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TITLE: Quantitative Tractography and Volumetric MRI in Blast and Blunt Force TBI: Predictors of Neurocognitive and Behavioral Outcome

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
Our primary aims have been to determine whether frontal WM microstructural integrity accounts for disparate cognitive outcomes in executive function following mild TBI (mTBI) and to determine if injury severity, as measured by loss of consciousness (LOC), is related to neuropsychological outcome and WM microstructural integrity. We examined a subgroup of mTBI participants with executive dysfunction and compared them to a group with intact executive functioning on DTI measures. Results showed that those with executive dysfunction showed significantly decreased fractional anisotropy (FA) values in the anterior corpus callosum as well as in the cingulum and prefrontal white matter regions. Additionally, across the entire sample, we have found that white matter integrity is strongly associated with performance on executive function measures. Finally, those participants with LOC revealed a higher proportion of executive impairment and a similar regional pattern of decreased FA, with additional group differences in the splenium of the corpus callosum.

**15. SUBJECT TERMS**
White matter, cognition, neuropsychology, blast TBI, blunt force TBI

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## INTRODUCTION

The major goals and aims of this study are to investigate whether differences in cognitive outcome are related to mechanism of injury as well as to hippocampal volumes and white matter DTI variables. We will also determine whether MR variables of interest are associated with psychosocial/clinical outcome and whether there are group differences by mechanism of injury. Specifically, we will use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

## BODY

We experienced considerable and unexpected delays regarding obtaining full IRB assurances from three major entities (UCSD IRB, VA San Diego R&D, and HRPPO). However, despite not obtaining these full assurances until this past Summer quarter 2011, we have made significant progress towards our stated goals as outlined in our approved Statement of Work. We delineate and describe our progress points below:

***Year 1:*** Much of the year (10 months versus the expected 6 months) was dedicated to obtaining all necessary regulatory reviews, institutional review board approvals, VA research and development approval, and any other necessary regulatory approvals. As stated in our SOW, we spent the first few months hiring both a research assistant/project coordinator and a graduate assistant who, with adequate and necessary training, assisted greatly with the initial phases of the study. Collectively, we have now begun a massive recruitment of participants for the study. Moreover, we have purchased necessary assessment tools, supplies, and equipment to meet the study's needs. Finally, optimization and finalization of imaging methodology (DT tractography and hippocampal volumetrics) has been undertaken and, at least in regards to the former [DT tractography], we have already processed and analyzed several datasets.

During this first year of the study under the DoD study, we have recruited and tested roughly 9 participants who represent either normal controls or patients who have sustained TBI. After scanning, data is immediately pre-processed and prepared for analysis by skilled staff with expertise in imaging processing and analysis techniques. Fidelity checks of the data collected are thus evaluated as it is collected given that processing occurs within a day or two of data collection. Ongoing recruitment of patients and collection of relevant neuropsychological and behavioral outcome data occurs in tandem with neuroimaging (collected within one week of scanning, after obtaining appropriate consents). Upkeep of regulatory approvals has also been necessary during this timeframe. We expect, per our SOW, that preliminary data analyses will be conducted at the start of year two and continuing until the end of year 3 (at the conclusion of data collection). By the end of year 2 (once an adequate sample size is garnered) and continuing until the end of the award, appropriate statistical analyses will be conducted and preliminary findings will be presented at professional meetings and conferences.

*All tasks listed above have been completed by the personnel listed above (Dr. Delano-Wood, Scott Sorg, and Elisa Lanni). Scott Sorg and Elisa Lanni have actively recruited and enrolled participants. They also assist Dr. Delano-Wood in imaging data collection, processing, and analysis, with the help of Norman Luc (another research assistant who has worked closely with*

*Dr. Delano-Wood for the past three years). Neuropsychological testing takes place within the Neuropsychology Unit at the VA San Diego as part of clinical care for each patient. Appropriate releases are obtained for access to those data. For any individual who was not tested clinically, we conduct a 1.5 hour neuropsychological battery of cognitive tests. Assessment has been coordinated by both Dr. Delano-Wood and Elisa Lanni. IRB continuing review has been spearheaded by Dr. Delano-Wood and Elisa Lanni. Finally, Elisa Lanni has coordinated the genetic testing (buccal swabbing) for the project.*

***Timeline of the IRB Assurances Process***

- September 23, 2010 – Initial study approval granted by the UCSD IRB
- March 16, 2011 – Letter from Nancy Englar (DoD) requesting for additional documents required for DoD approval
- March 25, 2011 – All requested documents and revisions submitted to IRB and DoD for approval
- June 1, 2011 – Email from Nancy Englar notifying us that she did not receive the documents. After some correspondence, it was determined that her Outlook Express was not properly receiving emails.
- June 2, 2011 – Email from Nancy requesting partial waiver of consent for phone screen
- June 2, 2011 – DoD required IRB approval letters for every DoD-requested revision to confirm that these amendments were processed and approved.
- June 17, 2011 – DoD approval – final IRB approval for partial waiver and phone screen needed to be sent to DoD once processed, but study was effectively DoD-approved in the meantime
- June 22, 2011 – DoD approval letter sent to VMRF with request for release of funds. VMRF required confirmation that IRB approved these amendments, which we did not yet have as they were still pending at this time
- July 27, 2011 – IBR approved all amendments, approval letters sent to DoD and VMRF
- July 29, 2011 – Study gained full HRPO and DoD approval
- September 19, 2011 – UCSD IRB reapproved study at continuing review

## KEY RESEARCH ACCOMPLISHMENTS

- In very preliminary analyses, we have been able to show executive impairment in a sample of OEF/OIF veterans with mTBI.
    - Interestingly, we show that executive dysfunction was related to reduced white matter integrity of the anterior cingulum (AC), even after adjusting for volume of the AC and PTSD symptom severity.
    - These preliminary results provide support that white matter integrity is affected in mild to moderate forms of TBI. FA of the AC may represent a sensitive marker and predictor of cognitive decline in the context of mTBI.
- In another small preliminary study, we identified a subgroup of mTBI participants with executive function impairment and compared them to a group with intact executive functions on DTI measures of fractional anisotropy (FA), radial diffusivity, and axial diffusivity in dorsal and ventral frontal cortices as well as in the genu, body, and splenium of the corpus callosum.
    - Results indicated that the executive dysfunction group had significantly decreased FA values relative to the unimpaired group in dorsal and ventral prefrontal cortical regions of interest, and correlational analysis further showed frontal white

matter integrity to be strongly associated with executive function measures in this sample.

## REPORTABLE OUTCOMES

We are in the process of collecting additional data to bolster our findings. At that time, we will write up these studies for publication in reputable, peer-reviewed journals.

## CONCLUSION

Although participant recruitment was considerably delayed, we have been able to meet many of our objectives. Given considerable delays obtaining full IRB assurances, much of the year was dedicated to obtaining all necessary regulatory reviews, institutional review board approvals, VA research and development approval, and any other necessary regulatory approvals. As stated in our SOW, we spent the first few months hiring both a research assistant/project coordinator and a graduate assistant who, with adequate necessary training, assisted greatly with the initial phases of the study. Collectively, we have now begun recruitment of participants for the study. Moreover, we have purchased necessary assessment tools, supplies, and equipment to meet the study's needs. Finally, optimization and finalization of imaging methodology (DT tractography and hippocampal volumetrics) has been undertaken and, at least in regards to the former [DT tractography], we have already processed and analyzed several datasets.

## REFERENCES

There are none to report at this time.

## SUPPORTING DATA

There is none to report at this time.

## APPENDICES

There are none to report at this time.