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TITLE: Frontoparietal priority maps as biomarkers for mTBI

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Frontoparietal priority maps as biomarkers for mTBI

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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.

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

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14. ABSTRACT

15. SUBJECT TERMS

19b. TELEPHONE NUMBER (include area code)

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18
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

<table>
<thead>
<tr>
<th>Specific Aim 1: behavioral characterization of convergence insufficiency, tracking in 3D, spatial attention, saccade execution and motion perception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Task 1: human subjects approval</td>
</tr>
<tr>
<td>Timeline (months)</td>
</tr>
<tr>
<td>Accomplishment</td>
</tr>
<tr>
<td>Submit necessary documentation to University of Minnesota IRB</td>
</tr>
<tr>
<td>Respond to stipulations and provide additional doc.</td>
</tr>
<tr>
<td>Major Task 2: preparation of task and training of study personnel</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Programming of tasks</td>
</tr>
<tr>
<td>Project coordinator practices running behavioral sessions on other study personnel</td>
</tr>
<tr>
<td>Analysis of pilot behavioral data to ensure all necessary tools are in place; make any necessary refinements to task</td>
</tr>
<tr>
<td>Milestone(s) Achieved: behavioral protocol established and rehearsed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Task 3: behavioral assessments</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Recruitment of subjects on VA Protocol 4581-B.</td>
<td>7-11</td>
<td>Protocol modified August, 2016, to add in-person recruiting for participants engaged in other studies</td>
</tr>
<tr>
<td>Scheduling of eligible subjects for behavioral assessments of 85 subjects (30 controls, 55 with TBI)</td>
<td>7-15</td>
<td>35 Subjects have completed the behavioral protocol as of 9/30/2016</td>
</tr>
<tr>
<td>Analysis of behavioral data and assignment to Phase II study group on rolling basis</td>
<td>7-15</td>
<td>Analysis of first cohort is beginning.</td>
</tr>
<tr>
<td>Milestone Achieved: 48 subjects identified for Phase II of study (48 subjects = 24 controls, 24 with visual complaints)</td>
<td>15</td>
<td>24 participants were identified and scanned during Year 2.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific Aim 2: correspondence between behavioral and imaging measures of visuospatial function</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Major Task 4: establish imaging protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis of pilot data acquired on healthy controls in the course of other studies</td>
<td>3-6</td>
<td>Underway.</td>
</tr>
<tr>
<td>Phantom studies on 7T scanner to establish QA protocol</td>
<td>7</td>
<td>Completed.</td>
</tr>
<tr>
<td>Milestone Achieved: MRI protocol prepared</td>
<td>8</td>
<td>Completed.</td>
</tr>
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<tr>
<th>Major Task 5: acquire MRI measures, which include DTI and fMRI</th>
<th></th>
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<tbody>
<tr>
<td>Complete scanning sessions (Visit 2) for 12 participants</td>
<td>9-12</td>
<td>Completed May, 2016.</td>
</tr>
<tr>
<td>Preliminary analysis of 12 datasets to verify quality</td>
<td>9-12</td>
<td>Completed June, 2016.</td>
</tr>
<tr>
<td>Visit 2 for remaining 36 participants</td>
<td>12-18</td>
<td>12 additional visits completed as of 9/30/2016.</td>
</tr>
<tr>
<td>Milestone Achieved: 48 subjects scanned</td>
<td>18</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Task 6: analysis and publication</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Analysis of imaging data</td>
<td>12-20</td>
<td>On-going.</td>
</tr>
<tr>
<td>Presentation of preliminary findings at Society for Neuroscience or similar conference</td>
<td>18</td>
<td>Preliminary behavioral results presented at annual meeting of Vision Sciences Society in St Pete’s Beach, Fl, May, 2016.</td>
</tr>
<tr>
<td>Writing and submission of manuscript</td>
<td>20-22</td>
<td></td>
</tr>
<tr>
<td>Milestone Achieved: publication of association between</td>
<td>24</td>
<td></td>
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</table>
What were the major goals of the project?

See SOW table above.

What was accomplished under these goals?

Behavioral data collection protocol is proceeding well.

Imaging data acquisition is completed on first cohort. Because behavioral and imaging data indicate a continuous, rather than bimodal, distribution between “TBI” and “control” groups, design is revised and correlational analysis across all participants. This reduces total number of participants required.

Preliminary analyses indicate strong associations between frontal white matter integrity and smooth pursuit eye movements, smooth pursuit eye movements correlate with reading speeds, and reading speeds correlate with parietal cortex white matter integrity.

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

- Study staff are being 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).

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.

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

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.

What was the impact on other disciplines?

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

What was the impact on technology transfer?

At completion, 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?

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

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 all participants are being analyzed 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**
  
  Slow progress on recruiting means that we carry a balance to fund future MR experiments, should they be necessary.

- **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**
  

- **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.

Tori Espensen-Sturges, Graduate Research Assistant – added to assist with data analysis after project coordinator left.

Essa Yacoub, consultant – no change.

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

- **What other organizations were involved as partners?**
  
  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. DTI data acquired on all participants (as part of previous studies) will be compared against behavioral data to discover predictors of deficits in reading and smooth pursuit eye movements. A subset will also participate in functional MRI experiments to assess association between visual behaviors and fMRI-measured attention competence.

Timeline and Cost

<table>
<thead>
<tr>
<th>Activities</th>
<th>CY 14</th>
<th>15/16</th>
<th>17</th>
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<tbody>
<tr>
<td>Regulatory compliance</td>
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<tr>
<td>Beh. data acquisition and analysis</td>
<td></td>
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<tr>
<td>MRI data collection/analysis</td>
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<td></td>
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<tr>
<td>Final analysis and publication</td>
<td></td>
<td></td>
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<tr>
<td>Estimated Budget (total $K)</td>
<td>$25</td>
<td>$150</td>
<td>$75</td>
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Updated: July 6, 2016 to reflect no-cost extension granted 6/8/2016

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 Goals – Connection of visual behaviors with imaging biomarkers
☐ Complete MRI data acquisition from subset of TBI patients and controls
☐ Increase sample size for results shown above

CY17 Goals (with no-cost extension) – study completion
☐ Publish analysis of behavioral and imaging data

Comments/Challenges/Issues/Concerns

• Combat veterans with and without documented TBI are not showing distinction, in most behavioral and imaging measures; visual deficits exist on a continuum.
• Study design is therefore revised from to rely correlations across population rather than simple group differences.

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