlation with PVT reaction time coefficient of variation (r=0.367). PSQI total scores and PVT outcomes exhibited no significant correlations.

Conclusion: Cerebellar GMV was larger for post-mTBI individuals reporting poorer sleep quality. Furthermore, GMV was associated with better overall, but more variable, PVT performance. Perceived sleep quality and PVT performance metrics were uncorrelated, suggesting that larger cerebellar GMV may be a compensatory mechanism for maintaining task performance in spite of perceived sleep decrement following mTBI.

Support: This work was supported by a grant to WDSK from 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 Medical Research and Material Command (USAMRMC, Award #W81XWH-12-0386). The opinions, interpretations, conclusions and recommendations in this paper are solely those of the authors and are not necessarily endorsed by the Department of Defense or the U.S. Army Medical Research and Material Command.

Post-mTBI White Matter Correlates of Self-Reported Sleep Quality: A DTI Study

Adam C. Raikes[1], Sahil Bajaj[1], Natalie S. Dailey[1], Anna Alkozei[1], Ryan Smith[1], William D.S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Background: Mild traumatic brain injuries (mTBIs) often result in lingering post-concussive symptoms, lasting months to years after the initial injury [5]. Sleep difficulties, especially self-reported insomnia and poor sleep quality, are among the most common persistent post-concussive symptoms [3,6]. Despite the prevalence of post-mTBI sleep-related complaints, the neurophysiological causes are not well understood. While the clinical presentation of mTBI is thought to reflect diffuse axonal injuries (i.e., damage to the axons and myelin sheaths), supporting findings are inconsistent [1,2]. There is, therefore, the need for further clarification as to both the overall effects of mTBI on neural structures as well as the specific implications for self-reported sleep quality. The purpose of this study was to examine whole-brain white-matter differences following mTBI as well as post-mTBI correlates of self-reported sleep quality.

Methods: 52 individuals (n = 34 post-mTBI, 13 males, age: 24.4 ± 7.4 years; n = 18 healthy controls, 9 males, age: 23.2 ± 3.4 years) completed a comprehensive neuropsychological battery, including the Pittsburgh Sleep Quality Index (PSQI). All individuals additionally underwent diffusion-weighted imaging (DWI). We analyzed the DWI data using Tract-Based Spatial Statistics, resulting in four diffusion-related metrics: fractional anisotropy (FA; a measure of white-matter fiber coherence), mean diffusivity (MD; average 3-dimensional water molecule diffusion rate), axial diffusivity (AD; water molecule diffusion rate parallel to underlying tissue), and radial diffusivity (RD; water diffusion rate perpendicular to underlying tissue). We computed voxel-wise whole-brain differences between the groups for each DWI metric, controlling for age and sex (family-wise error corrected at $\alpha < 0.05$). To understand the relationship between post-mTBI white-matter integrity and self-reported sleep quality, we fit within-group whole-brain correlations between the DWI metrics and PSQI total scores, controlling for age, sex, and days post-injury (mTBI only; family-wise error corrected at $\alpha < 0.05$).

Results: There were no whole-brain differences between the mTBI and healthy participants for any of the DWI metrics. DWI metrics were additionally not correlated with PSQI total scores for the healthy participants. In the mTBI participants, we observed a significant negative correlation ($r = -0.805$, $p < 0.001$) and positive correlation ($r = 0.793$, $p < 0.001$) between PSQI total scores and FA and RD, respectively. These correlations were observed bilaterally, primarily in the anterior and posterior limbs of the internal capsules, anterior and superior corona radiata, and superior fronto-occipital fasciculi.

Conclusions: We observed linear relationships between increasingly poor sleep quality, evidenced by increasing PSQI total scores, and lower white-matter fiber coherence (lower FA) as well as faster perpendicular water diffusion (higher RD). Increasing RD is an indicator of axon, and particularly myelin, damage [7,8]. Thus, poor sleep quality in our sample is associated with indicators of damage in white-matter tracts that are utilized in cognitive tasks (information

processing, attentional maintenance, executive function), emotion processing, and sleep regulation. Thus, damage to the association and projection white-matter tracts observed here may explain inter-related and overlapping post-mTBI sleep-related, emotional, and cognitive complaints [4,9]. Additionally, these findings support existing hypotheses that symptom manifestation following mTBI results from altered white-matter integrity, consistent with diffuse axonal injury models. Finally, these findings extend the currently available evidence for mTBI-related changes in white-matter integrity and pathways associated with clinically-relevant outcomes.

1. Asken BM, DeKosky ST, Clugston JR, Jaffee MS, Bauer RM. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): A systematic critical review. 2017 Mar 24:1–28. doi:10.1007/s11682-017-9708-9

2. Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, LaConte SM. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. 2014;4:283–294. doi:10.1016/j.nicl.2013.12.009

3. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. 2002;16(3):197–206. doi:10.1080/02699050110103940

4. Kontos AP, Covassin T, Elbin RJ, Parker T. Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. 2012;93(10):1751–1756. doi:10.1016/j.apmr.2012.03.032

5. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ, et al. Consensus statement on concussion in sport - The 5th international conference on concussion in sport held in Berlin, October 2016. 2017;51:838–847. doi:10.1136/bjsports-2017-097699

6. Ouellet M-C, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: A preliminary study. 2006;7(6):486–497. doi:10.1016/j.sleep.2006.03.017

7. Song S-K, Sun S-W, Ju W-K, Lin S-J, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. 2003;20(3):1714–1722. doi:10.1016/j.neuroimage.2003.07.005

8. Song S-K, Yoshino J, Le TQ, Lin S-J, Sun S-W, Cross AH, Armstrong RC. Demyelination increases radial diffusivity in corpus callosum of mouse brain. 2005;26(1):132–140. doi:10.1016/j.neuroimage.2005.01.028

9. Sufrinko A, Pearce K, Elbin RJ, Covassin T, Johnson E, Collins M, Kontos AP. The effect of preinjury sleep difficulties on neurocognitive impairment and symptoms after sport-related concussion. 2015;43(4):830–838. doi:10.1177/0363546514566193

Verbal Fluency following Mild Traumatic Brain Injury: The Strength of Switching

Natalie S. Dailey[1], Ryan Smith[1], Brieann C. Satterfield[1], Adam C. Raikes[1], and William D. S. Killgore[1]

[1]Social, Cognitive, and Affective Neuroscience Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

ABSTRACT

Clustering and switching abilities were investigated in 20 healthy-controls and 33 individuals with mTBI. We found that the number of reported mTBIs was associated with more clusters and that working memory positively predicted switching. More clusters may indicate impaired access to lexical-semantic knowledge in those with mTBI, resulting in a reliance on switching as an effective strategy for verbal fluency.

BACKGROUND

Over 1.5 million traumatic brain injuries (TBIs) are reported annually in the United States, and roughly 75% of reported cases are classified as mild. Mild TBI (mTBI) can result in a variety of cognitive deficits, including poor verbal fluency[1]. However, the extent to which mTBI-related deficits are associated with impaired verbal fluency is not well understood. Verbal fluency requires access to lexical-semantic knowledge as well executive functions, cognitive processes that can be measured through *clustering* (i.e. ability to generate words belonging to the same category) and *switching* (i.e. shifting from one category to another). In the present study, we hypothesized that individuals with mTBI would exhibit significantly reduced verbal fluency ability, compared to HCs. Furthermore, we explored lexical-semantic and executive function factors associated with clustering and switching abilities in those who have sustained an mTBI.

METHODS

Fifty-three participants were enrolled in the present study, including 20 healthy controls (HCs) and 33 individuals with mTBI. Those with mTBI were divided into one of two groups based on time since injury. The acute mTBI group (n = 16) included participants who were 2 or 4-weeks post-injury, and the chronic mTBI group (n = 17) included participants who were 6 or 12-months post injury. Injury severity was rated as mild based on Department of Defense guidelines[2]. All participants were between 18 and 40 years of age, native English speaking, and right handed. For participants with an mTBI, brain injury documentation from a medical or other relevant professional who either witnessed the event or was involved in immediate response or treatment was required prior to enrollment in the study. Exclusionary criteria included 1) a history of psychiatric or neurological disorder, 2) previous or ongoing alcoholism or substance abuse, 3) pregnancy, and 4) more than 3 TBIs in a lifetime. The current study was approved by the Institutional Review Board (IRB) at the University of Arizona and the U.S. Army Human Research Protections Office (HRPO), and all participants provided written informed consent prior to their participation. All participants completed an extensive battery of neuropsychological assessments, including a day of study questionnaire, the Wechsler Abbreviated Scale of Intelligence to assess IQ, the Delis-Kaplan Executive Functions System (D-KEFS) [3] to measure verbal fluency, the Psychological Vigilance Test to assess processing speed and reaction time, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to test working memory.

Verbal Fluency

Participants completed the phonemic fluency subtest of the D-KEFS, which requires participants to generate as many words as possible starting with the letters F, A, and S. Primary outcome measures included (1) number of correct words generated, (2) number of set-loss errors, and (3) number of repetition errors. Secondary outcome measures included mean number of clusters and mean number of switches[4]. The number of different cluster types were calculated for all participants. Cluster types

included consecutive words with the same initial phonemes (e.g. *full, fun*), rhyming words (e.g. *feet, fleet*), initial and final letter (e.g. *for, far*), homonyms (e.g. *four, for*), and semantic category (e.g. *seaweed, shell, seagull*).

RESULTS

The three groups were similar on age, sex, years of education, and intellectual ability. Contrary to our hypothesis, results from an analysis of covariance (controlling for the effects of age and gender) showed that the groups did not significantly differ on the number of words correctly produced ($F(2, 48) = 0.85$, $p = 0.43$), set-loss errors ($F(2, 48) = 0.07$, $p = 0.94$), or repetitions ($F(2, 48) = 1.48$, $p = 0.24$). The number of different cluster types significantly differed between the groups ($F(2, 48) = 4.24$, $p = 0.02$). Post-hoc comparisons determined that individuals in the chronic mTBI group used significantly fewer cluster types (M = 2.06; SD = 0.90), compared to HCs (M = 2.90; SD = 0.85). There were no significant differences between the chronic and acute mTBI groups, or between the acute mTBI and HC groups.

To assess underlying cognitive processes associated with verbal fluency following mTBI, lexical-semantic and executive function factors were entered into separate stepwise, linear regression models with clustering (mean number of clusters) and switching (mean number of switches) as the outcome variables. Number of mTBIs ($\beta = 0.54$, $p = 0.005$) was a significant predictor of clustering ability following an mTBI, accounting for 23% of the variance ($R^2 = 0.23$, $p = 0.005$), while working memory from the RBANS digit span ($\beta = 0.42$, $p = 0.003$) was a significant predictor of switching ability following mTBI, accounting for 25% of the variance ($R^2 = 0.25$, $p = 0.003$).

CONCLUSIONS

We found similar verbal fluency abilities between individuals in the acute phase of mTBI-recovery, chronic phase of mTBI-recovery, and HCs. However, those in the chronic mTBI group used significantly fewer clustering strategies compared to HCs, suggesting an overreliance on one type of strategy to maintain sufficient performance on verbal fluency. Following mTBI, switching was associated with working memory, and is consistent with previous literature in healthy individuals[5]. Interestingly, more reported mTBIs were associated with a greater number of clusters produced, suggesting that those with mTBI may struggle to access lexical-semantic knowledge within categories, resulting in more frequent category switches, a strategy associated with greater verbal fluency performance across participant groups.

Learner Outcomes

After attending this research session, participants will be able to compare and contrast clustering and switching, as related to a verbal fluency task.

After attending the research session, participants will be able to describe the lexical-semantic and executive function factors that significantly predict clustering and switching ability in those with mTBI.

After attending this research session, participants will be able to explain how switching is a successful strategy on a verbal fluency task, for those with mTBI.

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-12-0386), 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

Carroll, L., Cassidy, J. D., Peloso, P., Borg, J.,... & Pépin, M. (2004). Prognosis for mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Journal of Rehabilitation Medicine, 36(0), 84-105.

Department of Veterans Affairs/Department of Defense. (2009). VA/DoD Clinical Practice Guideline for Management of Concussion/mild Traumatic Brain Injury. Available at: www.healthquality.va.gov/guidelines/Rehab/mtbi/concussion_mtbi_full_1_0.pdf.

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). The Delis Kaplan Executive Function System: Examiner's Manual. San Antonio: The Psychological Corporation.

Troyer, A.K., Moscovitch, M., and Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. *Neuropsychology* 11(1)**,** 138-146. doi: 10.1037//0894-4105.11.1.138.

Unsworth, N., Spillers, G.J., and Brewer, G.A. (2011). Variation in verbal fluency: a latent variable analysis of clustering, switching, and overall performance. *Q J Exp Psychol (Hove)* 64(3)**,** 447-466. doi: 10.1080/17470218.2010.505292.

Time-Ordered Agenda

A Technical Research Session (30 minutes) is requested for the current submission. The time-ordered agenda allows for a 20-minute presentation and 10 minutes for questions and answers.

2 minutes – Introduction and Disclosures
5 minutes – Theoretical Background and Hypotheses
5 minutes – Methods
5 minutes – Results
3 minutes – Conclusion and Clinical Implications
10 minutes – Questions and Answers

Reduced Information Processing Speed: A Dynamic Deficit in Mild Traumatic Brain Injury

Brittany Forbeck[1], Natalie S. Dailey[1], Simon Esbit[1] and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

ABSTRACT

Thirty-two young adults participated in the study, including 11 healthy controls, 10 adults in the acute mTBI group (3-months or less post-mTBI), and 11 adults in the chronic mTBI group (6-months or more post-injury). We found reduced information processing speed only in the chronic mTBI group, compared to healthy controls, suggesting that observed cognitive deficits may be dynamic throughout recovery.

BACKGROUND

Mild traumatic brain injury (mTBI) is one of the most common injuries sustained by Service members. Importantly, mTBI can subtly and microscopically alter the structure of the brain resulting in a constellation of symptoms, including attention and memory deficits, reduced processing speed, and poor inhibitory control (Bigler & Maxwell). Impaired cognitive functioning is often reported following mTBI, however the recovery trajectory of such abilities remains poorly understood. Therefore, the current study aims to determine whether executive function (i.e. processing speed and sustained attention) is similar in the acute and chronic stages of recovery. We predicted reduced executive function in adults with mTBI compared to healthy controls. For those with mTBI, we hypothesized that adults in the acute stage of recovery (i.e. 3-months or less post-injury) would exhibit greater deficits in processing speed and sustained attention, compared to adults in the chronic stage of recovery (i.e., 6-months or more post-injury).

METHODS

Thirty-two right-handed adults participated in the current study, including 11 healthy controls (M_{age} = 24.54; SD = 3.27), 10 adults in the acute mTBI group (M_{age} = 24.01; SD = 6.45) and 11 adults in the chronic mTBI group (M_{age} = 24.04; SD = 5.90). Injury severity was rated as mild based on Department of Defense guidelines (DoD, 2009), and all participants were between 18 and 35 years of age, native English speakers, and right handed. Exclusionary criteria included 1) a history of psychiatric or neurological disorder, 2) previous or ongoing alcoholism or substance abuse, 3) pregnancy, and 4) more than 3 TBIs in a lifetime. The current study was approved by the Institutional Review Board (IRB) at the University of Arizona and the U.S. Army Human Research Protections Office (HRPO), and all participants provided written informed consent prior to their participation. All participants completed a day of study questionnaire providing demographic and time-since injury information, the Wechsler Abbreviated Scale of Intelligence to assess IQ, and the Psychomotor Vigilance Test (PVT) to measure processing speed and sustained attention.

RESULTS

The three groups did not significantly differ on age, years of education, or IQ. An analysis of covariance was used to compare executive function abilities between the three groups, while controlling for age and IQ. The groups significantly differed on reaction time ($F(2,33) = 3.66$, $p = .037$, $\eta^2 = .18$), but not false starts ($F(2,33) = .86$, $p = .432$, $\eta^2 = .05$), suggesting slowed processing speed but intact sustained attention. Post-hoc analyses showed that reaction time was significantly reduced in the chronic mTBI group (M = 321.39, SD = 11.012), compared to HCs (M = 276.97; SD = 12.04) ($p < .05$; FDR-corrected). Reaction time did not significantly differ between adults in the acute compared to chronic stage of recovery, or between the acute mTBI and HC groups.

CONCLUSIONS

Overall, we found that adults with mTBI, who are in the chronic stage of recovery, displayed reduced processing speed, but intact sustained attention. Contrary to our hypotheses, individuals with mTBI who are in the acute stage of recovery did not exhibit deficits in processing speed or sustained attention, responding similar to healthy controls. One possible explanation for the observed discrepancy between acute and chronic mTBI groups is that adults who are in the chronic phase of recovery may be more likely to participate in research studies if they continue to experience mTBI-related symptoms, while those in the acute mTBI group may be more likely to participate regardless of symptomology. Another interpretation of the current findings is that recovery from mTBI may represent a dynamic process in which symptoms present during the acute phase may not be present in the chronic phase and vice versa. Ongoing research is necessary to identify potential underlying neural mechanisms associated with the onset and duration of injury-related deficits. Furthermore, the manifestation of cognitive deficits at different times post-injury suggests that individuals may benefit from clinical support and/or intervention at different times following an mTBI.

Bigler, E. D., & Maxwell, W. L. (2012). Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging Behav, 6*(2), 108-136. doi:10.1007/s11682-011-9145-0

Department of Veterans Affairs/Department of Defense. (2009). VA/DoD Clinical Practice Guideline for Management of Concussion/mild Traumatic Brain Injury.

Learner Outcomes:

After completing this activity, participants will be able to:

1. Identify common cognitive deficits associated with mild traumatic brain injury.
2. Describe what is meant by ‘dynamic’ cognitive deficits following mild traumatic brain injury.
3. Explain the potential clinical implications associated with cognitive deficits that are dynamic.

Identifying Memory Retrieval Strategies Following a Mild Traumatic Brain Injury Using the CVLT-II

Corinne Meinhausen[1], Natalie S. Dailey[1], and William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Objective:
Mounting evidence suggests learning, memory and attentional deficits occur in the acute stage of mild traumatic brain injury (mTBI). However, the extent to which these deficits remain longer than 12 weeks is unclear. This study aimed to identify memory retrieval strategies used in the acute and chronic stages post-mTBI. It was predicted that the use of serial and semantic clustering would differ in the acute stage (2-12 weeks) compared to adults the chronic stage (6-12 months) and healthy controls.

Participants and Methods:
A total of 69 adults participated in the study and included 20 HCs, 26 adults in the acute phase, and 23 adults in the chronic phase. The California Verbal Learning Test, 2nd Edition (CVLT-II) was administered to identify the use of memory retrieval strategies including serial and semantic clustering. Serial clustering involves recalling words in the order in which they were heard and semantic clustering is a secondary memory strategy in which words are grouped by meaning.

Results:
Raw semantic and serial clustering scores were compared between the acute, chronic and HC groups using one-way ANOVAs. There was a main effect of group on serial clustering ($F(2,66)=3.142$, $p=0.05$, partial eta-squared=0.87). Post-hoc comparisons showed the acute group had significantly fewer serial clusters than HCs ($p=0.03$) and the chronic group ($p=0.04$). There was also an observed tendency in the acute group to perform semantic clustering over the HCs and the chronic group.

Conclusions:
Our findings show that serial recall was reduced in the acute group relative to the chronic and HC groups, suggesting the use of different memory retrieval strategies. These findings, in addition to an increased tendency to use semantic clustering may indicate a compensatory effect during early mTBI recovery in response to deficits in the memory process.

White Matter Structure Changes Associated with Depressive Symptoms Following Recent Mild Traumatic Brain Injury

Adam C. Raikes[1], Natalie S. Dailey[1], Sahil Bajaj[1], William D.S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

Background: Individuals with a history of mild traumatic brain injury (mTBI) often report subsequent onset of psychological distress, including depression. While these associations between mTBI and depression are known, there is little research supporting these observations from a neurophysiological perspective. The purpose of this study was to examine white-matter correlates of depression in mTBI.

Methods: As part of a larger DoD-funded study, 34 individuals with a recent mTBI (<12 months) and 16 individuals with no history of mTBI (HC) completed a comprehensive neuropsychological battery, including the Beck Depression Index (BDI), and neuroimaging protocol, including diffusion-weighted imaging (DWI). Diffusion-weighted images were analyzed using a standardized processing pipeline, yielding four diffusion-related metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Between-group whole-brain differences were computed, controlling age and sex, for each DWI metric. Within-group whole-brain correlations were computed between the DWI metrics and total BDI scores, controlling age, sex, and days post-injury (mTBI only). Post-hoc correlation values were computed as the mean DWI-metric value over all significant voxels.

Results: BDI scores were higher in the mTBI group than the HC group (Mann-Whitney U=89.5, p=0.0001). There were no between-group differences for any DWI metric. Additionally, no significant correlations were observed in the HC group. However, for mTBI, significant negative correlations between FA and BDI (r=-0.742, p<0.0001) were observed in one cluster. Significant positive correlations between MD and BDI (r=0.732, p<0.0001) and RD and BDI (r=0.762, p<0.0001) were observed in two and nine clusters, respectively. Correlations were primarily observed in the left and right anterior thalamic radiations.

Conclusions: Increasing depression symptoms, reported on the BDI, in individuals with a recent mTBI are linearly associated with white matter structure metrics throughout the brain. Specifically, this relationship manifests as lower white-matter fiber coherence (FA) and potentially reduced myelination and/or axonal density (RD). These findings are consistent with the proposal that functional outcomes following mTBI are the result of diffuse axonal injuries, affecting long, anterior-posterior white-matter tracts. The present findings extend the current evidence for changes in white-matter architecture following mTBI, which correlate with clinically-relevant outcomes.

Trait Anxiety Predicts Hostile Tendencies Post-Traumatic Brain Injury

Anmol Singh[1], Matthew D. Thurston[1], Melissa K. Gottschlich[1], Michael A. Miller[1], & William D.S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Lab, Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ

Background:
Uninhibited anger and aggression are commonly reported symptoms following a mild traumatic brain injury (mTBI), however, the mechanisms responsible for characterizing these behaviors are still unclear. We hypothesized that one such explanation may be that it is the result of a heightened state of anxiety. To elucidate the manifestation of pathological aggression, we tested our hypothesis by investigating the direct relationship between trait anxiety and hostility in individuals with a recent (<12 months) mTBI in comparison to healthy controls (HC).

Methods:
Fifty-seven right-handed individuals (23 males, mean age=23.2), consisting of 38 patients with a medically documented history of mTBI within the past 12 months, and 19 HC, were recruited. Trait anxiety and hostility were measured using the State-Trait Anxiety Inventory (STAI) and the Buss-Perry Aggression Questionnaire (BPAQ), respectively. All statistical analyses were performed using SPSS 24.0.

Results:
Within 1000 bootstrap samples, individuals with a mTBI displayed significantly greater trait anxiety (M = 35.79, SE = 1.40) than those with no history of TBI (M = 30.84, SE = 1.59), $t(55)$ = 2.17, p = .028, *Cohen's d* = 0.63. Furthermore, a linear regression, using 1000 bootstrap samples, showed that greater trait anxiety predicted hostile tendencies (p = 0.002) in mTBI $F(1,37)$ = 13.05, p = 0.001, R^2 = .27, but not in HC $F(1,18)$ = 0.57, p = 0.461, R^2 = .03.

Conclusion:
Individuals that have recently (within 12 months prior) suffered an mTBI showed greater trait anxiety than healthy controls. Greater trait anxiety predicted hostile tendencies in mTBI patients only. There were no sex differences observed in anxiety or hostility post-TBI. This implies there is an underlying pathological explanation for the hostile behaviors presented in mTBI patients. The data suggests that the onset of post-TBI psychological conditions, such as heightened threat perceptivity (i.e., anxiety), may be the causal link to a predisposition for hostile tendencies. Thus, we conclude that trait anxiety is significantly associated with the manifestation of hostile behaviors in mTBI patients, and may be a focal symptom to target in clinical treatments.

Increased Cerebellar Grey Matter in the Presence of Decreased Subjective Sleep Quality Following Mild Traumatic Brain Injury

Adam C. Raikes[1], William DS Killgore[1]

[1]Social, Cognition, Affect Neuroscience Lab, Department of Psychiatry, University of Arizona

Objective: Individuals with a history of mild traumatic brain injury (mTBI) often report insomnia, disturbed sleep, and lower general sleep quality than individuals with no history of concussion. These subjective complaints may persist long after injury, even without objective evidence of reduced sleep quality. To date, no neural correlates of such subjective complaints have been identified. In the present study, we correlated whole-brain grey matter with Pittsburgh Sleep Quality Index (PSQI) total scores in individuals within one year of an mTBI.

Participants and Methods: 39 right-handed individuals with a self-reported history of mTBI (14 males; mean age: 24.17 ± 7.11y) were administered the PSQI as part of a larger on-going study. Additionally, we obtained T1 high-resolution structural scans, which were segmented and normalized (CAT12) and smoothed (SPM12) prior to voxel-based morphometric analysis. Whole-brain grey matter volume (GMV) was correlated with total PSQI scores, after controlling for age, sex, total intracranial volume, and time since most recent mTBI. GMV in significant clusters was exported for further analysis.

Results: GMV in a cluster including portions of the left cerebellum's lobules 7 and 8 positively correlated with total PSQI score (FWE corrected, $p = 0.019$), indicating worse sleep. GM volume in this cluster was additionally significantly negatively correlated with faster psychomotor vigilance task mean reaction time ($R2 = 0.099$) and positively with PVT reaction time coefficient of variation ($R2 = 0.137$). PSQI total scores did not correlate with any PVT measures and prevented further mediation analysis.

Conclusions: Individuals with mTBI who reported lower sleep quality had greater GMV in the left cerebellum. The lack of correlation between total PSQI and PVT performance metrics suggests that increased GMV in the cerebellum may be a compensatory mechanism for maintaining task performance in spite of perceived sleep decrement following mTBI.

Abstract 2 for Organization for Human Brain Mapping (OHBM) 2017

Title: Dynamics of brain's cortical measures following a mild traumatic brain injury

Sahil Bajaj*[1], Anna Alkozei[1], & William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, University of Arizona, Tucson, AZ, USA.

Characters limit: 4000
Figure/table limit: 2

Email: sahil.neuro@gmail.com

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.

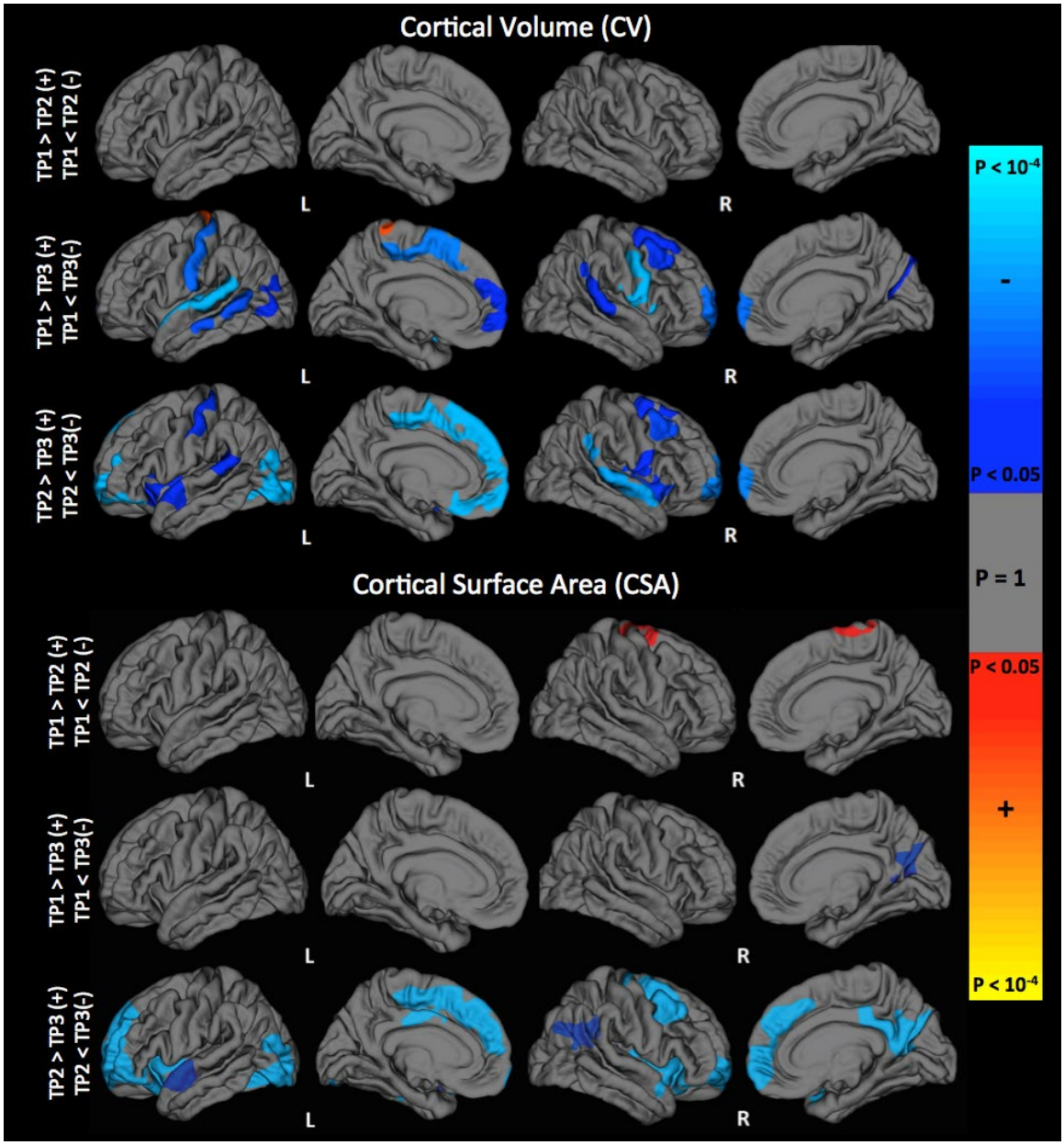


Table 1 Correlations between cortical measures and behavioral measures

#	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**

Abstract 2 for Society of Biological Psychiatry (SOBP) Meeting 2017

Title: Automatic brain recovery following a mild traumatic brain injury

Sahil Bajaj*[1], Anna Alkozei[1], & William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, University of Arizona, Tucson, AZ, USA.

Word limit: 250

**Email: sahil.neuro@gmail.com*

Background: Mild Traumatic Brain Injury (mTBI) might be responsible for unwanted alterations in brain's functional and cortical measures such as cortical thickness (CT), cortical volume (CV), cortical surface area (CSA), leading to several post-concussion symptoms. The mechanisms underlying brain recovery following a mild traumatic brain injury (mTBI) and associated changes in these measures are poorly understood.

Methods: We studied time-dependent differences in brain's CT, CV, CSA and neuropsychological functioning (daytime sleepiness, attention, and depression) for 54 mTBI survivors- within and across three time-points (N=18, 0-3 months post mTBI; N=22, 3-6 months post mTBI and N=14, >6 months post mTBI).

Results: We find that while CT did not change significantly after 3 months following mTBI, CV increased during this period and continued increasing even after 6 months. Also, CSA did not change prior to 6 months after mTBI but increased significantly after 6 months following mTBI compared to the first 3 months. Further, increases in CV and CSA with time and concomitant decreased daytime sleepiness and depression suggests that these time-dependent changes in brain structure are associated with improved functionality of the brain.

Conclusions: Our results suggest a complex picture of brain recovery processes following an mTBI. These findings provide preliminary guidelines for interpreting brain recovery following mTBI and may contribute to the development of more effective rehabilitation techniques for concussion survivors. A comparison of such functional and cortical measures of mTBI survivors with a control data set would further strengthen these findings. Such work is underway in our lab.

Post-Concussion Severity is Associated with Sleep Problems and Neuropsychological Status

Melissa K. Gottschlich, Simone Hyman, Melissa Milan, Derek Pisner, Anmol Singh, Sara A. Knight, Michael A. Grandner, & William D. S. Killgore

Mild traumatic brain injury (mTBI) is often associated with sleep problems. However, little is known about the relationship between sleep problems, post-concussion symptom severity, and common cognitive deficits such as difficulties with verbal fluency when given a category. We investigated whether post-concussive symptom severity was associated with sleep problems and deficits in verbal fluency in a sample of recent concussion survivors.

26 adults (11 males; 18-45 years old) with a documented history of mTBI within the preceding 12 months underwent a comprehensive neuropsychological test battery including the Rivermead Post Concussion Symptom Questionnaires (RPCSQ) and the verbal fluency subtest from the Delis-Kaplan Executive Function System (D-KEFS) to assess post-concussive symptom severity and word retrieval skills, respectively. A questionnaire was also administered to collect information about sleep habits, details of brain injury, and demographics.

Post-concussion symptom severity (RPCSQ) was associated with more severe self-reported sleep problems after the injury ($r=.62$, $p=.001$). In particular, symptom severity was associated with greater feelings of drowsiness when trying to concentrate ($r=.65$, $p<.001$), greater sleepiness during the day ($r=.66$, $p<.001$), feeling restless ($r=.42$, $p=.035$), and more frequent awakening throughout the night ($r=.429$, $p=.032$). Higher RPCSQ scores were also correlated with lower category fluency scores ($r=-.415$, $p=.039$). The deficits in category fluency were related to greater sleepiness during the day ($r=-.410$, $p=.037$).

These results suggest that post-concussive symptom severity is directly associated with greater severity of self-perceived sleep difficulties and poorer verbal category fluency. Notably, the sleep problems were also associated with the severity of word retrieval problems, raising the possibility that some cognitive deficits following concussion may be secondary to sleep-related issues. Future work will explore the mediating role of sleep between concussion severity and neuropsychological performance.

Neural Correlates of Aggression during Chronic and Post-acute Stages of Recovery from Mild Traumatic Brain Injury

Natalie S. Dailey[1], Sahil Bajaj[1], Anna Alkozei[1], & William D. S. Killgore[1]

[1]Social, Cognitive and Affective Neuroscience Laboratory (SCAN Lab), Department of Psychiatry, University of Arizona, Tucson, AZ, USA.

Background

Mild traumatic brain injury (mTBI) is one of the leading injuries among Service members returning from the recent conflicts in Iraq and Afghanistan, and is often associated with chronic post-concussive symptoms. Affected personnel often report increases in aggression following an mTBI, but the underlying neural correlates of such behavioral changes are not well understood. This is, in part, because neural consequences of mTBI are difficult to identify using conventional imaging methodology. Diffusion tensor imaging (DTI) is a neuroimaging approach used to detect microstructural changes to white matter pathways. We investigated the neural correlates of aggression in two different groups of adults with mTBI – those at a post-acute vs. chronic phase of recovery.

Methods

Twenty-four right-handed adults with mTBI, ranging from 18 to 45 years of age, were recruited. MTBI was clinically defined as loss of consciousness less than 30 minutes and posttraumatic amnesia less than 24 hours. Twelve participants (M = 25.25; SD = 8.58; 6 female) were included in the post-acute group (1 month or less post-TBI) and 10 participants (M = 22.40; SD = 6.38; 7 female) were included in the chronic group (6 months or greater post-TBI). Aggression was measured using the Buss Perry Aggression Questionnaire.

Neuroimaging

DTI data were obtained using single-shot echo planar imaging (EPI). Diffusion gradients were applied along 78 directions using b-value of 0 and 1000 s/mm^2. DTI sequences were acquired in the axial plane with 78 contiguous sections (thickness = 2 mm; voxel size = 2 x 2 x 2 mm; TR = 9600; TE = 88; FOV = 100; matrix = 128 x 128 x 74). Fractional anisotropy and mean diffusivity maps were created using the FSL Diffusion Toolbox. Voxel-wide analysis of fractional anisotropy (FA) was carried out using Tract-Based Spatial Statistics (TBSS). The relationship between white matter structure and aggression was investigated using a general linear model in FSL.

Results

The chronic and post-acute groups did not significantly differ on age, years of education, or IQ. Additionally, the two groups did not differ on the self-report measure of aggression (t(1,20) = .70, p > .05). Positive linear relationships between FA and aggression were found in frontal and temporal pathways for the chronic group. Only clusters containing more than 20 voxels are reported (threshold of p < .05, corrected for multiple comparisons). Higher levels of aggression were correlated with increased fractional anisotropy in the superior longitudinal fasciculus, bilaterally, left inferior fronto-occipital fasciculus, body of the corpus callosum, and genu of the corpus callosum.

Conclusions

White matter integrity, as measured by FA, was positively associated with greater aggression scores, but only among those in the chronic phase of recovery from mTBI. This suggests that the associations between large tract myelination and emotional behavior are complex and

dynamic throughout the recovery process and cannot be fit to a single static model that does not consider time since injury. Future comparisons with healthy controls will clarify whether these data reflect a pathological worsening or a normalization with time since injury.

A Voxel Based Morphometric Analysis of Ventromedial Prefrontal Cortex Volume related with Executive Function Task Performance Post Mild Traumatic Injury

Prabhjyot Singh, Derek Pisner, Andrew Fridman, Anmol Singh, Melissa Millan, William D Killgore

Objective:
Recovery from mild traumatic brain injury (mTBI) is usually complete within a matter of days or weeks. A substantial minority of patients, however, will show persistent symptoms and mild cognitive complaints for much longer. We investigated the time dependent effects of mTBI on gray matter volume (GMV) and its relationship with performance on executive function tasks up to one year post injury.

Participants and Methods:
Voxel based morphometric analysis (VBM8) was used to analyze T1 high resolution structural scans of 26 right handed mTBI participants (mean age=23.38) and 12 healthy control participants (mean age=25.00). VBM data were correlated with time since injury, and compared to healthy controls. Data were then extracted and correlated with metrics from the Delis-Kaplan executive function system (DKEFS).

Results:
After controlling for age, gender and intracranial volume (ICV), GMV in ventromedial prefrontal cortex (VMPFC) correlated positively with time since injury (FWE corrected, $p<0.05$), and this cluster correlated with performance on several DKEFS tasks such as DKEFS-design fluency 1 (R^2 =0.177), DKEFS-design fluency 2 (R^2 = 0.164) and DKEFS-sorting test (R^2 = 0.230). Moreover, the larger GMV seen among the more chronic individuals was significantly greater than healthy controls, suggesting possible enlargement of these regions with time since injury.

Conclusions:
These findings are interpreted in light of burgeoning evidence suggesting that cortical regions often exhibit structural changes following experience or practice, and suggest that with greater time since an mTBI, the brain displays compensatory remodeling of cortical regions involved in emotional regulation, which may reduce distractibility during attention demanding visuo-motor tasks.

Resilience Following Mild Traumatic Brain Injury is associated with Gray Matter Volume in the Left Precentral Gyrus

Derek Pisner, Prabhjyot Singh, Andrew Fridman, & William D.S. Killgore

Objective

The ability to rebound from disruptive life challenges, often referred to as "cognitive resilience," is known to contribute to more successful outcomes following mild traumatic brain injury (mTBI). Since the neurobiological profile of resilient individuals following mTBI has yet to be established, the present study investigated the relationship between resilience and gray matter volume (GMV) in individuals who have recently incurred an mTBI.

Participants & Methods

Twenty-six right-handed mTBI participants (11 males, mean age = 23.4) underwent high resolution T1 structural neuroimaging and completed the Connor-Davidson Resilience Scale (CD-RISC), a Likert-type self-report assessment of personality traits that enable one to thrive in the face of adversity. Controlling for time since injury, intra-cranial volume, age, and gender, a voxel-based morphometric (VBM) multiple regression analysis was used to explore the association between GMV in the frontal lobe and CD-RISC scores.

Results

Utilizing a small volume correction (SVC) for the frontal lobe, CD-RISC scores were found to be positively correlated with greater GMV in the left precentral gyrus (13 voxels, $p<.05$, FWE corrected). Exploratory analysis further revealed that this association is significantly more prominent in the acute (less than 3 months), as opposed to the chronic stage (between 3 and 12 months) following an mTBI.

Conclusions

The present findings suggest that GMV in the left precentral gyrus may predict cognitive resilience following an mTBI. Although the precentral gyrus is primarily thought to be responsible for voluntary movement, studies have shown that the left precentral gyrus may be associated with subthreshold depression risk and negative self-attributional bias in response to adverse life events. Early identification of gray matter deficits in this region following mTBI may therefore alert clinicians to the need to devote greater attention towards cultivating cognitive resilient skills.

Time Dependent Differences in Gray Matter Volume in Individuals Post Mild Traumatic Brain Injury: A Voxel Based Morphometric Study

Prabhjyot Singh, Andrew Fridman, Derek Pisner, William D.S. Killgore

Objective:
Mild Traumatic brain injury (mTBI) is known to cause diffuse axonal injury, but may also affect gray matter (GM) structures in the brain. This damage is dependent on multiple factors such as site of injury and time since injury (TSI), which can vary clinical manifestations of mTBI. Due to their location, the occipital and temporal lobes have shown to be prone to the effects of mTBI. Damage to these regions may lead to disturbances in the visual pathways and object and facial recognition.

Participants and Methods:
Twenty-six right-handed mTBI individuals participated in the study. Two groups were formed on the basis of TSI: 13 acute (≤92 days) and 13 chronic (>92days). Voxel-based morphometry (VBM8) was used to analyze T1 high-resolution structural magnetic resonance imaging (MRI) scans. Segmented GM images were analyzed to determine regions in which acute and chronic groups had significant differences in volume.

Results:
After controlling for age, gender and intra-cranial volume, the acute group had significantly ($p<0.05$, FDR corrected) less GM volume in the right fusiform gyrus and right inferior temporal gyrus as compared to the chronic group. The fusiform gyrus region was found to be significantly correlated ($R^2 = 0.172$) with the psychomotor vigilance task (PVT) average reaction time performance as compare to chronic group ($R^2 =0.044$).

Conclusions:
Significant differences were found in GM volumes in the acute and chronic groups particularly in the regions involving ventral visual processing. This finding shows that some of the visual processes in the acute phase of mTBI might be compromised more as compared to chronic phase. Early intervention post mTBI might be helpful at this stage. Future studies will need to examine other effects of mTBI in acute and chronic stages, which can help in developing better targeted intervention strategies.

Gray Matter Volume in Left Medial Prefrontal Cortex Is Related to Life Satisfaction in Individuals with Mild Traumatic Brain Injury

Andrew Fridman, Derek Pisner, Prabhjyot Singh, & William D.S. Killgore

Objective
The prefrontal cortex (PFC) is involved in linking emotion and motivation with situational appraisal to influence goal directed behavior. Considerable evidence supports the functional asymmetry of the PFC for emotional processes, where the left hemisphere is biased toward positive and approach emotions, and the right hemisphere is biased toward negative and withdrawal emotions. We hypothesized that gray matter (GM) volume in the PFC of individuals who have incurred mild traumatic brain injury (mTBI) would correlate with life satisfaction in accordance with prior models of affective asymmetry.

Participants & Methods
Twenty-six right-handed mTBI participants (11 males, mean age = 23.4) underwent high resolution T1 structural neuroimaging and completed the Satisfaction with Life Scale (SWLS). After covarying for age, gender, time since injury and intra-cranial volume, a voxel-based morphometric (VBM) multiple regression analysis was conducted within Statistical Parametric Mapping (SPM8) to explore the association between gray matter volume in the PFC and SWLS scores.

Results
Utilizing a small volume correction for the frontal lobe region-of-interest (ROI), greater GM volume in the left hemisphere of the superior frontal gyrus was positively correlated with SWLS scores (7 voxels, $p<0.05$, FWE corrected). No association was found in the right PFC.

Conclusions
Consistent with the theory of lateralized affective processing, we find that greater volume of the left anterior prefrontal cortex was associated with greater satisfaction with life among individuals with recent brain injuries. Future work should compare these findings to that of healthy controls and whether larger left PFC volume might be predictive of subsequent recovery. Considering the detrimental effects on mood that individuals often experience following mTBI, brain-imaging techniques like VBM can be used to aid risk assessment for subsequent mood changes.

Volumetric Differences in Gray Matter in Healthy Versus Overweight Individuals Post Mild Traumatic Brain Injury: A Voxel Based Morphometric Study

Prabhjyot Singh, Derek Pisner, Andrew Fridman, William D.S. Killgore

Objective:
Mild traumatic brain injury (mTBI) typically involves diffuse injury to axonal pathways, but may also affect core gray matter structures. Due to its location deep within the brain, the striatum is often vulnerable to damage during mTBI. Striatal damage could have important implications for behavior, as this region plays a critical role in cognition, reward processing, and motivation, including food consumption. In the present study, we compared the whole brain gray matter volume of healthy normal weight individuals versus overweight/obese individuals with recent history of mTBI.

Participants and Methods:
Participants included twenty four right handed mTBI individuals,12 healthy (BMI ≤ 25) and 12 overweight (BMI > 25). Voxel-based morphometry (VBM8) was used to analyze T1 high resolution magnetic resonance imaging (MRI) structural scans. Segmented gray matter images were analyzed to determine regions in which healthy and overweight groups were different.

Results:
After controlling for age, gender, intra-cranial volume, and time since injury, gray matter volume was significantly greater ($p<0.005$) in the healthy group compared to the overweight group in a number of brain regions, including the bilateral caudate nucleus (head) regions, nucleus accumbens, bilateral parahippocampal gyrus, left inferior temporal gyrus, and left medial frontal gyrus.

Conclusions:
Significant differences in gray matter volumes were found between healthy and overweight individuals, particularly within regions involved in reward, executive functioning, memory, and emotion. Interestingly, the direction of findings for the ventral striatum is opposite of that often reported for non-brain injured individuals, raising the possibility that mTBI might alter these associations. Future research will need to examine the role of mTBI in weight gain and motivational deficits relative to non-injured individuals.

A Voxel Based Morphometric Analysis of Ventromedial Prefrontal Cortex Volume related with Executive Function Task Performance Post Mild Traumatic Injury

Prabhjyot Singh, Derek Pisner, Andrew Fridman, Anmol Singh, William D Killgore

Objective:
Mild traumatic brain injury (mTBI) is often associated with subtle changes in executive functions. The frontal lobes, which contribute to complex executive functioning, are extremely vulnerable to traumatic brain injury because of their size and location. Ventromedial prefrontal cortex (VMPFC) is one of the areas of prefrontal cortex closely associated with executive function tasks such as decision-making, judgment and self-monitoring. It is not known how the VMPFC and its associated capacities change during the months following an mTBI. We investigated the time dependent effects of mTBI on the volume of VMPFC and its relationship with performance on executive function tasks.

Participants and Methods:
Voxel based morphometric analysis (VBM8) was used to analyze T1 high resolution structural scans of twenty six right handed mTBI participants (mean age=23.38). Segmented images were used to create a custom DARTEL template, and then images were normalized and smoothed prior to analysis. VBM data were correlated with time since injury. The volume data from the resulting cluster were then extracted and correlated with metrics from the Delis-Kaplan executive function system (DKEFS).

Results:
After controlling for age, gender and intracranial volume (ICV), GM volume in VMPFC correlated positively with time since injury (FWE corrected, $p<0.05$). VMPFC volume from this cluster was also found to be positively correlated with performance on several DKEFS tasks such as DKEFS-design fluency 1 (R^2 =0.177), DKEFS-design fluency 2 (R^2 = 0.164) and DKEFS-sorting test (R^2 = 0.230).

Conclusions:
VMPFC volume was greater with longer time since injury post mTBI. While causal inference cannot be made, we speculate that the greater volume in VMPFC with longer time since injury might reflect a compensatory phenomenon of neural plasticity aiding in recovery of cognitive functions post mTBI. Future work should examine whether such volume changes can be facilitated by cognitive training.

Neural Correlates of Cognitive and Emotional Impairments in Acute Versus Chronic Mild Traumatic Brain Injury: a Diffusion Tensor Imaging Study.

Aleksandra Klimova, Derek Pisner, William D. Killgore

Objective: Mild traumatic brain injury (mTBI) is a neurological insult, commonly associated with physical complaints, emotional problems and cognitive deficits. MTBI has been frequently referred to as an "invisible injury" as it can be hard to diagnose while potentially having devastating effects on the individual. Recent studies suggest that neural and psychological profiles of this condition may be time-dependent. In the present study we examined white matter (WM) integrity of individuals in the acute versus chronic phases of mTBI.

Participants and Methods: Thirty healthy controls and 26 mTBI participants (14 acute (<3 months post-injury); 12 chronic (>6 months post-injury to 1 year)). A 3T spin-echo DTI-Echo Planar Imaging sequence was used to acquire diffusion-weighted images (DWIs). Seventy contiguous, axial, 2.0 mm-thick slices were acquired in 72 directions. Data were analyzed using Tract-Based Spatial Statistics (TBSS) and correlated with several behavioral outcome measures.

Results: Both acute and chronic mTBI were associated with reduced WM integrity as indicated by reduced FA compared to healthy controls (p<.05; family-wise error (FWE) corrected). There was also a trend increase in FA in the acute mTBI group compared to the chronic group in the right superior corona radiata (p <.1; FWE corrected). Across all mTBI participants, decreased FA was associated with significantly increased sleep impairment, greater post concussive symptoms, decreased vigilance, greater hostility and lower resilience. In the acute group, decreased FA was associated with increased aggression, whereas there was no such association in the chronic group.

Conclusions: Results indicate that both acute and chronic mTBI are characterized by compromised WM coherence with a trend towards decreased WM integrity among patients with chronic versus acute mTBI. These WM reductions are associated with increased cognitive and emotional problems, particularly among those in the chronic stage.

Curriculum Vitae

DATE PREPARED: **January 23, 2020**

NAME: WILLIAM DALE (SCOTT) KILLGORE

OFFICE ADDRESS: 7303B
Department of Psychiatry
University of Arizona HSC
1501 North Campbell Ave.
PO Box 245002
Tucson, AZ 85724 United States

WORK PHONE: (520) 621-0605

WORK EMAIL: Killgore@psychiatry.arizona.edu

WORK FAX: (520) 626-6050

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 - 6/17	Associate Professor of Psychology in the Department of Psychiatry 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 Postdoctoral Research Program Training Supervisor, Walter Reed Hospital, Washington, DC
8/07 -6/17	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
1/19-	Senior Statistical Analyst: TechWerks, LLC; 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
2018-2020 Long-Distance High School Research Mentor, Taleen Postian, Byram Hills HS, NY
2019 External Reviewer, Doctoral Thesis Reviewer, William Ryan McMahon, Monash University, Australia.
2020- Long-Distance High School Research Mentor, Shivani Desai, Phoenix, AZ

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
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
2019-2020	Member, Masters Thesis Committee, Veronica Kraft, Department of Psychology, University of Arizona, Tucson, AZ

2019-2020 Faculty Advisor, Undergraduate Honors Thesis Committee, Giovanna Gutierrez, Department of Neuroscience and Cognitive Science, University of Arizona, Tucson, AZ
2019-2020 Faculty Advisor, Undergraduate Honors Thesis Committee, Corinne Meinhausen, Department of Neuroscience and Cognitive Science, University of Arizona, Tucson, AZ
2019-2020 Faculty Advisor, Undergraduate Honors Thesis Committee, Jared Kleiner, Department of Neuroscience and Cognitive Science, University of Arizona, Tucson, AZ
2020 Member, Comprehensive Examination Committee, Sophie Pinkston, Department of Psychology, University of Arizona, Tucson, AZ
2020- Co-Chair, Dissertation Committee, John Vanuk, Department of Psychology, University of Arizona, Tucson AZ.
2020- Member, Comprehensive Examination 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
2020 Sleep & Circadian Science Center Construction Manager at Risk Search Committee, Tucson, AZ
2020- Sleep & Circadian Science Center Oversight Committee, 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 (106 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
2006-2020	Reviewer, Journal of Sleep Research
2006-2016	Reviewer, Physiology and Behavior
2006-2021	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
2013-2020	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
2015-2021	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
2020	Reviewer, Journal of Experimental Psychology: Learning, Memory, and Cognition
2020	Reviewer, Psychiatry Research
2020	Reviewer, Health Promotion international
2021	Reviewer, Medicine & Science in Sports & Excercise

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, Dailey, 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. 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, 4, 135-147 (2019).

177. Bajaj, S, & **Killgore, WD**. Sex differences in limbic network and risk-taking propensity in healthy individuals. Journal of Neuroscience Research, 98, 371-383 (2020).

178. Satterfield, BC & **Killgore, WD**. Habitual sleep duration predicts caloric and macronutrient intake during sleep deprivation. Sleep Health, 6, 88-91 (2020).

179. Bajaj, S, & **Killgore, WD**. Vulnerability to mood degradation during sleep deprivation is influenced by white-matter compactness of the triple-network model. NeuroImage, 202, 116123 (2020).

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, 134, 104679 (2020).

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, 208, 116288 (2020).

182. Grandner, MA, Olivier, K, Gallagher, R, Hale, L, Barrett, M, Branas, C, **Killgore, WD**, Parthasarathy, S, Gehrels, J, & Alfonso-Miller, P. Quantifying impact of real-world barriers to sleep: The Brief Index of Sleep Control (BRISC). Sleep Medicine (in press).

183. Grandner, MA, Hall, C, Jaszewski, A., Alfonso-Miller, P, Gehrels, J, **Killgore, WD**, & Athey, A. Mental health in student athletes: Associations with sleep duration, sleep quality, insomnia, fatigue, and sleep apnea symptoms. Athletic Training and Sports Care (in press).

184. Raikes, AC, Dailey, NS, Shane, BR, Forbeck, B, Alkozei, A, & **Killgore WD**. 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 press).

185. Khader, W, Tubbs, AS, Haghighi, Athey, A, **Killgore, WD**, Gehrels, J, Alfonso-Miller, P, Perlis, ML, Fernandez, F, & Grandner, MA. Onset insomnia and insufficient sleep duration predict suicide ideation in university students and athletes. Journal of Affective Disorders, 274, 1161-1164 (2020).

186. **Killgore, WD**, & Kamimori, GH. Multiple caffeine doses maintain vigilance, attention, complex motor sequence expression, and manual dexterity during 77 hours of total sleep deprivation. Neurobiology of Sleep and Circadian Rhythms (in press).

187. **Killgore, WD**, Cloonan, SA, Taylor, EC, & Dailey, NS. Loneliness: A signature mental health concern in the era of COVID-19. Psychiatry Research, 290, 113117 (2020).

188. **Killgore, WD**, Cloonan, SA, Taylor, EC, Fernandez, F, Grandner, MA, & Dailey, NS. Suicidal ideation during the COVID-19 pandemic: The role of insomnia. Psychiatry Research, 290, 113134 (2020).

189. **Killgore, WD**, Taylor, EC, Cloonan, SA, & Dailey, NS. Psychological resilience during the COVID-19 lockdown. Psychiatry Research (in press).

190. **Killgore, WD,** Dailey, NS, Raikes, AC, Vanuk, JR, Taylor E, & Alkozei, A. Blue light exposure enhances neural efficiency of the task positive network during a cognitive interference task. Neuroscience Letters, 735, 135242 (2020).

191. Khader, WS, Fernandez, FX, Seixas, A, Knowlden, A, Ellis, J, Williams, N, Perlis, ML, 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. Sleep Health (in press).

192. Martin, LF, Patwardhan, AM, Jain, SV, Salloum, MM, Freeman, J, Khanna, R, Gannala, P, Goel V, Jones-MacFarland, FN, **Killgore, WD**, Porreca, F, & Ibrahim, MM. The effect of green light exposure on headache frequency and quality of life in migraine patients: A preliminary one-way cross-over clinical trial. Cephalalgia (in press).

193. **Killgore, WD**, Cloonan, SA, Taylor, EC, Allbright, MC, & Dailey, NS. Trends in suicidal ideation over the first three months of COVID-19 lockdowns. Psychiatry Research, 293, 113390 (2020).

194. **Killgore, WD**, Cloonan, SA, Taylor EC, Miller, MM, and Dailey, NS. Three months of loneliness during the COVID-19 lockdown. Psychiatry Research (in press).

195. **Killgore, WD**. Lightening the mood: Evidence for blue light exposure in the treatment of post-concussion depression. Expert Review of Neurotherapeutics, 20, 1081-1083 (2020).

196. Martin, L, Porreca, F, Mata, EE, Salloum, M, Goel, V, Gunnala, P, **Killgore, WD**, Jones-MacFarland, FN, Khanna, R, Patwardhan, A, & Ibrahim, MM. Exposure to green light improves pain scores and quality of life in patients with fibromyalgia: A cross over clinical trial. Pain Medicine (in press).

197. Nunez, A, Rhee, JU, Haynes, P, Chakravorty, S, Patterson, F, **Killgore, WD**, Gallagher, RA, Hale, L, Branas, C, Carrazco, N, Alfonso-Miller, P, Gehrels, J, & Grandner, MA. Smoke at night and sleep worse? The associations between cigarette smoking with insomnia severity and sleep duration. Sleep Health (in press).

198. **Killgore, WD**, Cloonan, SA, Taylor, EC, Lucas, DA, & Dailey, NS. Loneliness during the first half-year of the COVID-19 lockdowns. Psychiatry Research (in press).

199. **Killgore, WD**, Cloonan, SA, Taylor, EC, Lucas, DA, & Dailey, NS. Alcohol dependence during COVID-19 lockdowns. Psychiatry Research (in press).

200. Bajaj, S. & **Killgore, WD**. Association between emotional intelligence and effective brain connectome: A large scale spectral DCM study. NeuroImage (in press).

201. Raikes, AC, Dailey, NS, Forbeck, B, Alkozei, A, & **Killgore, WD**. Daily morning blue light therapy for post-mTBI sleep disruption: Effects on brain structure and function. Frontiers in Neurology (in press).

202. Bajaj, S., Raikes, AC, Razi, A, Miller, MA, & **Killgore, WD**. Blue-light therapy strengthens resting-state effective connectivity with default mode network after mild TBI. Journal of Central Nervous System Disease (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).

23. Raikes, AC, Athey, A, Alfonso-Miller, P, **Killgore, WD**, & Grandner, MA. Author response: Concussion assessment tools—A possible measure of sleepiness? Sleep Medicine, 66, 260-261, 2020.

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]*

2020 Lecture Entitled *Introduction to Chronobiology (Part 1)*, Sleep Research Seminar Series, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2020 Lecture Entitled *Introduction to Chronobiology (Part 2)*, Sleep Research Seminar Series, Walter Reed Army Institute of Research, Silver Spring, MD *[Invited Lecture]*

2020 Lecture Entitled *Modulating Sleep and Circadian Rhythms to Facilitate Recovery from PTSD,* McLean Hospital Neuroscience Seminar Speaker Series, Harvard Medical School, Belmont, MA *[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]*

2020 Oral Platform presentation entitled GABA Levels at Baseline Predict Resistance to Time-on-Task Deficits During Sleep Deprivation. Presentation given at the DoD Sleep Workshop, Feb 2020, Arlington, VA *[Invited Lecture]*

2020 Oral Platform presentation entitled Resilience to Inhibitory Deficits During Sleep Deprivation is Predicted by Prefrontal Gray Matter Volume. Presentation given at the DoD Sleep Workshop, Feb 2020, Arlington, VA *[Invited Lecture]*

2020 Oral Platform presentation entitled Resilience to Inhibitory Deficits During Sleep Deprivation is Predicted by Gray Matter Volume in the Ventrolateral and Ventromedial Prefrontal Cortex. Presentation given at the SLEEP 2020 Virtual Meeting, Philadelphia, PA *[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 predicts 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 appetite 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 (MHSRS), 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 measurable 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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 19-22, 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**. 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. Vanuk, JR, Alkozei, A, Burns, AI, Bullock, AD, & **Killgore, WD**. Sleep and fear extinction recall in PTSD improves with morning blue light exposure therapy. Abstract accepted for oral presentation at the 78th Annual Scientific Meeting of the American Psychosomatic Society, Long

Beach, CA, March 11-14, 2020.

591. **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.

592. **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.

593. **Killgore, WD**, Skalamera, J, Vanuk, J, Woods-Lubert, R, Cloonan, S, Alkozei, A, Dailey, N, Lane, R, Weihs, K, Allen, J, and Smith, R. Preliminary validation of a web-based emotional intelligence training program for enhancing emotional resilience. 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,** & 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.

595. **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.

596. 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.

597. 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.

598. 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.

599. **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.

600. **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.

601. **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.

602. **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.

603. 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.

604. 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.

605. 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.

606. 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.

607. 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.

608. 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.

609. 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.

610. 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.

611. 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.

612. 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.

613. 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.

614. 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.

615. 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.

616. 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.

617. 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.

618. 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.

619. 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.

620. 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.

621. **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.

622. **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.

623. 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.

624. 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.

625. 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.

626. 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.

627. 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.

628. 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.

629. 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.

630. 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.

631. 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.

632. 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.

633. 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.

634. 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.

635. 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.

636. 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.

637. 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.

638. 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.

639. 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.

640. 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.

641. 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.

642. 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.

643. 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.

644. 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.

645. Valencia, LR, Bullock, A, Miller, M. Johnson, J, **Killgore, WD**. Incorporation of cardio exercise is associated to increased levels of gratitude among PTSD patients. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

646. Cloonan, S, Persich, M, Woods-Lubbert, RA, Smith, R, Skalamera, J, & **Killgore, WD**. Examining changes to perceived and ability emotional intelligence following emotional intelligence-specific training. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

647. Johnson, J., Anlap, I, Taylor, EC, Valencia, LR, Bullock, A, Swift, N, Wellman, C, Vanuk, J, & **Killgore, WD**. The association between anxiety and intelligence is moderated by sex. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

648. Persich, M, Cloonan, S, Woods-Lubbert, RA, Smith, R, Skalamera, J, & **Killgore, WD**. Emotional intelligence training and improvements to emotional regulation. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

649. Vanuk, J, Bullock, A, Forbeck, B, Dailey, NS, & **Killgore, WD**. Severity of PTSD symptoms is associated with greater levels of depression and deficits in short-term memory. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

650. **Killgore, WD**, Cloonan, S, Woods-Lubbert, RA, Vanuk, J, Persich, M, Dailey, NS, Strong, MJ, King, RJ, Lane, RD, & Smith, R. Enhancing emotional awareness with an online training program. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

651. **Killgore, WD**, Cloonan, S, Woods-Lubbert, RA, Vanuk, J, Persich, M, Dailey, NS, Strong, MJ, King, RJ, Lane, RD, and Smith, R. Training interoceptive awareness. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

652. **Killgore, WD**, Vanuk, J, Woods-Lubbert, RA, Cloonan, S, Persich, M, Dailey, NS, King, RJ, Strong, MJ, Lane, RD, and Smith, R. Can emotional resilience be trained? Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

653. **Killgore, WD**, Skalamera, J, Ozcan, M, Cloonan, S, Woods-Lubbert, RA, Persich, M, & Smith, R. Development and validation of the Interpersonal Affect Regulation Test (IPART). Abstract

submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

654. Dailey, NS, Raikes, AC, Alkozei, A, Vanuk, J, & **Killgore, WD**. A shared biomarker of cognitive ability and sleep disruptions in mild traumatic brain injury. Abstract submitted for presentation at the Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA, February 3-6, 2021.

655. Mason, BJ, Tubbs, AS, **Killgore, WD**, Fernandex, FX, & Grandner, MA. How much do blue-blockers block do block blue? Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

656. Bobadilla, V, Mason, BJ, Tubbs, AS, Fernandez, FX, **Killgore, WD**, & Grandner, MA. Blue blockers' ability to filter circadian-active light emitted from a tablet. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

657. Rupple, D, Mason, BJ, Tubbs, AS, Fernandex FX, **Killgore, WD**, & Grandner, MA. Spectrophotometric properties of 31 different commercially available blue blocking glasses under room lighting. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

658. Mason, BJ, Tubbs, AS, Fernandex, FX, **Killgore, WD**, & Grandner, MA. Spectrophotometric properties of commercial blue-blocking lenses in sunlight. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

659. Abdi, H, Kennedy, KE, **Killgore, WD**, Wills, CC, Charest, J, & Grandner, MA. Changes in physical activity during the COVID-19 pandemic associated with changes in sleep. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

660. Jajoo, A, Kennedy, KE, Lujan, M, **Killgore, WD**, Wills, CC, & Grandner, MA. Chanigni sleep during the COVID pandemic associated with daytime cognitive function. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

661. Ghani, SB, Kennedy, KE, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Changes in sleep due to COVID pandemic associated with changes to dietary patterns. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

662. Wills, CC, Kennedy, KE, Bastien, C, Ruby, P, **Killgore, WD**, & Grandner, MA. Changes in dream recall during the COVID-19 pandemic: Associations with sleep, stress and dream content. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

663. Holbert, C, Kennedy, KE, **Killgore, WD**, Wills, CC, & Grandner, MA. Changes in sleep due to the COVID pandemic associated with sleep environment. Abstract submitted for presentation at

the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

664. Lujan, M, Kennedy, KE, **Killgore, WD**, Wills, CC, & Grandner, MA. Sleep disturbance during the COVID-19 pandemic associated with worries and fears about possible infection. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

665. Kennedy, KE, Bastien, C, Ruby, P, **Killgore, WD**, Wills, CC, & Grandner, MA. Nightmare content during the COVID-19 pandemic: Influence of COVID-related stress and sleep disruption. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

666. VAnencia, D, Ghani, S, Delgadillo, ME, Madhivan, P, Krupp, K, Ruiz, J, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. COVID-19 pandemic sleep disturbances related to dietary behavior at the US-Mexico border. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

667. Isalva, L, Vanencia, D, Ghani, S, Delgadillo, ME, Bastien, C, Madhivan, P, Krupp, K, Ruiz, J, **Killgore, WD**, Wills, CC, & Grandner, MA. COVID-19 pandemic sleep and dreams at the US-Mexico border. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

668. Arce, R, Valencia, D, Ghani, S, Delgadillo, ME, Madhivan, P, Krupp, K, Ruiz, J, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. COVID-19 pandemic sleep changes related to social and financial impacts at the US-Mexico border. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

669. Begay, T, Valencia, D, Ghani, S, Delgadillo, ME, Bastien, C, Madhivan, P, Krupp, K, Ruiz, J, **Killgore, WD**, Wills, CC, & Grandner, MA. COVID-19 pandemic nightmares at the US-Mexico border. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

670. Begay, T, Valencia, D, Ghani, S, Delgadillo, ME, Madhivan, P, Krupp, K, Ruiz, J, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. COVID-19 pandemic sleep disturbances related to stress experiences at the US-Mexico border. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

671. Grandner, MA, Ruby, P, **Killgore, WD**, Kennedy, KE, Wills, CC. An election during a pandemic: Relationship between political affiliation and pandemic-related sleep and dreams. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

672. Kennedy, KE, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Changes in sleep due to the COVID-19 pandemic associated with COVID-related general, financial, food, housing, family and relationship stress. Abstract submitted for presentation at the 35th Annual SLEEP Conference,

Virtual, June 10-13, 2021.

673. Barker, M, Gilles, A, Ghani, S, **Killgore, WD**, Wills, CC, & Grandner, MA. Sociodemographic, behavioral, and health-related factors associated with sleep duration and quality among a nationally-representative sample of native Hawaiians and other Pacific Islanders. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

674. Craig, C, Kennedy, KE, Perlis, ML, Seixas, A, **Killgore, WD**, Wills, CC, & Grandner, MA. Relationships between habitual sleep duration and chronic pain conditions in the US population over a 10-year period: Implications for sleep health disparities. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

675. Hanley, B, Gorovoy, S, Chamberlain, S, Bushan, B, Ghani, S, **Killgore, WD**, Wills, CC, & Grandner, MA. Parent and child sleep quality and nighttime activities. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

676. **Killgore, WD**, Cloonan, SA, Taylor, EC, Grandner, MA, & Dailey, NS. Insomnia as a risk for PTSD during the COVID-19 pandemic. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

677. **Killgore, WD**, Capaldi, VF, Grandner, MA, & Kamimori, GH. Trait extraversion is associated with increased suicidal ideation during total sleep deprivation and insomnia. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

678. Cloonan, SA, Grandner, MA, & **Killgore, WD**. Loneliness and lockdowns: The effects of the COVID-19 pandemic on insomnia symptoms. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

679. Janowski, S, Cloonan, SA, Grandner, MA, & **Killgore, WD**. Sleeping well during a pandemic: The role of various forms of social support in protecting against insomnia. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

680. Le, AJ, Dailey, NS, Grandner, MA, & **Killgore, WD**. Obstructive sleep apnea symptoms predict cognitive function following mild traumatic brain injury. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

681. Persich, M, Cloonan, SA, Grandner, MA, & **Killgore, WD**. Self-reported sleep and resilience. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

682. Persich, M, Cloonan, SA, Grandner, MA, & **Killgore, WD**. Sleep quality and duration are associated with greater trait emotional intelligence. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

683. Taylor, EC, Cloonan, SA, Grandner, MA, & **Killgore, WD**. Insomnia in those diagnosed with COVID-19. Abstract submitted for presentation at the 35th Annual SLEEP Conference, Virtual, June 10-13, 2021.

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:)

2004-2005 Sleep/wake Schedules in 3ID Aviation Brigade Soldiers.
Defense Advanced Research Projects Agency
(DARPA) PI: **Killgore** (Total Award: .)

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: .)

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:)

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:)

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:)
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:
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:)
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:)
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:
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:)
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:)
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:)
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:)
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:)
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:
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: **Killgore** (Total Award:)
Percent Effort: 4%
Major Goal: To identify the subcortical systems responsible for acute cognitive improvement associated with blue light exposure in the scanner.

2020-2022 Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep
USAMRDC
PI: **Killgore** (Total Award:)
Percent Effort: 5%
Major Goal: Determine whether continuous theta burst stimulation of the default mode network can improve sleep among individuals with insomnia.

2020 Real-Time Caffeine Optimization during Total Sleep Deprivation
USAMRDC
Site PI: **Killgore** (Total Award:)
Percent Effort: 40%
Major Goal: Determine the effectiveness of the 2B-Alert Caffeine Optimization Program during an in-laboratory sleep deprivation study.