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TITLE: Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of Mild TBI

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  The objective of this study ("Fusion") is to validate methods combining EEG and eye tracking for assessment of mild traumatic brain injury (mild TBI). Phase 1, the Fusion Pilot Study (n=30) was completed in Y3Q1. Phase 2, the Fusion Primary Phase (n=67) completed data collection in Y4Q4. The majority of Phase 2 data analysis is complete, and has produced results providing robust support for study hypotheses and validation of Fusion assessment approaches. Dissemination and additional follow-up analyses are underway. Phase 3, the Fusion Clinical Optimization Phase, was initiated in Y5Q1. Implementation of the Fusion-AMP (Advanced Mobile Prototype) was completed in Y5Q2; additional refinements to software and hardware are underway. Phase 3 data collection began in Y5Q2 at Naval Medical Center San Diego (NMCSD) and in Y5Q4 at Naval Hospital Camp Pendleton (NHCP). MRI was added to Phase 3 at NMCSD to make up for MRI collection shortfalls in the Primary Phase; a research scientist was also hired to take the lead in finalizing the MRI protocol and performing imaging analysis. To date, n=42 participants have been enrolled in the Phase 3 study at NMCSD/NHCP, n=7 of whom have also completed the MRI portion of the study. Additional Y5 accomplishments include presentation of Primary phase results at multiple scientific meetings and colloquia and submission of multiple grant proposals leveraging Fusion technology and results.					
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## Introduction

The objective of this project (the “Fusion Study”) is to validate methods combining EEG and eye tracking for assessment of mild traumatic brain injury (mild TBI). Research suggests that the neural injuries resulting from mild TBI do not always produce observable performance deficits. However, subjective ratings suggest that the level of effort required to perform at a given level can be higher with mild TBI; associated neuroimaging data reveal a broader recruitment of cortical neurons to accomplish tasks in mild TBI relative to uninjured individuals [1-3]. This research project combines information from two distinct physiological sensing approaches to make inferences about injury-related changes in cognitive function using measures that are sensitive to cognitive effort. The goal is to develop methods for neurodiagnostic assessment that can be used in a broad range of contexts in which cognitive assessment is relevant. Validation of the integrated EEG and eye tracking system will include evaluation of these measures based on characterizations of injury severity, performance on conventional neurocognitive tests, and self-report measures. We will also include fMRI and DTI measurements to provide an objective basis for cross-validating the EEG and eye tracking system. Both the EEG and eye tracking data will be collected in the context of a dual-task experimental paradigm with visual target detection.

## Keywords

TBI, concussion, saccadic, eye tracking, EEG, cognition

## Overall Project Summary

Phase 1, the Fusion Pilot Study (n=30) was completed in Y3Q1. The Pilot phase was used to define methods for further study. Phase 2, the Fusion Primary Phase (n=67) completed data collection in Y4Q4. The majority of Primary Phase data analysis is complete, and has produced results providing robust support for study hypotheses and validation of Fusion assessment approaches. Dissemination and additional follow-up analyses are underway. Phase 3, the Fusion Clinical Optimization Phase, was initiated in Y5Q1. Implementation of the Fusion-AMP (Advanced Mobile Prototype) was completed in Y5Q2; additional refinements to software and hardware are underway. Phase 3 data collection began in Y5Q2 at NMCS D and in Y5Q4 at Naval Hospital Camp Pendleton (NHCP). MRI was added to Phase 3 at Naval Medical Center San Diego (NMCS D) to make up for MRI collection shortfalls in the Primary Phase; a research scientist was also hired to take the lead in finalizing the Optimization phase MRI protocol and performing imaging analysis. To date, n=42 participants have been enrolled in the Clinical Optimization study at NMCS D/NHCP, n=7 of whom have also completed the MRI portion of the study. Progress is outlined below for milestones delineated in the statement of work:

**Data Analysis and Dissemination for USU Primary Study.** The USU Primary Study data set was finalized in Y5Q1. The majority of Primary Study data analysis has been completed; additional follow-up analyses are underway. Primary variables of interest include saccadic latency, saccadic duration, saccadic reaction time, manual reaction time, pupillary response, and several EEG/ERP components. Analyses were conducted, including assessing differences in behavioral (manual and saccadic) performance and psychophysiological responses (EEG/ERP and pupillometry) between-groups (Controls, Mild TBI, and Moderate-Severe TBI participants) and within-subjects on the Fusion cognitive tasks. Findings: Consistent with prior results from the pilot study and preliminary findings, we observed a dose-response relationship between TBI severity and saccadic performance as well as EEG/ERP response. Additional differences were demonstrated between Control and TBI groups in pupillary and EEG responses. Results show that between-group differences are particularly salient for more challenging task components. We also observed an overall effect of cognitive workload and trial type

within-subjects (decreased performance and altered psychophysiological responses as task difficulty increases). In summary, Primary Study findings provide strong support for study hypotheses and validation of Fusion assessment approaches. During Year 5, Primary study results were disseminated via four scientific conference presentations and three invited seminars. This included presentations completed at the Annual Meeting of the International Neuropsychological Society as well as the annual meeting of the Military Health System Research Symposium. Additionally, Fusion methods and results were presented at a series of colloquia regarding effects of TBI and cognitive load on saccadic responses. Please see Publications, Abstracts, and Presentations section below for additional details about dissemination. Additional conference presentations are planned for Primary Study results, and multiple manuscripts are currently being finalized for publication.

### **Optimization of Sensors and Algorithms for Optimization Study**

During Year 5, core features of the software and hardware configuration for the Fusion-AMP (Advanced Mobile Prototype) were finalized for the purposes of Optimization Study data collection. Continued software development for Fusion-AMP has led to the development of data processing features which help to ensure that data collected are high quality and to improve clinical feasibility of Fusion-AMP. Study personnel are continuing to work to improve processes for quality control and quality assurance.

**Data Collection for Optimization Study 1 – EEG/Eye Tracking.** As of the end of Year 5, 42 participants have been enrolled in the EEG/eye tracking portion of the Clinical Optimization Phase of the study. This has included 40 participants at NMCS D and 2 participants at NHCP, which was brought on as a data collection site at the end of Year 5. Total enrollment includes the following (Controls: n = 10; Mild TBI: n = 26; Moderate-to-Severe: n = 2; excluded due to unclear TBI history n = 4). Continued expansion of the recruitment plan was a primary focus during this POP. Electronic advertisements have been posted on the NMCS D command website to increase recruitment efforts at NMCS D. In addition, staff members at NHCP have participated in outreach events to create awareness of the study and boost recruitment numbers. New study advertisements have been created to better communicate study purpose and eligibility. These new ads are awaiting NMCS D IRB approval but will be posted at high-traffic areas throughout the NMCS D and Camp Pendleton sites. The study team conducts biweekly meetings to regularly track the success of our current recruitment efforts and brainstorm new sources of recruitment. Overall, we are on track to achieve enrollment targets.

**Data Collection for Optimization Study 2 – MRI.** A research scientist was hired to take the lead in developing the Optimization phase MRI protocol and to perform imaging analysis at NMCS D. In total, 7 enrolled participants have taken part in the MRI portion of the study thus far. While MRI procedures have been initiated only recently, participant interest in this part of the study is high, and so far we are on track to achieve MRI acquisition targets.

### **Key Research Accomplishments for this Year**

- Completed the majority of analyses from Primary Phase data. Disseminated results supporting study hypotheses and methods.
- Finalized Fusion-AMP prototype for rapid collection of eye tracking and EEG data in clinical settings.
- Continued Fusion-AMP software development for enhancement of clinical feasibility and utility.
- Conducted eye tracking and EEG data collection at NMCS D; Initiated data collection at NHCP. Overall enrollment on target.
- Continued to enhance participant recruitment pipeline for Optimization Phase of study.
- Hired research neuroscientist to finalize and implement Fusion MRI protocol for NMCS D and perform MRI analysis.

- Initiated MRI data collection at NMCSO.
- Submitted multiple grant proposals leveraging results from Fusion study.
- Obtained POP extension to continue study into Year 6.

## Conclusions

The primary goal of the Fusion project is to develop and validate methods for improved TBI assessment by evaluating changes in behavioral performance, saccadic performance, pupil response, and brain activation that occur at different levels of cognitive load. Consistent with our hypotheses, we have obtained strong evidence that individuals with TBI demonstrate more significant performance trade-offs and changes in brain activation with increasing load. Analyses indicate that the Fusion tasks used for integrated eye tracking and neural monitoring are able to successfully discriminate cognitive workload across difficulty levels, and that individuals with TBI demonstrate signs of cognitive strain at levels of high load. This provides a promising basis for the extraction of valuable data relevant to detecting neurocognitive changes after TBI. The final, ongoing phase of the study is evaluating the Fusion Advanced Mobile Prototype (Fusion-AMP) within an Active Duty TBI clinic setting, and examining potential neural mechanism of effects observed.

## Publications, Abstracts, and Presentations Completed within Study Year 5

Manuscripts: None to report for this study period. Multiple manuscripts in preparation.

The following scientific presentations disseminated scientific methods and results from the USU primary study of this research effort:

1. Ettenhofer, M.L., Hershaw, J.H., Safford, A., Barry, D.M., Constanzo, M., Kegel, J., Cordero, E., & Roy, M.J. (2017, August). The Fusion Project: Multi-Modal Neurocognitive Assessment of Traumatic Brain Injury. Paper presented at the annual meeting of the Military Health System Research Symposium.
2. Engle, J.R., Hershaw, J., Safford, A., Cordero, E., Kegel, J., & Ettenhofer, M.L. (2018, February). *Subjective Mental Workload and Motor Impairment in Traumatic Brain Injury*. Poster presented at the 2018 Annual Meeting of the International Neuropsychological Society, Washington, D.C.
3. Hershaw, J.N., Safford, A.S., Cordero, E., & Ettenhofer, M.L. (2018, February). *Identification of Measurable Cognitive Processing Differences in Chronic TBI Using Pupillometry*. Poster presented at the 2018 Annual Meeting of the International Neuropsychological Society, Washington, D.C.
4. Ettenhofer, M.L., Hershaw, J.N., Engle, J.R., Safford, A., Cordero, E., Kegel, J. & Roy, M. (2018, February). *Saccadic Evidence for Reduced Cognitive Efficiency in Chronic Traumatic Brain Injury*. Poster presented at the 2018 Annual Meeting of the International Neuropsychological Society, Washington, D.C.

The following invited colloquia have included dissemination of scientific methods and results of this study:

1. March, 2017. "Emerging Technologies for Assessment and Rehabilitation of TBI." 4<sup>th</sup> Annual

TBI Symposium, Naval Medical Center San Diego.

2. March, 2017. "Windows to the Brain: What Can Eye Movements Tell Us About TBI?" 7<sup>th</sup> Annual TBI Research Forum: Detection and Treatment of Sensory Deficits, VA Palo Alto.
3. April, 2017. "The Eyes Have It: Development and Validation of Neurocognitive Eye Tracking." Annual Meeting of the Society for Brain Mapping and Therapeutics, Los Angeles, CA.

## **Inventions, Patents, and Licenses**

None to report.

## **Reportable Outcomes**

1. Implementation of Fusion-AMP (Advanced Mobile Prototype). The eye tracking portion of this system and associated methods are ready for final prototyping and commercialization.

## **Other Achievements**

1. Submitted grant proposal, "*Sensor-Based Oculomotor and Cognitive Profiling for Personalized Treatment of Mild TBI*", JPC-6 Combat Casualty Care Research Program, Precision Trauma Care Research Award, Funding Opportunity Number: W81XWH-18-DMRDP-PTCRA
  - a. This proposal examined the use of Fusion and Oculogica technology for guiding care among service members receiving care for TBI.
  - b. Proposal not funded.
2. Submitted grant proposal, "*Objective Multimodal Assessment of Cognitive and Sensorimotor Function after Mild TBI in Static and Dynamic Environments*", JPC-8 CRM RP PH/TBI Research Program, Clinical Research Award, FON: W81XWH-17-CTTR-CRA.
  - a. This proposal focuses on use of Fusion technology for measurement and prediction of operationally-relevant abilities after mTBI.
  - b. Proposal currently under review.
3. Submitted grant proposal, "*Personalized, Augmented Cognitive Training (PACT) for Service Members and Veterans with a History of TBI*", JPC-8 CRM RP PH/TBI Research Program, Clinical Trial Award, FON: W81XWH-17-CTTR-CTA.
  - a. This proposal focuses on validation of an intervention for TBI; Fusion technology is included secondarily as a measurement of TBI-related cognitive impairment.
  - b. Proposal currently under review.
4. Submitted grant proposal, "*Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Personalized Treatment for Cognitive Rehabilitation in Complex TBI*," JPC-8 CRM RP PH/TBI Research Program, Clinical Trial Award, FON: W81XWH-17-CTTR-CTA.
  - a. This proposal focuses on validation of an intervention for TBI; Fusion technology is included secondarily as a measurement of TBI-related cognitive impairment.
  - b. Proposal currently under review.

## **References**

1. McAllister, T.W., et al., *Differential working memory load effects after mild traumatic brain injury*. Neuroimage, 2001. **14**(5): p. 1004-12.
2. Chen, J.K., et al., *Functional abnormalities in symptomatic concussed athletes: an fMRI study*. Neuroimage, 2004. **22**(1): p. 68-82.
3. McAllister, T., et al., *Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study*. Neurology, 1999. **53**(6): p. 1300-8.

## **Appendices**

There are no appendices for this report.

## **Supporting Data**

None.

# Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of Mild TBI



Psychological Health, Polytrauma, and Operational Health (PHPOH), Award W81XWH-13-1-0095

PI: Mark L. Ettenhofer, Ph.D. Org: Henry Jackson Foundation (HJF) / Uniformed Services University (USU)

Award Amount: \$3,311,604

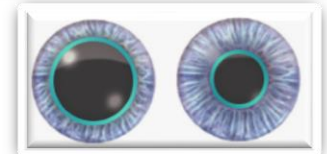
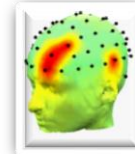
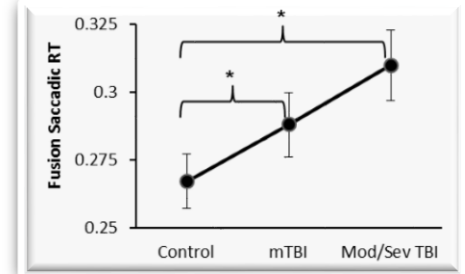
## Study Aims

This project will develop and validate methods of integrated eye tracking/EEG to assess persistent neurocognitive effects of TBI.

- Aim 1:** Develop and validate algorithms to measure cognitive efficacy after TBI using combined EEG and eye tracking.
- Aim 2:** Identify mechanisms for reduced cognitive efficacy after mild TBI and cross-validate EEG-based results with eye-tracking enabled fMRI and DTI.
- Aim 3:** Optimize a clinically-feasible integrated EEG/eye tracking assessment system for future commercialization.

## Approach

- Fusion Tests will be validated through comparison of healthy controls and mild and moderate TBI, as well as cross-validation with fMRI and DTI. Methods will be optimized for clinical feasibility.



Enrollment for the Fusion Optimization Phase is on track (total n = 42; Controls: n = 10; Mild TBI: n = 26; Moderate-to-Severe: n = 2; excluded n = 4). MRI acquisition was initiated. Primary Phase results provide robust support for study hypotheses; dissemination ongoing.

## Timeline and Cost

Activities	Y1	Y2	Y3	Y4	Y5	Y6
IRB, Startup, and Pilot Testing	█					
Collect eye tracking / EEG data (Aim 1)		█				
Collect MRI data (Aim 2)				█		
Optimize sensors & algorithms for clinical use (Aim 3)				█		
Data Analysis & Dissemination			█			
Estimated Total Budget (\$K)	683	697	498	513	660	261

## Goals & Milestones

- Pilot Phase
  - █ Study Startup, Approval, and System Development
  - █ Complete pilot data collection & analyses
- Primary Phase
  - █ Complete data collection for primary study
  - █ Complete primary phase analyses
- Optimization Phase
  - █ Optimize Fusion system for clinical environment
  - █ Complete optimization phase data collection
  - █ Complete optimization phase analyses

## Comments/Challenges/Issues/Concerns

Efforts are currently focused on phase 3 recruitment and enrollment. Phase 3 MRI cross-validation of eye tracking/EEG measurements has begun. Additional staff have been hired to support and complete phase 3 efforts at NMCS and Marine Corp Base Camp Pendleton.

## Budget Expenditure to Date

Projected Expenditure (Year 6): **\$261,000** (est)

Actual Expenditure (Y5Q4): **\$152,211**

Actual Expenditure to date (not including open expenses): **\$2,868,094**