AWARD NUMBER: W81XWH-14-1-0534

TITLE: Frontoparietal Priority Maps as Biomarkers for mTBI

PRINCIPAL INVESTIGATOR: Cheryl A Olman

CONTRACTING ORGANIZATION: University of Minnesota
Minneapolis, MN 55455-2070

REPORT DATE: December 2018

TYPE OF REPORT: Final

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Dec 2018	Final	30 Sept 2014– 29 Sept 2018

4. TITLE AND SUBTITLE

Frontoparietal Priority Maps as Biomarkers for mTBI

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0534

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Cheryl A Olman

E-Mail: caolman@umn.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of Minnesota
Office of Sponsored Projects
200 Oak St SE
Minneapolis, MN 55455-2009

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

This project involves a series of behavioral and magnetic resonance imaging (MRI) experiments that will determine the degree to which difficulties with visual attention, saccade targeting and motion perception associated with mild traumatic brain injury (mTBI) can be attributed to damaged cortical brain networks serving attention and eye movement planning. The hypothesis being tested is that spatial attention and eye movement deficits associated with mTBI result from disruption of the gray matter and/or the white matter in cortical networks that control attention allocation and eye movements. A combination of functional MRI and diffusion-weighted imaging will allow us to measure (1) integrity in cortical networks in frontal and parietal brain regions responsible for attention allocation and eye-movement planning, (2) integrity in the white matter carries outputs from these regions to the sub-cortical nuclei that control eye movements, and (3) correlation between these biomarkers and behavioral measures of visual performance in veterans who have and have not experienced mTBI. At the time of writing, preliminary analyses have been completed on all data collected during the study; a single final manuscript is in preparation.

15. SUBJECT TERMS

mTBI, fMRI, DTI, psychophysics, vision, convergence insufficiency

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION 1

KEYWORDS 1

ACCOMPLISHMENTS 1

IMPACT 5

CHANGES/PROBLEMS 5

PRODUCTS 6

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS 6

SPECIAL REPORTING REQUIREMENTS 6

APPENDICES 6

INTRODUCTION

This project involves a series of behavioral and magnetic resonance imaging (MRI) experiments that will determine the degree to which difficulties with visual attention, saccade targeting and motion perception associated with mild traumatic brain injury (mTBI) can be attributed to damaged cortical brain networks serving attention and eye movement planning. The hypothesis being tested is that spatial attention and eye movement deficits associated with mTBI result from disruption of the gray matter and/or the white matter in cortical networks that control attention allocation and eye movements. A combination of functional MRI and diffusion-weighted imaging will allow us to measure (1) integrity in cortical networks in frontal and parietal brain regions responsible for attention allocation and eye-movement planning, (2) integrity in the white matter that contains the axons that carry the outputs of these cortical computations to the sub-cortical nuclei that actually control eye movements, and (3) correlation between these biomarkers and behavioral measures of visual performance in veterans who have and have not experienced mTBI.

KEYWORDS

mTBI
fMRI
DTI
psychophysics
vision
convergence insufficiency

ACCOMPLISHMENTS

Specific Aim 1: behavioral characterization of convergence insufficiency, tracking in 3D, spatial attention, saccade execution and motion perception		
Major Task 1: human subjects approval	Timeline (months)	Accomplishment
Submit necessary documentation to University of Minnesota IRB	1	Completed 8/8/2014
Respond to stipulations and provide additional doc.	2	Completed 9/22/2014

Local IRB approval	3	Received 10/2/2014
Submit necessary documentation to HRPO	3	Completed 10/2/2014
Milestone Achieved: HRPO Approval	6	Veteran Affairs Medical Center (VAMC) IRB approval received on 5/20/2015. Change in protocol approval received from University of Minnesota IRB on 6/19/2015. HRPO approval received 6/28/2015.
Major Task 2: preparation of task and training of study personnel		
Programming of tasks	1-3	Completed 12/15/2014.
Project coordinator practices running behavioral sessions on other study personnel	3-4	Completed.
Analysis of pilot behavioral data to ensure all necessary tools are in place; make any necessary refinements to task	4-6	Completed 6/30/2015.
Milestone(s) Achieved: behavioral protocol established and rehearsed	6	Completed 6/30/2015.
Major Task 3: behavioral assessments		
Recruitment of subjects on VA Protocol 4581-B.	~~7-11~~ 7-45	Completed.
Scheduling of eligible subjects for behavioral assessments of 85 subjects (30 controls, 55 with TBI)	~~7-15~~ 7-45	All participants in the planned recruitment pool were contacted. 64 subjects completed the behavioral protocol.
Analysis of behavioral data and assignment to Phase II study group on rolling basis	~~7-15~~ 7-45	Completed.
Milestone Achieved: 48 subjects identified for Phase II of study (48 subjects = 24 controls, 24 with visual complaints)	15	24 participants were identified and scanned during Year 2. The design was modified to remove between-group design because many participants recruited as controls (because they had never received TBI diagnosis) reported blast exposure or other history of concussion. Analysis of the first half of the dataset showed a trend in relationship between fMRI responses and reported vision difficulties that disproved our underlying hypothesis. So recruitment was discontinued for the second half.
Specific Aim 2: correspondence between behavioral and imaging measures of visuospatial function		
Major Task 4: establish imaging protocol		
Analysis of pilot data acquired on healthy controls in the course of other studies	3-6	Completed.
Phantom studies on 7T scanner to establish QA protocol	7	Completed.
Milestone Achieved: MRI protocol prepared	8	Completed.
Major Task 5: acquire MRI measures, which include DTI and fMRI		
Complete scanning sessions (Visit 2) for 12 participants	9-12	Completed May, 2016.
Preliminary analysis of 12 datasets to verify quality	9-12	Completed June, 2016.
Visit 2 for remaining ~~36~~ 12 participants	12-18	Completed September, 2016.

Milestone Achieved: ~~48~~ 24 subjects scanned	18	Completed
Major Task 6: analysis and publication		
Analysis of imaging data	12-20	Completed.
Presentation of preliminary findings at Society for Neuroscience or similar conference	18	Preliminary behavioral results presented at annual meeting of Vision Sciences Society in St Pete's Beach, Fl, May, 2016.
Writing and submission of manuscript	20-22	Manuscript in preparation.
Milestone Achieved: publication of association between behavioral and imaging measures	24	In progress.

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

  See SOW table above.

What was accomplished under these goals?

Primary findings are divided into three categories: behavioral findings, diffusion tensor imaging (DTI) findings, and functional MRI (fMRI) findings.

Behavioral findings

Several surveys were completed by participants: Visual Function Questionnaire (standard NIH quality of life survey), a Personal and Family History of Strabismus (to rule out congenital problems with eye coordination or problems that pre-dated TBI), and a Convergence Insufficiency Symptom Survey (CISS). Data from the CISS showed strong correlation with performance on visual tasks performed during study visits and was therefore the most useful (and easily administered) marker of visual complaints.

Several visual tasks were performed by participants: motion detection, contrast discrimination, acuity, accommodation, convergence, smooth pursuit and reading. Performance on motion detection, dontrast discrimination, acuity, accommodation, and convergence tasks did not discriminate between participants with and without a history of TBI. Even the convergence measurement (ability to keep eyes focused together as an object gets closer to the face) did not correlate with responses on the CISS, presumably because fatigue is a strong factor in determining whether eyes work together.

The reading and smooth pursuit tasks showed the greatest discriminatory power. The reading task (Wilkin's Rate of Reading) was done with and without a color overlay, selected by the participant under the instructions "pick out the transparency that makes the underlying text easiest to read." Participants with a history of TBI had, on average, lower reading speeds and also showed a greater increase in reading speeds with the color transparency (Panel B, Quad Chart). One participant said "I would go back to reading books for fun if I had that purple overlay!" Smooth pursuit is measured while participants track a smoothly moving dot; good performance is measured as a low number of "jumps" or catch-up saccades that occur when the eye movements to not keep up with the dot movement. Smooth pursuit performance correlated with reading speed (and was therefore better in participants without a history of TBI). The finding of impaired smooth pursuit performance associated with history of TBI was anticipated from the literature. Since the smooth pursuit task was performed only with a blue dot on a gray monitor, the relationship between color filtering and smooth pursuit will have to be the focus of future research.

Summary of behavioral findings: the Convergence Insufficiency Symptom Survey is an easily administered tool that provides a valuable measure of visual quality of life. Scores on the CISS can predict reading speeds; participants with TBI are more likely to experience an increase in reading speed when using a self-selected color transparency over the reading material. Manuscript in preparation.

Diffusion Tensor Imaging (DTI) findings

Anatomical and DTI data had been collected on all participants as part of a previous study, so was available for all 64 participants who completed the behavioral portion of the study. Integrity of white matter was measured as Fractional Anisotropy (FA, as well as Mean Diffusivity, MD, but both metrics showed the same pattern, so only FA is reported) in 2 *a priori* regions of interest (ROIs): white matter adjacent to the Frontal Eye Fields, which are associated with eye movement planning, and white matter adjacent to the intraparietal sulcus, which is associated

with spatial mapping of attention. A weak association between frontal white matter integrity and smooth pursuit eye movements; no other associations between visual behaviors and DTI data were found.

Summary of DTI findings: smooth pursuit eye movement performance can be predicted by white matter integrity in caudal middle frontal cortex, which is adjacent to the frontal eye fields that plan eye movements. Manuscript in preparation.

Functional MRI (fMRI) findings

The over-arching goal of the imaging portion of this study was to determine whether white matter integrity, measured by DTI, or gray matter function, measured by fMRI, was a better predictor of visual complaints following mild to moderate traumatic brain injury (mTBI) in cases in which there was no obvious damage to the eyes, eye muscles or nerves controlling the eyes and eye muscles. Twenty-four participants participated in fMRI scanning sessions to measure gray matter function; of these 20 were able to complete the scanning session and 19 datasets were of sufficient quality to evaluate whether fMRI responses were useful predictors of TBI status or scores on the Convergence Insufficiency Symptom Survey. One dataset was discarded due to artifacts caused by excessive motion during the scanning session.

In the group of 19 participants for whom fMRI data were analyzed, the primary behavioral finding of an association between CISS scores and reading speed was replicated, as well as the tendency for people with TBI and higher CISS scores to benefit from color overlays during reading. Functional MRI responses were quantified in two *a priori* ROI clusters: early visual areas (V2/3/4) and areas in intraparietal sulcus (IPS1/2/3). (V1 was excluded from analysis because it is very large, with a more detailed representation of the visual field than other retinotopic regions, so it was only weakly stimulated, on average, because stimuli occupied only a small portion of the screen.) Both clusters of visual areas contain maps of the visual world. The early visual areas are expected to contain only spatial maps; the higher areas in IPS are expected to represent not only spatial location but also spatial attention or intention. Participant completed two kinds of scans: one in which visual stimuli (consisting of clusters of moving dots) moved around in the visual field ("visual field mapping") and one in which visual stimuli were always present at all locations, but the participants were cued (by subtle changes in the motion coherence at different visual locations) to move their attention around in the visual field. This second type of scan was called "attention mapping". In both types of scans, subjects were instructed not to move their eyes away from a dot at the center of the screen, and eye-tracking was used to ensure compliance with instructions. Behavioral data collected before the scanning session verified that participants in TBI and control groups had, on average, the same ability to detect motion coherence.

To analyze the fMRI data, the two clusters of *a priori* ROIs, termed VX and IPS and described above, were defined from a standard visual atlas, tailored to each participant's cortical anatomy. Functional MRI response was quantified as the percentage (by volume) of a given ROI that was significantly modulated by a task. Across all 15 participants, fMRI response to visual field mapping in neither VX nor IPS was associated with CISS scores. This lack of association was expected and confirms that overall fMRI response is independent of visual function.

The dependent variable of interest was the *relative* modulation of an ROI by *attention* mapping vs. *visual field* mapping. In early visual areas, modulation is expected to be (and was confirmed to be) much stronger during visual field mapping than during attention mapping: the ratio of response strength during attention mapping to response strength during visual field mapping, averaged across participants, was 0.25 (s.e.m.: 0.03) in VX. In higher visual areas, modulation by attention mapping was stronger, relative to visual field mapping: the attention mapping/visual field mapping ratio was 0.57 (0.09), averaged across 19 participants. This finding confirms that the experiment design was sensitive to the different roles of VX and IPS ROIs, with IPS showing stronger modulation by attention than VX.

If reduced function of spatial attention networks in IPS are the source of visual challenges that follow TBI, then participants with higher CISS scores should show lower attention/visual field mapping ratios in IPS. However, although the association is not significant in the preliminary sample, *higher* attention/visual field mapping ratios were actually associated with higher scores on the CISS. Data collection for this portion of the study were discontinued after preliminary analysis of the data from the first half of the cohort.

The rationale for discontinuing fMRI data collection was two-fold. First, eye-tracking data (which are very difficult to collect in a 7 Tesla scanning environment; the lens on the eye-tracking camera routinely shook out of focus during the scan) were not of sufficient quality to rule out the possibility that reduced fixation stability during the attention mapping scans was the source of the association between attention modulation of the fMRI signal and CISS scores. Second, even if eye-tracking data could rule out this confound, additional data would either (1) confirm an increase in IPS responses associated with CISS, which is possibly present as a compensatory mechanism but nonetheless

rules out IPS gray matter impairment as a source of visual spatial attention deficits, or (2) show that there is no association between IPS responses and visual complaints subsequent to TBI, which also rules out IPS gray matter as a source of visual spatial attention deficits. Because this is a Hypothesis Development Award, discontinuing data collection rather than pursuing data collection in the hopes of publishing a null result was deemed the best option. The additional funds allocated for collection of the second half of the fMRI data (~$10,000) were therefore not spent and are being returned at the end of the granting period.

Summary of fMRI findings: no evidence for a relationship between gray matter function in parietal cortex and visual deficits following TBI.

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

  - Study staff have been trained to analyze DTI, fMRI and eye-tracking data.

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

  Presentation at vision conference in May, 2016 (see table above). Publication is planned.

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

  Nothing to report.

IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**
  Impact on principle discipline will be evidence for involvement of the brain's white matter in visual dysfunction following mTBI, and refinement of hypotheses about the specific mechanisms by which brain damage may contribute to visual dysfunction. CISS and reading speed are validated as useful behavioral markers of mTBI effects on vision.

- **What was the impact on other disciplines?**
  Impact on other disciplines will be improved measures for correlating behavioral and MRI (DTI, fMRI) data.

- **What was the impact on technology transfer?**
  Impact on technology transfer will be progress of DTI as a biomarker in the clinical setting.

- **What was the impact on society beyond science and technology?**
  Impact on society will be improved understanding of the effects of mTBI on the brain, leading to better policies regarding treatment of TBI.

CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

  Study design moved away from group differences because even control participants report experiences that make it likely they experienced some kind of TBI, so most analyses were performed on a continuum defined by behavioral measures rather than a group distinction (formerly based on clinical interviews).

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to report.

- **Changes that had a significant impact on expenditures**

  Early termination of fMRI experiment resulted in a small portion of funds being returned to funding agency.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to report.

PRODUCTS

- **Publications, conference papers, and presentations**

  "Visual Attention and Eye Movement Deficits in Patients with Traumatic Brain Injury", Tori D. Espensen-Sturges, Timothy J. Hendrickson, Andrea N. Grant, Scott R. Sponheim, Cheryl A. Olman. Poster presentation at Vision Sciences Society Annual Meeting, St Pete's Beach, Florida, May 13-17, 2016.

  Manuscript describing behavioral and DTI findings in preparation.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report.

- **Other Products**

  Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Cheryl Olman, PI – no change.
Andrea Grant, staff scientist – no change.
Essa Yacoub, consultant – no change.
Tori Espensen-Sturges, Graduate Research Assistant – assisted with data analysis after project coordinator left.
Phil Burton, College of Liberal Arts Neuroimaging Staff Scientist – assisting with diffusion MRI analysis.
Jessica Hargreaves, Research Assistant – assisting with participant recruitment.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

PI Olman has received an R21 and an R01 from NIH, and is co-investigator in a newly awarded U01 and R01 to Scott Sponheim.

- **What other organizations were involved as partners?**

Minneapolis VAMC, overseeing participant recruitment.

SPECIAL REPORTING REQUIREMENTS

Quad Chart attached.

APPENDICES

None.

Frontoparietal priority maps as biomarkers for mTBI

ERMS/Log Number and Task Title: MR130374

Award Number: W81XWH-14-1-0534

PI: Olman **Co-Is**: Sponheim, Jerde **Org:** University of Minnesota/Minneapolis VA **Award Amount:** $250,000 / 2 years

Study/Product Aim(s)

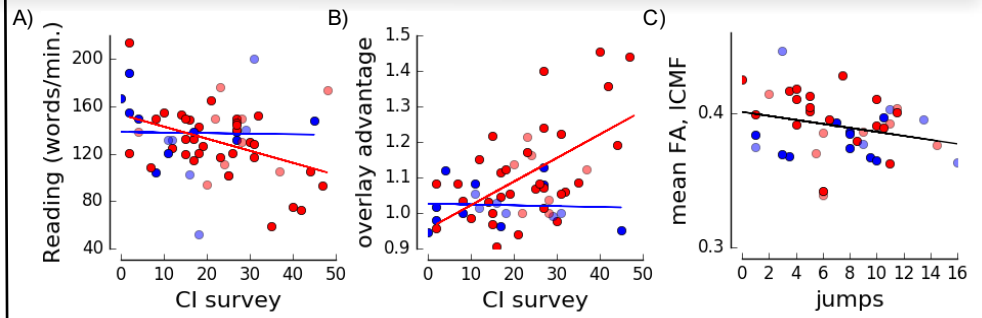
- Hypothesis: visual performance deficits in attention and eye-movements are driven by cortical damage
  - Aim 1: to determine strength of correlation between performance on attention allocation and eye-movement tasks and functional neuroimaging markers of attention regulation
  - Aim 2: to quantify association between white matter integrity and these behaviors.

Approach

In a cohort of 64 combat veterans, behavioral data were acquired on visual tasks that measured motion detection, smooth pursuit eye movements, and reading speed, as well as various surveys about quality of life.

DTI data acquired on all participants (as part of previous studies) were compared against behavioral data to discover predictors of deficits in reading and smooth pursuit eye movements.

A subset also participated in functional MRI experiments to assess association between visual behaviors and parietal attention networks.



A) Reading speed and the Convergence Insufficiency Symptom Survey, which documents discomfort and double vision during close work, proved most useful at characterizing visual deficits. CISS predicted lower reading speeds for participants with documented TBI (red, n=43) but not controls (blue, n=16; some participants did not complete reading test). Lighter points: age > 45. B) Participants with mTBI and low reading speeds showed speed improvement when using a color overlay. C) Reading speed correlates with stability of smooth pursuit eye movements (not shown). Impairment of smooth pursuit eye movements is, in turn, associated with decreased white matter integrity in left caudal medial frontal cortex, as measured by the fractional anisotropy (FA) in MRI diffusion tensor imaging data.

Timeline and Cost

Activities CY	14	15/16	16/17	17/18
Regulatory compliance				
Beh. data acquisition and analysis				
MRI data collection/analysis				
Final analysis and publication				
Estimated Budget (total $K)	**$25**	**$150**	**$50**	**$25**

Updated: Oct 1, 2017 to reflect no-cost extension granted 9/28/2017

Goals/Milestones

CY14 Milestones Completed – Study initiation

☐ Received U of M IRB approval on 10/2/2014; VA IRB approval on 5/20/2015

☐ Received HRPO approval on 6/28/2015

CY15 Milestones Completed– Comparison of different visual behaviors

☐ Conducted initial behavioral and DTI data analysis (see above)

CY16 Milestones Completed – Connect visual behaviors to imaging biomarkers

☐ Completed MRI data acquisition from subset of TBI patients and controls

CY17/18 Milestones Completed (during no-cost extension)

☐ Increased sample size for results shown above

☐ Completed analysis of behavioral and imaging data

Comments/Challenges/Issues/Concerns

- fMRI experiment was terminated at mid-point due to non-significant findings. 50% of imaging budget was returned.

Annual Budget: annual direct costs $83k

Personnel: 8-10% effort for co-Is:	$20.0k
Project coordinator, consultant, support staff:	$40.0k
Equipment time (MRI) and subject compensation:	$20.0k
Travel to annual meeting; conference travel Y1, pub fees Y2	$ 3.0k