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TITLE: Frontoparietal Priority Maps as Biomarkers for mTBI

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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. No results are available at the time of writing; preliminary data analysis is underway.					
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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	Continued practice on study personnel.
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	Invitation letters continue to be mailed out in weekly batches, with follow-up phone calls a week later
Scheduling of eligible subjects for behavioral assessments of 85 subjects (30 controls, 55 with TBI)	7-15	18 Subjects have completed the behavioral protocol as of 10/29/2015 (annual report deadline)
Analysis of behavioral data and assignment to Phase II study group on rolling basis	7-15	Analysis of first cohort is beginning.
Milestone Achieved: 48 subjects identified for Phase II of study (48 subjects = 24 controls, 24 with visual complaints)	15	We anticipate this will not occur until Month 18 due to delays in human subjects approval.
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	Underway.
Phantom studies on 7T scanner to establish QA protocol	7	Delayed to month 15 due to recruitment delays.
Milestone Achieved: MRI protocol prepared	8	Delayed to month 15 due to recruitment delays.
Major Task 5: acquire MRI measures, which include DTI and fMRI		
Complete scanning sessions (Visit 2) for 12 participants	9-12	New estimate for start date: Jan 1, 2016.
Preliminary analysis of 12 datasets to verify quality	9-12	
Visit 2 for remaining 36 participants	12-18	
Milestone Achieved: 48 subjects scanned	18	
Major Task 6: analysis and publication		
Analysis of imaging data	12-20	
Presentation of preliminary findings at Society for Neuroscience or similar conference	18	
Writing and submission of manuscript	20-22	
Milestone Achieved: publication of association between	24	

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

See SOW table above.

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

Behavioral data collection protocol is proceeding well, albeit 6 months behind schedule.

Imaging data acquisition is accordingly delayed, but involvement of Minneapolis VA IRB means that we were able to create a mechanism (HIPAA authorization signed by participants) to transfer already-acquired DTI and anatomical data from previous studies to this study, shortening future imaging protocol and allowing us to start some of imaging data analysis on time even though full data acquisition is delayed.

No results or products to report yet because data analyses are just beginning.

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

- Study staff are being trained to analyze DTI, fMRI and eye-tracking data.
- PI attended ARVO satellite session on TBI in Denver, CO, in April, 2015.

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

Nothing to report.

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

Plans for upcoming reporting period will adhere to the SOW, above.

IMPACT

For each of the statements below, there is nothing to report because the project remains in preliminary phases. However, brief statements about anticipated impact when the project meets its goals are also included.

o **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

At completion, impact on principle discipline will be evidence for involvement of the brain's gray and white matter in visual dysfunction following mTBI, and refinement of hypotheses about the specific mechanisms by which brain damage may contribute to visual dysfunction.

o **What was the impact on other disciplines?**

Nothing to report.

At completion, impact on other disciplines will be improved measures for correlating behavioral and MRI (DTI, fMRI) data.

o **What was the impact on technology transfer?**

Nothing to report.

At completion, impact on technology transfer will be progress of DTI as a biomarker in the clinical setting.

o **What was the impact on society beyond science and technology?**

Nothing to report.

At completion, 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

o Changes in approach and reasons for change

None.

o Actual or anticipated problems or delays and actions or plans to resolve them

Unexpected addition of VA IRB oversight delayed project 6 months but is progressing smoothly now.

Loss of project coordinator (who could be funded for only the first year, during which the bulk of the behavioral data collection was supposed to happen) means that behavioral data collection is proceeding more slowly than anticipated (rate of 2 subjects/week instead of 6-8). See note below re: applications for additional internal funding to address this problem.

o Changes that had a significant impact on expenditures

Delay in recruitment meant that project coordinator (only funded for first year, due to budget restrictions) has left the project. PI has submitted several internal (University of Minnesota) requests for bridge funding in the hopes of hiring another project coordinator to speed recruitment rates and data acquisition rates, but at the time of writing it is expected that a no-cost extension will be required to complete project goals.

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

Nothing to report.

PRODUCTS

o Publications, conference papers, and presentations

Nothing to report.

o Website(s) or other Internet site(s)

Nothing to report.

o Technologies or techniques

Nothing to report

o Inventions, patent applications, and/or licenses

Nothing to report.

o 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.

Tim Hendrickson, project coordinator – no change.

Essa Yacoub, consultant – no change.

o **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.

o **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

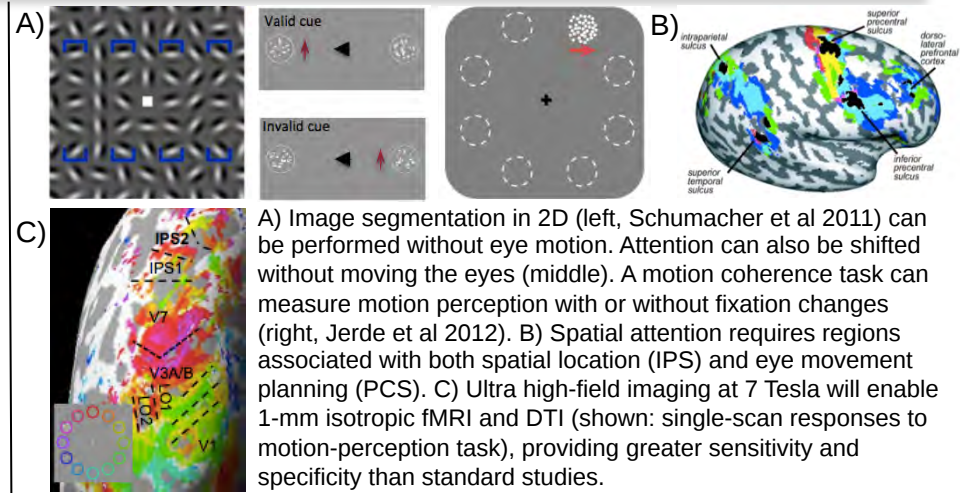
Award Amount: \$250,000 / 2 years

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 85 subjects who have experienced mTBI and controls, behavioral data will be acquired on the tasks illustrated at right. A subset (n=24) of each group will also participate in combined structural (DTI) and functional MRI experiments measuring white matter integrity and ability to allocate attention to spatial targets. Analysis will focus on strength of association between fractional anisotropy of WM in *a priori* regions of interest, fMRI-measured attention competence, and visual behavior.



Accomplishment: Dr. Sponheim has successfully completed a DOD-funded study dissociating effects of PTSD and TBI. Dr. Jerde has recently characterized frontoparietal priority encoding. Dr. Olman has recently validated a series of visual tasks and associated imaging markers.

Timeline and Cost

Activities	CY	14	15	16
Regulatory compliance				
Beh. data acquisition and analysis				
MRI data collection/analysis				
Final analysis and publication				
Estimated Budget (total \$K)		\$25	\$150	\$75

Updated: Oct 1, 2015

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 6/28/2014
- ☐ Designed and practiced behavioral session on other study personnel

CY15 Goal – Comparison of different visual behaviors

- ☐ Continue behavioral assessments from cohort of TBI patients and controls
- ☐ Conduct initial behavioral and DTI data analysis

CY16 Goal – Connection of visual behaviors with imaging biomarkers

- ☐ Finalize behavioral data analysis and submit for publication
- ☐ Complete MRI data acquisition from subset of TBI patients and controls
- ☐ Complete functional imaging analysis
- ☐ Publish analysis of behavioral and imaging data

Comments/Challenges/Issues/Concerns

- Delay in human subjects' approval requires a more aggressive data acquisition timeline

Projected 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