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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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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 white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether MR variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we 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 ϵ 4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

BODY

Year 2: Despite unexpected IRB delays in year one from the four major entities involved (UCSD IRB, VA San Diego R&D, HARPO, and DoD), we have made considerable strides toward our stated goals as outlined in our Statement of Work. Indeed, this has been an explosive year for our laboratory in terms of growth and productivity. First, through collaboration with another VA investigator (Dawn Schiehser, Ph.D.) who began a 5-year imaging study of cognitive fatigue last year, our TBI laboratory has grown 3-fold. We now consist of 2 PIs, 2 graduate students, 1 post-doctoral fellow, 3 full-time RAs, and 1 undergraduate RA. So far, we have completed 8 studies in just this past year, with one study expected to be published in the Journal of Head Trauma and Rehabilitation within the next month or two. Two other studies are very close to being finalized for submission, and all other completed studies are in various stages of write-up.

During this second year of our DoD study, we have recruited and tested roughly 40 participants who represent either combat controls or patients who have sustained mild to moderate 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. Per our SOW, preliminary data analyses have been well underway over this past year.

All tasks listed above have been completed by the following personnel (Dr. Delano-Wood, Scott Sorg, Elisa Lanni, and Norman Luc). Scott Sorg and Elisa Lanni have actively recruited and enrolled participants. They also assist Dr. Delano-Wood in imaging data collection, processing, and analysis. 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 2 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.

KEY RESEARCH ACCOMPLISHMENTS

We list below our major key accomplishments from this past year. Abstracts describing all projects completed this past year are in the Reportable Outcomes section below.

- **Executive dysfunction and white matter study:** Our first paper that is currently under revised revision and for which we expect to be published by the end of the year, represents an important piece of work that we strongly believe fills in some of the gaps in current studies reported in the literature. Importantly, in a sample of carefully selected participants who displayed adequate effort, we have been able to show executive impairment in a subset of OEF/OIF veterans who have sustained mild to moderate TBI. These findings showed that, although there were no significant overall group differences between control and mTBI participants on DTI measures, a subgroup of mTBI participants with executive dysfunction demonstrated reduced white matter integrity of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without executive dysfunction. Interestingly, participants with TBI with loss of consciousness (LOC) were more likely to evidenced executive function difficulties and disrupted ventral prefrontal white matter integrity when compared to either TBI participants without LOC or control participants. Findings suggest that altered white matter integrity contributes to reduced executive functioning in subgroups of veterans with history of TBI and LOC may be a risk factor for reduced executive function as well as associated changes to ventral prefrontal white matter.
- **Fornix and Cognition study:** In another study close to being ready for submission, we found that fornix white matter integrity is positively associated with performance on tasks of working memory and executive function but not post-concussive symptoms (e.g., headache, imbalance, incoordination, dizziness) in veterans with TBI. Findings suggest that mild-to-moderate TBI affects connectivity between temporal and fronto-limbic circuits—particularly in those at more advanced ages at time of injury—and that these neuropathologic changes may lead to chronic working memory deficits and executive dysfunction.
- **Quality of Life study:** In this study that should be submitted for publication by the end of the year, findings showed that, although cognitive factors (i.e., verbal fluency and memory) are important factors in quality of life (QoL), negative mood—particularly depressive symptomatology—is a particularly strong predictor of QoL in our sample of OEF/OIF veterans with a history of chronic mTBI. These results underscore the importance of better understanding neuropsychiatric and cognitive factors that contribute to poor QoL in veterans with mTBI, and they support the need for the systematic screening and treatment of cognitive and neuropsychiatric symptoms in this vulnerable population.
- **Iowa Gambling Test study:** Given that decision-making likely affects long-term functional outcome following neurotrauma, we examined performance on the Iowa Gambling Task (IGT), a test used to examine reward-related decision-making ability across many clinical populations, in 47 OEF/OIF veterans with a history of chronic mild-to-moderate TBI and normal control (NC) participants. We hypothesized that TBI patients would demonstrate decision-making deficits and that IGT performance would relate to other measures of executive function. Findings demonstrate that mild-to-moderate TBI is associated with subtle reward-related decision-making impairment, and they suggest that the IGT is a sensitive index of this aspect of executive dysfunction in veterans with chronic TBI.

REPORTABLE OUTCOMES

We have the following manuscript to report (provisionally accepted at J of Head Trauma Rehabilitation) as well as several abstracts to report. These studies were completed with joint funding from the VA and DoD:

Manuscript Provisionally Accepted:

Sorg, S.F., **Delano-Wood, L.**, Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W. (Under revised review). White matter integrity in veterans with mild traumatic brain injury: Associations with executive function and loss of consciousness. *Journal of Head Trauma and Rehabilitation*. (**Delano-Wood: Corresponding Author**).

Abstracts to be presented at the International Neuropsychological Society, Waikoloa, HI February, 2013:

Title: Fornix Integrity is Related to Cognition but not Postconcussive Symptoms in Chronic Military Traumatic Brain Injury: A Quantitative Tractography Study **Authors: Delano-Wood, L., Sorg, S.F, Luc, N.K, Schiehser, D., Lanni, E.B, Jacobson, M.W., Nation, D.A., Jak, A.J., Hanson, K.L., Frank, L.R., Meloy, M.J., Delis, D.C., Lohr, J.B., & Bondi, M.W.** **Objective:** Though histopathologic and imaging studies have shown that the fornix—a limbic white matter (WM) structure connecting the hippocampus and mammillary bodies—is a predilection site for neurotrauma, few if any DTI tractography studies of military mild-to-moderate traumatic brain injury (TBI) exist. Given this structure’s potential role in the emergence of cognitive and postconcussive symptomatology (PCS) following TBI, we examined associations between the fornix, cognition, and PCS in veterans with TBI. **Participants and Methods:** 68 OEF/OIF veterans (mTBI: n=48; NC; n=20); mean age=29.2; mean time since injury=2.3 years) were administered 3T DTI scans (61 directions) and comprehensive cognitive and psychiatric assessments. Tractography was employed by seeding ROIs in bilateral contiguous slices on registered T1 images, and mean DTI values were derived from fractional anisotropic (FA) maps. **Results:** Compared to NCs, TBI participants showed lower fornix FA ($t=-2.34, p=.02$) and increased MD ($t=2.15; p=.04$), and changes were observed with respect to axial diffusivity (AD; $t=2.01; p=.05$) but not radial diffusivity (RD: $p=.38$). Age at most significant TBI was negatively related to fornix integrity, even after adjusting for current age ($r=-.55, p=.02$). Fornix DTI indices were associated with WAIS-III Digit Span (FA: $r=.58, p=.01$; MD: $r=-.53, p=.04$), and DKEFS Verbal Fluency Switching (FA: $r=.66, p=.006$) and Switching Accuracy (FA: $r=.64, p=.01$). Fornix DTI indices were not associated with PCS symptomatology (PTSD, depression, anxiety, and quality of life). **Conclusions:** Results show that fornix WM integrity is positively associated with performance on tasks of working memory and executive function but not PCS symptoms in veterans with TBI. Findings suggest that mild-to-moderate TBI affects connectivity between temporal and fronto-limbic circuits—particularly in those at more advanced ages at time of injury—and that these neuropathologic changes may lead to chronic working memory deficits and executive dysfunction.

Title: Processing Speed and Memory Deficits in Veterans with Mild to Moderate TBI: Associations with Anterior White Matter Integrity. Scott F. Sorg, M.S.¹, Lisa Delano-Wood, Ph.D.^{2,3,4}, Dawn M. Schiehser, Ph.D.^{2,3,4}, Norman Luc, B.S.,² Elisa Lanni, B.A.², Amy J. Jak, Ph.D.^{2,3,4}, Karen L. Hanson, Ph.D.^{2,3,4}, Daniel A. Nation, Ph.D.,² Lawrence R. Frank, Ph.D.^{2,3,5}, Jim Lohr, M.D.^{2,3,4} & Mark W. Bondi, Ph.D.^{2,3,4} **Introduction:** High rates of mild to moderate traumatic brain injuries (mTBI) are reported in veterans of the Iraq and Afghanistan wars. The long-term neuropsychological outcome of these injuries and their relationship with cerebral

white matter microstructure is unclear. Using 3D diffusion tensor imaging (DTI) tractography, this study investigated the effects of TBI on a sample of veterans in terms of cognition and white matter integrity. **Methods:** Thirty-eight veterans with TBI and 17 veteran normal control (NC) participants completed neuropsychological and psychiatric testing, and they underwent a DTI scan an average of x.x years following their TBI event(s). Fractional anisotropy (FA), a measure of white matter integrity, was extracted from 7 frontal white matter tracts of interest. **Results:** Controlling for age, depression, and PTSD symptoms, ANCOVA revealed that TBI participants performed worse than NCs on a memory composite ($p=.02$, $\eta^2=.11$) and on a test of psychomotor processing speed ($p=.02$, $\eta^2=.11$), whereas the two groups did not differ on an executive function composite ($p=.37$, $\eta^2=.02$) or on a measure of attention ($p=.56$, $\eta^2=.01$). The TBI group evidenced lower FA in the left cingulum bundle ($p=.01$, $\eta^2=.13$) and in the genu of the corpus callosum ($p=.03$, $\eta^2=.09$). Partial correlations adjusting for age and education showed significant positive associations psychomotor processing speed and FA in the left cingulum ($r=.38$, $p=.04$), genu ($r=.50$, $p<.01$) and body of the corpus callosum ($r=.52$, $p<.01$), and left posterior internal capsule ($r=.45$, $p=.01$). **Conclusions:** Results suggest that, in veterans with mTBI, the cognitive consequences of mTBI appear to be enduring, and they are specifically associated with poorer performance in memory and processing speed domains. Findings further suggest that slowed processing speed may be a consequence of TBI-related damage to anterior white matter pathways.

Title: Iowa Gambling Task Impairment is Associated with Executive Dysfunction in Veterans with Chronic Mild-to-Moderate Traumatic Brain Injury. *Authors: Luc, N.K., Nation, D.A., Sorg, S.F., Schiehser, D.M., Hanson, K.L., Lanni, E., Jak, A.J., Matsevovyan, A., Kim, R., Jacobson, M.W., Bondi, M.W., Lohr, J.B., & Delano-Wood, L.* **Objective:** The Iowa Gambling Task (IGT) has been used to examine reward-related decision-making ability across many clinical populations; however, few studies have investigated IGT performance in the context of traumatic brain injury (TBI). Given that decision-making likely affects long-term functional outcome following neurotrauma, we examined IGT performance in OEF/OIF veterans with a history of chronic mild-to-moderate TBI and normal control (NC) participants. We hypothesized that TBI patients would demonstrate decision-making deficits and that IGT performance would relate to other measures of executive function. **Participants and Methods:** Forty-seven demographically-matched participants (TBI: $n=26$; NC: $n=21$; mean age = 32.7; mean months since TBI = 80.7) were administered a comprehensive neuropsychological battery, including a computerized version of the IGT. Participants were divided into impaired and unimpaired performance on IGT based on a T-score cutoff of more than one SD below the mean ($T \leq 39$). **Results:** TBI participants were more likely to exhibit impairment on the IGT total score relative to the NC group (% Impaired: TBI = 20.7%; NC = 0%; $p=.02$). Repeated measures ANOVA indicated a group by block interaction ($p=.04$), whereby the TBI group performed worse than NCs on block 4 ($p=.03$) and were more likely to exhibit impairment on 2 or more blocks (% Impaired: TBI = 19.2%; NC = 0%, $p = .03$). Within the whole sample, IGT performance was correlated with worse performance on executive function measures (DKEFS Trails Switching [$r= -.36$, $p=.02$], WCST Perseverative Responses [$r= -.35$, $p=.02$], and WCST Set Losses [$r= -.30$, $p=.049$]). **Conclusions:** Findings demonstrate that mild-to-moderate TBI is associated with subtle reward-related decision-making impairment, and they suggest that the IGT is a sensitive index of this aspect of executive dysfunction in veterans with chronic TBI.

Title: Neuropsychological Predictors of Quality of Life in Veterans with Chronic Mild-Moderate Traumatic Brain Injury. *Matsevovyan A, Delano-Wood L, Alhassoon, Lanni EB, Luc NK, Kim R, Jak AJ, Jacobson MW, Meloy MJ, Hanson KL, & Schiehser DM.* **Objective:** Individuals with chronic mild to moderate traumatic brain injury (TBI) frequently report poor quality of life (QoL); however, how QoL relates to injury severity characteristics and

neurocognitive outcome is unclear. We therefore investigated the association between QoL, TBI injury variables (e.g., loss of consciousness [LOC]), and cognitive function in OEF/OIF veterans with chronic TBI. **Participants and Methods:** Thirty-four OEF/OIF veterans with TBI (mean age=29.8; mean months since injury=48.9) underwent cognitive testing (letter fluency and verbal memory [CVLT-II]) and completed measures of psychiatric status (anxiety, depression, and post-traumatic stress disorder [PTSD]). The World Health Organization Quality of Life Measure-Abbreviated Version (WHOQOL-BREF) which measures Physical, Psychological, Social, and Environmental QoL was also administered. **Results:** QoL was related to negative mood (depression, anxiety, and PTSD symptoms; all p -values $< .01$) but was not related to age, education, number of TBIs, or LOC. Lower overall QoL was associated with reduced letter fluency performance (all p -values $< .05$) as well as verbal learning ($p = .057$). Subscale analysis showed that lower Social, Psychological, and Environmental QoL were associated with poorer Letter Fluency performance; Social QoL was positively related to verbal recall and recognition; and Physical QoL was positively related to verbal learning (all p -values $< .01$). **Conclusion:** Results demonstrate that, in our sample of OEF/OIF veterans with chronic TBI, neuropsychological functioning is an important factor in veterans' appraisals of their QoL. Specific cognitive domains that are associated with poorer QoL include verbal fluency and memory, both of which are frequently impaired following TBI. Findings underscore the importance of better understanding cognitive and neuropsychiatric factors that contribute to poor QoL in veterans with TBI, and they support the need for comprehensive systematic screening and treatment of this vulnerable population.

Title: Cognitive Discrepancy-Based Analysis of Chronic Military Traumatic Brain Injury Suggests Mild Executive Dysfunction. Karen L. Hanson, Ph.D.^{1,2,3}, Daniel A. Nation, Ph.D.,¹ Henry Orff, Ph.D.^{1,2,3}, Scott F. Sorg, M.S.,⁴ Lisa Delano-Wood, Ph.D.^{1,2,3}, Schiehser, D.M.,^{1,2,3} Amy J. Jak, Ph.D.^{1,2,3}, Lohr, J.B.,^{1,2,3} Dean C. Delis, Ph.D.^{1,2,3} **Objective:** The long-term cognitive sequelae of chronic mild-to-moderate traumatic brain injury (TBI) are unclear. We examined traditional single-test analysis and a novel discrepancy-based analysis to detect subtle cognitive deficits among veterans with chronic TBI. Baseline executive function components (thought to be less sensitive to brain injury) were compared to higher-order components (thought to be more sensitive to brain injury). **Methods:** 420 demographically-matched participants (TBI: $n=227$ veterans; normal controls [NC]: $n=193$) completed the DKEFS Color-Word Interference (CWI), Verbal Fluency, and Trailmaking tests. Veterans (mean age = xx) were patients who presented for neuropsychological assessment at the VA San Diego Healthcare System. Groups were compared on individual subtest age-scaled scores and discrepancy scores (dual-level executive skill – baseline cognitive skill). **Results:** One-way ANOVAs revealed that TBI participants performed worse than NCs on CWI Color Naming ($p=.02$), Inhibition ($p=.01$), and Inhibition Switching ($p=.001$), and they demonstrated a larger discrepancy between the baseline conditions and Inhibition Switching ($p=.07$). The TBI group scored higher than NCs on Category Fluency ($p=.04$) but performed worse on Letter Fluency ($p=.09$); they also showed a greater discrepancy between these two subtests ($p<.001$) and between Category Switching and Letter Fluency ($p=.04$). Finally, TBI veterans scored worse on the dual-level Switching condition ($p=.03$) and had a greater discrepancy between the baseline and Switching conditions ($p<.001$). **Conclusions:** Findings provide further evidence that chronic mild-to-moderate TBI among veterans is associated with impaired executive function. Results also show that veterans with TBI demonstrate greater decline from basic cognitive components of those tests to the higher-order components of the same tests relative to healthy controls. These findings suggest that a discrepancy-based analysis may be superior to mean single-test analysis in detecting mild enduring effects of TBI.

Title: The Relationship Between Fornix White Matter Integrity and Memory Performance in Mild Cognitive Impairment Subtypes: A Diffusion Tensor Tractography Study

Authors: Luc, N., Sorg, S., Lanni, E., Schiehser, D., Bondi, M.W., Jak, A.J., Delis, D.C., Frank, L.R., & Delano-Wood, L. **Objective:** The fornix is a white matter (WM) structure within the Papez circuit connecting the hippocampus to the frontal lobe. Since studies have suggested that hippocampal atrophy may precipitate cognitive decline in the context of mild cognitive impairment (MCI); we investigated the association between fornix integrity, hippocampal volume, and cognition in MCI subtypes. **Participants and Methods:** Forty-seven older adults were divided into two demographically-comparable groups on the basis of their cognitive status (MCI: n=27; Normal Control [NC]: n=20). Comprehensive neuropsychological evaluations were administered as well as a 61-direction 3T-DTI scan. DTI values were extracted from fornix tracking, seeded from an ROI drawn on a T1 image and using an FA color-map as a reference. Hippocampal and intracranial volume were estimated using FreeSurfer. **Results:** Despite no differences in hippocampal volume, MCI participants demonstrated lower fornix FA after adjusting for age and intracranial volume ($p=.001$). Additionally, the Amnesic MCI subgroup showed poorer WM fornix FA when compared to the Nonamnesic MCI subgroup, and fornix DTI values were positively related to performance on tasks of verbal memory (recall, retention, and recognition). **Conclusions:** Our results demonstrated that, when compared to normally aging participants, those with MCI showed poorer fornix WM integrity. Additionally, the Amnesic MCI subgroup demonstrated poorer fornix integrity than the Nonamnesic MCI subgroup, and fornix FA was positively related to performance on verbal memory tasks. Findings suggest that fornix integrity may be more sensitive than hippocampal volumes to early MCI-related cognitive decline, and lend further support to the notion that WM integrity plays a role in MCI-related changes.

CONCLUSION

Despite some unexpected IRB delays in year one of this award, we have made considerable progress this past year towards our stated goals as outlined in our Introduction above. Given greater collaborations with other VA TBI investigators, our laboratory has grown considerably and productivity has increased significantly. Collectively, my laboratory has completed 8 studies in just this past year, with one study expected to be published in the *Journal of Head Trauma and Rehabilitation* (citation below) next month. Two other studies are very close to being finalized for submission, and all other completed studies are in various stages of write-up. Moreover, recruitment has ramped up considerably. During this second year, we have recruited and tested roughly 50 participants, and we have several potential participants waiting to be scanned and tested through our protocol. At this pace, we expect year 3 of this award to be especially productive, and we are currently actively pursuing additional funding to complement the aims and goals of this award.

REFERENCES

Sorg, S.F., Delano-Wood, L., Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W. (Under revised review). White matter integrity in veterans with mild traumatic brain injury: Associations with executive function and loss of consciousness. *Journal of Head Trauma and Rehabilitation*.

APPENDICES

We have attached our first DTI paper which is under review at the *Journal of Head Trauma and Rehabilitation*. Reviewers had only minor concerns (it was provisionally accepted) so we expect publication within the next month or two.

Journal of Head Trauma Rehabilitation

White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness --Manuscript Draft--

Manuscript Number:	JHTR-D-12-00093
Full Title:	White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness
Article Type:	Original Article (unsolicited)
Section/Category:	Unsolicited (Focus on Clinical Research)
Keywords:	Traumatic Brain Injury; Executive Functions; Diffusion Tensor Imaging; White Matter
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Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED STATES
Abstract:	Objective: To investigate using diffusion tensor imaging (DTI) whether white matter integrity accounts for disparate cognitive outcomes in executive function (EF) in post-acute mild TBI (mTBI) and whether injury severity, as measured by loss of consciousness (LOC) versus alterations in consciousness (AOC), is associated with white matter microstructural alterations and neuropsychological outcome. Participants: Thirty-two Iraq and Afghanistan War era veterans with a history of mTBI and 15 healthy veteran control participants. Results: There were no significant overall group differences between control and mTBI participants on DTI measures after multiple comparison correction. However, a subgroup of mTBI participants with EF decrements (n = 13) demonstrated significantly decreased fractional anisotropy (FA) of prefrontal white matter, corpus callosum, and

cingulum bundle structures compared to mTBI participants without EF decrements (n = 19) and control participants. mTBI participants with LOC were more likely to evidence reduced EF performances and disrupted ventral prefrontal white matter integrity when compared to either mTBI participants without LOC or control participants.

Conclusions: Findings suggest that altered white matter integrity contributes to reduced EF in subgroups of veterans with a history of mTBI and that LOC may be a risk factor for reduced EF as well as associated changes to ventral prefrontal white matter.

July 12, 2012

Dear Dr. Corrigan:

Accompanying this letter is a manuscript titled “White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness”. The authors would appreciate being considered for publication in *The Journal of Head Trauma Rehabilitation*. Please let us know if there are any difficulties with the attachments.

The manuscript contains original work that has not been published or submitted for publication elsewhere. The authors report no conflicts of interest related to the content of this manuscript. All procedures complied with the local UCSD and VA institutional review boards.

All correspondences regarding this manuscript may be sent to the corresponding author (email is preferred):

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Thank you for your time and consideration.

Sincerely,

Scott F. Sorg

1 Running head: WHITE MATTER AND EXECUTIVE FUNCTION IN MILD TBI

2

3 White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive

4 Function and Loss of Consciousness

5

6

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8 Text Word Count: 5,172

9

ABSTRACT

Objective: To investigate using diffusion tensor imaging (DTI) whether white matter integrity accounts for disparate cognitive outcomes in executive function (EF) in post-acute mild TBI (mTBI) and whether injury severity, as measured by loss of consciousness (LOC) versus alterations in consciousness (AOC), is associated with white matter microstructural alterations and neuropsychological outcome.

Participants: Thirty-two Iraq and Afghanistan War era veterans with a history of mTBI and 15 healthy veteran control participants.

Results: There were no significant overall group differences between control and mTBI participants on DTI measures after multiple comparison correction. However, a subgroup of mTBI participants with EF decrements ($n = 13$) demonstrated significantly decreased fractional anisotropy (FA) of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without EF decrements ($n = 19$) and control participants. mTBI participants with LOC were more likely to evidence reduced EF performances and disrupted ventral prefrontal white matter integrity when compared to either mTBI participants without LOC or control participants.

Conclusions: Findings suggest that altered white matter integrity contributes to reduced EF in subgroups of veterans with a history of mTBI and that LOC may be a risk factor for reduced EF as well as associated changes to ventral prefrontal white matter.

Key Words: Traumatic Brain Injury, Executive Functions, Diffusion Tensor Imaging, White Matter

INTRODUCTION

Mild traumatic brain injury (mTBI) is common among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans, with estimated prevalence rates ranging from 15% to 30%^{1,2}. Unfortunately, the long-term neuropsychological consequences of mTBI in this population are not well defined. Although deficits in processing speed, attention, working memory, memory, and executive functions have been frequently demonstrated in the acute phase following mTBI^{3,4}, the prevalence and severity of cognitive deficits in the post-acute phase (i.e., after 3-6 months) are much less clear. Although there are reports showing chronic neuropsychological difficulties following mTBI⁵⁻⁷, meta-analytic studies using unselected and prospective samples report only transient impairments in multiple cognitive domains that tend to return to the normal range by three months post-injury⁸⁻¹¹. However, when studies using clinical samples (i.e., self-referred and/or with persisting cognitive complaints) are included, mTBI has a medium to large effect on neuropsychological functioning in the post-acute phase^{12,13}. Those factors that relate to enduring post-acute symptomatology remain elusive, although some studies have shown associations with injury severity as well as confounding psychiatric conditions such as depression and anxiety^{6,14-16}. Additionally, problems associated with effort and litigation have also been implicated^{12,17}.

As suggested by the aforementioned meta-analyses⁸⁻¹¹, any long-term effects of mTBI, if present, are likely subtle. Given these suggestions coupled with the well documented finding that the structural vulnerability of the frontal lobes in TBI may contribute to impaired executive function (EF) performance¹⁸⁻²⁰, it may be that mTBI preferentially affects specific higher-order cognitive skills such as EF that rely on the integration of multiple component cognitive processes. In support of this possibility, a meta-analysis by Rohling et al.¹⁰ reported that, although the overall effect of mTBI was negligible after three months, a small but significant decrement remained in the working memory domain. In addition, Hartikainen et al.²¹ reported that protracted recovery following mild to moderate TBI was associated with poorer performance measures of EF. Finally, Vanderploeg et al.²² found indications of executive

dysfunction in the form of heightened proactive interference in U.S. military personnel eight years post mTBI, and Nolin²³ has reported deficient encoding strategies in mTBI.

The high prevalence of mTBI in OEF/OIF veterans underscores the need for improved understanding of its possible long-term cognitive consequences, its underlying brain changes, and for enhanced characterization of those factors that may contribute to poorer outcomes. White matter is particularly vulnerable to the effects of the shearing and stretching forces characteristic of neurotrauma and some studies using diffusion tensor imaging (DTI) have found evidence for disrupted white matter integrity following mTBI²⁴⁻³⁰. DTI is a non-invasive neuroimaging method used to investigate and characterize the microstructural integrity of the white matter³¹. This imaging modality is sensitive to the random motion of water molecules within white matter and yields measures such as fractional anisotropy (FA), an index of white matter microstructural integrity gleaned by the intravoxel directional coherence of water molecules in tissue^{32,33}. Thus, higher FA values are indicative of healthy tissue with uniform microstructure, whereas relatively lower values suggest a disruption of microstructure implying tissue damage³². Reductions in FA may result from a decrease in axial diffusivity (AD) (diffusion along the principal diffusion direction [along the axon]), an increase in radial diffusivity (diffusion perpendicular to the primary diffusion direction), or an additive or synergistic effect of the two. Although there is some debate as to the specific meaning of the component diffusion measures^{34,35}, AD has most commonly been interpreted as describing axonal integrity, and radial diffusivity (RD) has been described as a proxy for myelin integrity³⁶.

Injury characteristics such as loss of consciousness (LOC) are used to assign the severity of injury as “mild,” although they have often been shown to be unrelated to cognitive outcomes within mTBI samples³⁷. Among OEF/OIF veterans who have experienced a TBI, the distinction between LOC versus an altered state of consciousness (AOC)—but without LOC—following a head injury has been a focus of recent research^{1,38-40}. However, it remains unclear to what degree these potential differences in severity

within mTBI are associated with outcome, and the neuropsychological consequences of LOC versus AOC in the context of military TBI have not been fully explored.

The goals of the current study were to (1) assess whether OEF/OIF veterans with a history of mTBI demonstrate alterations in white matter microstructure; (2) determine whether our mTBI sample shows executive function decrements; (3) investigate the extent to which executive dysfunction is associated with frontal white matter alterations; and (4), in an exploratory analysis, examine whether injury severity as indexed by LOC is associated with white matter damage and concomitant executive dysfunction. Given prior discrepant findings across studies of chronic mTBI, we did not expect our overall sample of chronic mTBI participants to show gross alterations in white matter microstructure or cognitive dysfunction relative to healthy control participants; however, a subgroup of mTBI participants with evidence suggestive of cognitive dysfunction was expected to show poorer white matter microstructural integrity. We also examined whether and how differences in AD or RD explain any significant subgroup differences in white matter integrity in terms of axonal or myelin compromise. Finally, in an exploratory analysis, we posited that mTBI participants with LOC (versus those with AOC) would evidence poorer white matter integrity, particularly in anterior regions.

METHODS

Participants

Forty-seven OIF/OEF veterans were recruited for the current study (mTBI: $n = 32$; normal controls [NC]: $n = 15$). All mTBI participants were diagnosed with a mild closed head injury during outpatient evaluation of TBI at the Veterans Affairs <masked> Healthcare System (VA--HS). We used the following criteria delineated by the Department of Defense (DoD) and Department of Veterans Affairs Traumatic Brain Injury Task Force⁴¹ for mTBI: (1) AOC or LOC ≤ 30 minutes; (2) an initial Glasgow Coma Scale⁴² (GCS) score between 13-15 (which is often not available in a combat setting); (3) a period of post-traumatic amnesia (PTA) ≤ 24 hours; and (4) no visible lesions on MRI or CT scan.

LOC was not required for a TBI diagnosis, as any AOC lasting less than 24 hours following a head injury event, regardless of mechanism, was sufficient to warrant a diagnosis as defined by the United States DoD⁴³. As is typical of many military and civilian TBI studies, LOC or AOC duration was often determined via self-report given the paucity of patient medical information that is typically available surrounding mTBI events, particularly in combat settings.

No participants included in the current study demonstrated obvious lesions on standard neuroimaging. Exclusion criteria for all mTBI and NC participants included: (1) moderate to severe TBI (LOC > 30 min, PTA > 24 hours, GCS < 12); (2) a history other neurological condition (e.g., multiple sclerosis, seizure disorder); (3) developmental learning disability; (4) current substance or alcohol abuse according to DSM-IV criteria; (5) pre-injury metabolic or other diseases known to affect cognition (e.g., diabetes); (6) history of psychiatric disorder prior to the TBI event; (7) current or pending litigation; (8) any contraindications to MRI scanning (e.g., claustrophobia, shrapnel); or (9) below threshold cut-off scores on effort testing. Participants were, on average, approximately 2-4 years removed from their TBI event or events at the time of testing. All participants provided written informed consent, and all procedures complied with the local UCSD and VA institutional review boards.

Participants' demographic and injury characteristics are presented in Table 1. The normal control and mTBI groups did not significantly differ on any demographic characteristics (e.g., age, education level, sex distribution), although the mTBI group evidenced significantly higher levels of depressive (Beck Depression Inventory-II⁴⁴, BDI-II, $p < .01$) and PTSD-related symptomatology (PTSD Check List – Military Version⁴⁵, PCL-M, $p < .001$). However, the two mTBI subgroups (detailed below) did not differ from one another on either measure of depressive or PTSD-related symptoms, nor did they differ on any of the TBI injury severity characteristics with the exception of LOC percentage ($p = .03$; see Table 1).

[Insert Table 1 here]

Neuropsychological Assessment

Participants were administered a battery of neuropsychological tests selected for its sensitivity to TBI. The following tasks were used to evaluate executive functions: the Wisconsin Card Sorting-Task 64-Card Version^{46,47} and the Delis-Kaplan Executive Functioning System⁴⁸ Trail Making and Verbal Fluency Switching tests. Participants were also administered the Wide Range Achievement Test-4⁴⁹ (WRAT-4) Reading subtest as a measure of premorbid intellectual functioning. Demographically-adjusted *T*-scores⁴⁷ and scaled scores⁴⁸ were used for all analyses. Participants were also administered the PLC-M and the BDI-II. Administration time for the entire neuropsychological battery was approximately 2.5 hours.

Reduced Executive Function Subgroup Criteria. Participants were classified as having reduced executive function performances if any of the following criteria were met: *T*-score less than 40 for WCST Perseverative Responses (PR) or a Scaled Score less than 7 for D-KEFS Verbal Fluency Category Switching Total Correct or Trails Letter-Number Switching. Of the 13 mTBI participants identified with reduced executive function performances, 6 demonstrated impairment on the WCST-PR, 5 on Category Fluency Switching and 7 on Letter-Number Switching. Nine of the 13 had impaired scores on only one of the three executive function measures; 3 had impaired scores on two of the measures; and 1 was impaired on all three measures.

Symptom Validity Test Measures. The Test of Memory Malingering⁵⁰ (TOMM) and the Forced-Choice Recognition Trial of the California Verbal Learning Test-II⁵¹ (CVLT-II) were used to assess effort. Cut-off scores for identifying inadequate effort (TOMM Trial 2 < 45 and CVLT-II Forced-Choice Recognition Trial < 15) were based on recommendations from Tombaugh⁵⁰ and Moore & Donders⁵², respectively.

Brain Imaging

All participants underwent structural MRI and DTI on 3T General Electric (GE) MRI scanners housed within the UCSD Functional Magnetic Resonance Imaging (fMRI) Center on the UCSD La Jolla campus. Thirty-seven participants were scanned on with the scanner equipped with the Excite HDx

platform and, following the FMRI Center's scanner upgrade, data on 10 subjects were acquired with the scanner running the MR750 platform. There were no significant differences in regional FA values between those 10 participants scanned on the MR750 platform and 10 randomly selected age-matched participants scanned on the Excite HDx platform (p 's = .21 - .99 for all regions of interest).

Structural Scanning: A sagittally-acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: FOV 24 cm, 256 x 256 x 192 matrix, 0.94 x 0.94 x 1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms; flip angle 12°, scan time was roughly 7 minutes.

Diffusion Tensor Imaging: DTI images were collected with a dual spin echo EPI acquisition⁵³ with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 X 128, in-plane resolution = 1.875 x 1.875, TR = 10900 ms, TE = 93 ms. The ten scans from the MR750 platform used identical scanning parameters though TR was shortened to 8000 ms to reduce scan time without affecting image quality. Across scanners, thirty-four slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model⁵⁴ and a b-value of 1500 s/mm², as well as one T2 image with no diffusion weighting (b = 0). Two field maps with the same spatial parameters as those of the DTI scan were collected in order to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12-16 minutes.

DTI Data Processing: The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Package⁵⁵ (FSL) was used for image processing. The two field maps were used to unwarp the EPI acquisitions. Images were then corrected for motion and eddy currents using the *eddy correct* FSL command. Each image was visually inspected for quality and data from three participants did not meet quality standards and therefore were removed from analyses. The FSL program *bet* removed non-brain voxels from the analysis. The FSL program *dtifit* fit a diffusion tensor model at each voxel to provide DTI variables such as fractional anisotropy and eigenvalues on a voxel-by-voxel basis. Per Song et al.³⁶, axial diffusivity was defined by the principal eigenvalue (i.e., AD = L1), and radial diffusivity (RD) was defined as the average of the second and third eigenvalues: RD = (L2 + L3)/2.

Semi-Automated Regions of Interest: Region of Interest (ROI) placement was guided by a multi-step process, and all ROIs were placed in MNI standard space as shown in Figure 1. First, the Tract-based Spatial Statistics (TBSS) algorithm was used to align all FA images to a standard space, as well as to identify those fiber tracts common to all participants (see Smith et al.⁵⁶ for a complete description). An FA threshold of .20 was used to restrict the white matter skeleton to voxels comprising only white matter and to reduce partial voluming effects. Next, ROIs were placed in the genu, body, and splenium subsections of the corpus callosum (CC), and bilaterally in the cingulum bundles and the anterior and posterior internal capsules (AIC, PIC) following the ICBM-DTI-81 white matter labels atlas available within FSL⁵⁷. The cingulum bundle was segmented into posterior and anterior components wherein anterior cingulum was defined as those voxels anterior to the CC body and CC genu division, and posterior cingulum was defined as those voxels posterior to the CC body and CC splenium division. Two additional ROIs were placed in the prefrontal white matter identified as the dorsal prefrontal white matter (DPWM) and ventral prefrontal white matter (VPWM). Prefrontal white matter was defined as all skeleton voxels anterior to the genu of the CC. The ventral/dorsal boundary was defined by a parasagittal line connecting the anterior and posterior commissures⁵⁸. Mean FA, RD and AD values for each ROI were extracted for each subject and exported to SPSS 18 for statistical analyses.

Statistical Analyses

Group comparisons were conducted using analysis of variance (ANOVA) followed by contrast testing (t-tests), including comparisons of the executive function subgroup status and AOC vs. LOC group comparisons of the DTI metrics. Effect size statistics (Cohen's *d*) for the significant *p*-values for each of the group comparisons were also calculated. Categorical data were analyzed using likelihood-ratio chi-square tests (e.g., LOC by executive function subgroups) due to the relatively small sample size. Multiple comparison corrections were conducted using false discovery rate (FDR) methodology⁵⁹ for the primary DTI analysis between reduced and intact EF subgroups and control participants with FDR set at .05. Multiple comparison corrections were not performed on the LOC vs. AOC analyses due to their

exploratory nature.

RESULTS

Mild TBI vs. Normal Control Group Comparisons

As shown in Table 2, comparisons of the regional DTI values between the mTBI and NC groups revealed significantly lower FA in the anterior (Cohen's $d = .57, p = .01$) and posterior cingulum (Cohen's $d = .51, p = .003$), although these group differences of medium effect sizes did not survive FDR correction for multiple comparisons (p -corrected $> .10$). Group comparisons between healthy control and mTBI participants in all other DTI regions of interest did not reach significance ($p > .10$).

As shown in Table 3, the mTBI group performed significantly worse than the NC participants on category fluency switching (Cohen's $d = .80, p = .002$). Importantly, a post-hoc analysis of co-variance (ANCOVA) adjusting for BDI-II and PCL-M scores found that the lower score on category fluency switching remained significant, suggesting that co-morbid psychiatric disturbance did not account for the lower scores observed in the mTBI sample.

[Tables 2 and 3 about here]

Reduced vs. Intact Executive Function mTBI Subgroup Comparisons

Approximately 41% percent (13/32) of the mTBI sample demonstrated reductions on executive function (EF) measures based on the criteria described above. As shown in Table 1, there were no significant differences on demographic characteristics or psychiatric symptomatology between the two subgroups. Of the injury characteristics, LOC status significantly differed between subgroups, with higher rates of LOC in the reduced EF subgroup ($p = .03$). Additionally, the number of months since the most recent mTBI significantly differed between subgroups. Specifically, the reduced EF subgroup had more recently experienced an mTBI event ($p = .03$), with a mean time since injury of roughly two years for the reduced EF subgroup versus four years for the intact EF subgroup. However, mTBI subgroups did not differ in frequency of blast exposure or total number of mTBI events (all p -values $> .70$).

[Figure 1 about here]

Executive Function mTBI Subgroup Differences by DTI Indices of White Matter Integrity

Table 2 lists the means, standard deviations, and results of comparisons of the control group and two mTBI subgroups on the DTI measures across each of the regions of interest. The group FA comparisons for each ROI are further illustrated in Figure 1. It is important to note that the intact EF mTBI subgroup did not significantly differ from control participants on any DTI measure (including all fractional anisotropy and radial and axial diffusivity measures) across all ROIs (all p -values $> .10$). However, as can be seen in Figure 1, statistically significant (p -corrected $< .05$) FA reductions with large effect-sizes were found for the reduced EF mTBI subgroup when compared to the intact EF subgroup in the DPFWM (Cohen's $d = 1.05$), VPFWM (Cohen's $d = .96$), CC genu (Cohen's $d = .98$), CC body (Cohen's $d = 1.07$), CC splenium (Cohen's $d = .99$), the posterior cingulum (Cohen's $d = 1.28$), and with a trend toward significance (p -corrected $< .10$) in the anterior cingulum (Cohen's $d = .76$). These findings were unchanged after adjusting for months since injury in analyses of co-variance (ANCOVA). All other FA ROIs (i.e., AIC and PIC) did not reach significance (all p -values $> .10$). When compared to control participants, the reduced EF mTBI subgroup showed significantly lowered (p -corrected $< .05$) FA values in the VPFWM (Cohen's $d = .98$), the anterior cingulum (Cohen's $d = .97$) and the posterior cingulum (Cohen's $d = 1.28$) with trends in this direction for the CC genu (Cohen's $d = .79$) and CC splenium (Cohen's $d = .73$).

The reduced EF mTBI subgroup showed significantly higher (p -corrected $< .05$) radial diffusivity (RD) than the intact EF subgroup within the VPFWM (Cohen's $d = 1.02$), the CC body (Cohen's $d = .94$), and the posterior cingulum (Cohen's $d = .94$), with trends (p -corrected $< .10$) in the CC genu (Cohen's $d = .75$) and splenium (Cohen's $d = .74$). Compared to NCs, there was a trend (p -corrected $< .10$) toward higher RD in both the VPFWM (Cohen's $d = .98$) and posterior cingulum (Cohen's $d = .88$) in the reduced mTBI subgroup. Regarding axial diffusivity (AD), the reduced EF mTBI subgroup showed significantly lower (p -corrected $< .05$) AD values within the AIC (Cohen's $d = 1.10$) and the PIC (Cohen's $d = 1.26$) relative the intact EF subgroup. All other AD ROIs did not reach significance, and there were no significant differences between the control and reduced EF mTBI groups.

[Figure 2 about here]

Exploratory Group Comparisons by LOC vs. AOC

Since the reduced EF subgroup demonstrated a higher percentage of participants with LOC compared to the intact EF subgroup (see Table 1), exploratory analyses were conducted to investigate the associations among LOC, cognition, and white matter integrity. The mTBI sample as separated by LOC/AOC status [LOC ($n = 20$) versus AOC ($n = 12$)] did not significantly differ in terms of age, education, WRAT-Reading scores, or injury and psychiatric characteristics (p values $> .05$). Group comparisons of AOC vs. LOC on the individual executive function scaled scores and T -scores were not significantly different (p values $> .05$). However, the LOC subgroup was found to have significantly lower D-KEFS Category Fluency Switching Total Correct scaled score compared to NCs ($M_{\text{Control}} = 12.5$, $SD_{\text{Control}} = 3.2$, $M_{\text{LOC}} = 10.0$, $SD_{\text{LOC}} = 3.3$, $p = .04$, Cohen's $d = .77$).

An analysis of the regional DTI values did reveal significant group differences in white matter integrity. As can be seen in Figure 2, the LOC subgroup evidenced significantly higher RD in the VPFWM than the AOC subgroup (RD $\times 10^{-3}$ mm²/sec: $M_{\text{AOC}} = 0.54$, $SD_{\text{AOC}} = 0.02$, $M_{\text{LOC}} = 0.57$, $SD_{\text{LOC}} = 0.04$, $p = .02$, Cohen's $d = .87$) with a trend toward higher VPFWM AD (AD $\times 10^{-3}$ mm²/sec: $M_{\text{AOC}} = 1.07$, $SD_{\text{AOC}} = 0.03$, $M_{\text{LOC}} = 1.09$, $SD_{\text{LOC}} = 0.03$, $p = .08$, Cohen's $d = .65$). Similarly, when compared with control participants, VPFWM RD was significantly higher in the LOC subgroup ($M_{\text{Control}} = 0.54$, $SD_{\text{Control}} = 0.03$, $M_{\text{LOC}} = 0.57$, $SD_{\text{LOC}} = 0.04$, $p = .03$, Cohen's $d = .73$) with a trend toward lower FA values ($M_{\text{Control}} = 0.42$, $SD_{\text{Control}} = 0.02$, $M_{\text{LOC}} = 0.41$, $SD_{\text{LOC}} = 0.03$, $p = .06$, Cohen's $d = .63$). The LOC subgroup also significantly differed from the normal control group in the anterior cingulum FA ($M_{\text{Control}} = 0.48$, $SD_{\text{Control}} = 0.03$, $M_{\text{LOC}} = 0.46$, $SD_{\text{LOC}} = 0.03$, $p = .05$, Cohen's $d = .71$). Comparisons of other ROIs did not approach significance (p 's $> .10$).

DISCUSSION

Our finding that reduced EF performance may be present in a subgroup of OEF/OIF veterans with a history of mTBI is consistent with other reports showing chronic neuropsychological difficulties

1 following mTBI⁵⁻⁷. Results further revealed that this subgroup of mTBI participants demonstrated
 2 significantly lower white matter integrity (FA) when compared to either mTBI participants with intact EF
 3 or healthy control participants within prefrontal, commissural, and posterior association tracts, and
 4 findings are consistent with other reports showing lower white matter integrity in a mTBI subgroup with
 5 protracted recovery^{21,30}. In addition, the RD analysis suggests that compromised myelin integrity may
 6 contribute to the lower white matter integrity within frontal white matter, the corpus callosum, and
 7 posterior cingulum within this reduced EF subgroup. These findings were in contrast to the mTBI group
 8 as a whole, which did not significantly differ from our normal control group in terms of white matter
 9 integrity. Taken together, our results demonstrate that (1) executive dysfunction is strongly associated
 10 with white matter integrity in a subgroup of OEF/OIF veterans with mTBI across frontal and more
 11 posterior regions, and (2) further suggest that the observed impairment in executive functioning, in some
 12 cases, may be a result of persisting neuronal damage from mild TBI.

13 The exploratory LOC analyses offer some provisional support to the notion that the observed EF
 14 reductions and concomitant white matter compromise in our sample of mTBI participants are perhaps
 15 related to neurotrauma history and are not solely due to normal variation in EF scores. First, LOC was
 16 associated with higher rates of impaired EF scores when compared to those reporting AOC (without
 17 LOC). This distinction is generally consistent with some mTBI studies that have tied LOC to poorer
 18 health outcomes and a more prolonged recovery^{1,39,40}. However, the effect of LOC in these studies was
 19 significantly attenuated after accounting for psychiatric symptomatology such as PTSD symptom
 20 severity. Moreover, Belanger et al.³⁸ reported that PTSD symptom severity, but not LOC, was associated
 21 with increased reporting of post-concussive symptoms. In contrast, in our sample, LOC was not
 22 associated with higher levels of psychiatric distress when compared to those who did not lose
 23 consciousness.

24 Additionally, the DTI findings show that LOC was associated with ventral prefrontal white matter
 25 integrity degradation, as indicated by RD and AD. The specificity of these findings suggests potential

1 differences in frontal myelin and neural integrity in terms of injury severity (indexed by LOC vs. AOC).
 2 The injury severity findings are further consistent with other recent studies indicating persisting white
 3 matter damage associated with mTBI in OEF/OIF samples^{60,61}, though they contrast with the results
 4 reported by Levin and colleagues⁶² wherein no main effect or graded severity effect (mild vs. moderate)
 5 of TBI was found. However, it is important to note that Levin and colleagues⁶² examined only blast-
 6 related mild to moderate TBI, whereas most of our mTBI sample (56%) reported a mixed history of both
 7 blunt and blast force mTBI and multiple mTBI events. Recently, Goldstein et al.⁶³ found
 8 neuropathologic evidence for persistent chronic traumatic encephalopathy (CTE) in the brains of military
 9 veterans with blast exposure and/or blunt concussive injury, suggesting that TBI induced by different
 10 insults under different conditions can trigger common pathogenic mechanisms leading to similar
 11 neuropathology and sequelae. Notably, within the small autopsy sample they examined, the effects of
 12 blast exposure, blunt concussive injury, and mixed trauma were indistinguishable. Note too that Belanger
 13 et al.⁶⁴ failed to show neuropsychological differences between blast vs. blunt trauma TBI subgroups.
 14 Given the high prevalence of blast and/or blunt concussive exposures among OEF/OIF veterans, the
 15 chronic effects of TBI and potential for long-term CTE-linked neuropathologic changes among our retired
 16 warfighters warrants further investigation.

17 The elevated psychiatric symptom ratings (i.e., PTSD-related or depressive symptom ratings) in
 18 the mTBI group relative to control participants are consistent with other reports that self-reported
 19 neurotrauma, in general, and psychiatric distress are highly co-morbid among OEF/OIF veterans^{1,65,66}.
 20 However, our executive function subgroups did not significantly differ in PTSD-related or depressive
 21 symptom ratings, suggesting that psychiatric distress alone cannot account for the observed group
 22 differences in white matter integrity. In addition, the intact executive function (EF) mTBI subgroup did
 23 not differ from normal control participants on any of the DTI or cognitive comparisons, despite their
 24 higher levels of PTSD-related and depressive symptom ratings, further supporting the notion that
 25 psychiatric distress did not contribute to the regional white matter differences.

1 Our finding of worse performance on a speeded test of category fluency switching in the mTBI
2 group relative to control participants, even after statistically adjusting for the higher rates of depression
3 and PTSD symptom severity scores, somewhat contrasts with the results of meta-analytic studies that
4 generally show no or very mild effects of mTBI⁸⁻¹². However, the clinical significance of this finding is
5 limited as the mean performance of the mTBI group, as a whole, falls within the average range. Category
6 fluency is thought to rely on both frontal and temporal regions, and the added switching component may
7 draw more heavily on frontally-mediated attentional and executive function processes⁶⁷. Indeed,
8 Zakzanis and colleagues⁶⁸ report that switching within category fluency tasks may be especially sensitive
9 to frontal brain dysfunction. It is possible then that the observed damage to frontal and posterior
10 association tracts in the reduced EF subgroup relative to control participants may collectively disrupt the
11 concerted integration of the many cognitive subprocesses responsible for optimal performance on this
12 task.

13 Our findings are derived from one of the few investigations of cognitive dysfunction as it relates
14 to white matter integrity in a sample of OEF/OIF veterans. None of the participants in the current sample
15 were involved in litigation and none of the 47 participants on whom the analyses were performed
16 evidenced performances below expectations on symptom validity testing. Our exclusion criterion based
17 on symptom validity testing may, in part, explain some of the differences between the results of our study
18 and those of other studies where it was not conducted or reported (e.g., Levin et al.⁶², Hoge et al.¹). It
19 is noteworthy that the study by Levin et al.⁶², which did not show DTI differences between OEF/OIF
20 veterans with blast TBI and controls, did not report effort testing in their sample. If some participants
21 with insufficient effort were included in their sample, one might expect to see cognitive test score
22 differences but no DTI differences, and inconsistent or non-significant correlations of DTI variables with
23 symptom measures, all of which were demonstrated in their study. Our finding of comparable PTSD- and
24 depressive-symptom severities across subgroups, combined with formal effort testing, further supports the

1 notion that psychiatric distress or insufficient effort were not contributors to the cognitive test score
 2 findings or regional white matter differences in our reduced mTBI subgroup.

3 There are limitations to this study that warrant discussion. First, our data are cross-sectional, and
 4 it is possible that the observed differences in FA and neuropsychological performance may reflect
 5 premorbid differences that are perhaps unrelated to the mTBI. However, the groups were comparable on
 6 educational attainment and reading level. Second, the generalizability of our findings to single-event
 7 mTBIs is limited as most of our mTBI participants endorsed having sustained more than one TBI. Third,
 8 a little more than 40% of our clinical sample showed reductions on tests of executive function, although
 9 the impairment criteria described above were designed to be liberal in order to increase our sensitivity to
 10 detect possible impairment for the research purposes specific to this study. They are not meant to
 11 represent the basis for a clinical diagnosis of a cognitive disorder. Fourth, insufficient sample size limited
 12 our ability to study the effects of blast only ($n = 5$) vs. blunt only ($n = 9$) injury mechanisms, though as
 13 noted the presence of any blast injury was not associated with EF impairment or LOC. Moreover, at
 14 present, those investigations comparing blast only and blunt only mTBI in OEF/OIF veterans have found
 15 no strong evidence of disparate outcomes whether in post-concussive symptom reporting or
 16 neuropsychological performance^{38,64}. Finally, the tensor model of diffusion-weighted is limited in
 17 regions with more complex architecture (e.g., where crossing fibers exist within a single voxel), and thus
 18 the measured FA may be attenuated in some regions⁶⁹. Although this possibility may have altered the FA
 19 measures to some degree, this effect is assumed to be consistent across the groups such that differences in
 20 diffusivity measures, while imprecise, continue to signify altered white matter integrity.

22 CONCLUSION

23 Although direct main effects of mTBI were limited, we identified a subgroup of OEF/OIF
 24 veterans with mild, but demonstrable, executive function reductions and concomitant brain changes
 25 associated with their history of mTBI, suggesting that neuronal and cognitive recovery may be protracted

1 in some cases, especially in patients who experienced a loss of consciousness. Given the lack of
2 differences between those with and without executive function decrements on PTSD-related or depressive
3 symptom severities, it is less likely that psychiatric symptomatology can fully explain the pattern of
4 cognitive and brain findings. Clearly, additional research within this population is warranted to better
5 understand the cognitive and neurostructural effects of mild TBI and to better identify veterans who may
6 continue to struggle cognitively (and potentially psychiatrically) in the aftermath of their brain injuries.

7

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- 9

1 Table 1. Demographic, TBI severity, and psychiatric characteristics of control participants and mTBI
 2 subgroups (unimpaired and impaired executive function [EF])

	Control	Intact EF	Reduced EF	<i>p</i>
<i>n</i>	15	19	13	-
Age (years)	32.9 (8.2)	29.3 (7.7)	32.8 (10.8)	.41
Years of Education	14.3 (1.8)	13.6 (1.6)	13.3 (0.9)	.19
WRAT-4 Reading (SS)	105.7 (9.0)	106.2 (10.7)	104.0 (13.1)	.85
% Male	73%	90%	85%	.46
% Caucasian	73%	63%	46%	.33
Months Since mTBI	-	52.3 (34.3)	28.2 (19.1)	.03
Mean Number of mTBIs	-	2.9 (2.4)	3.1 (2.4)	.81
% > 1 mTBI	-	74%	69%	.78
% Combat mTBI	-	58%	69%	.51
% Reporting Any LOC at TBI	-	47%	85%	.03
% Reporting Blast Related mTBI	-	74%	69%	.78
BDI-II *	5.1 (10.1)	16.1 (9.5)	17.5 (5.4)	< .01
PCL-M *	22.8 (14.5)	41.5 (14.5)	41.0 (18.6)	< .001

* Reduced and Intact mTBI subgroups did not significantly differ ($p > .50$).

Notes. mTBI = mild traumatic brain injury; SS = scaled score; LOC = loss of consciousness; WRAT-4 = Wide Range Achievement Test, Fourth Edition; BDI-II = Beck Depression Inventory-2; PCL-M = Post-traumatic Stress Disorder Check List- Military Version.

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Table 2. Means (M), standard deviations (SD), and group comparisons of regional values on diffusion tensor imaging in control participants and mTBI subgroups (intact and reduced executive function [EF])

	ROI	Control		Intact EF		Reduced EF		<i>p</i> values		
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	Control vs. TBI	Intact vs. Reduced EF	Control vs. Reduced EF
FA	DPFWM	.40	.02	.40	.01	.39	.02	.35	.01**	.05
	VPFWM	.42	.02	.42	.02	.40	.02	.09	.009**	.009**
	CC Genu	.67	.04	.67	.03	.64	.03	.22	.02**	.03*
	CC Body	.66	.04	.68	.03	.64	.05	.80	.006**	.12
	CC Splenium	.76	.02	.76	.02	.73	.04	.27	.006**	.03*
	Ant. Cing.	.48	.03	.47	.03	.45	.03	.05	.04*	.01**
	Post. Cing.	.50	.03	.50	.02	.47	.02	.04	.004**	.003**
	Ant. IC	.57	.02	.57	.02	.56	.02	.61	.21	.31
	Post. IC	.68	.02	.67	.02	.67	.02	.51	.58	.42
RD x 10⁻³ mm²/s	DPFWM	.55	.03	.55	.02	.56	.03	.33	.16	.14
	VPFWM	.54	.03	.54	.03	.57	.04	.11	.006**	.009*
	CC Genu	.39	.04	.39	.03	.42	.05	.23	.05*	.05
	CC Body	.40	.05	.38	.04	.43	.07	.70	.009**	.11
	CC Splenium	.29	.02	.29	.01	.31	.04	.39	.03*	.09
	Ant. Cing.	.51	.04	.52	.03	.54	.04	.13	.10	.04
	Post. Cing.	.45	.02	.44	.02	.47	.02	.22	.005**	.02*
	Ant. IC	.40	.02	.41	.02	.40	.03	.67	.84	.79
	Post. IC	.33	.02	.33	.02	.32	.02	.80	.22	.71
AD x 10⁻³ mm²/s	DPFWM	1.02	.03	1.03	.03	1.03	.03	.51	.48	.83
	VPFWM	1.07	.04	1.07	.04	1.09	.03	.61	.38	.40
	CC Genu	1.39	.07	1.40	.05	1.39	.06	.69	.60	.94
	CC Body	1.40	.05	1.42	.05	1.40	.06	.52	.54	.81
	CC Splenium	1.40	.05	1.41	.06	1.37	.05	.74	.04	.20
	Ant. Cing.	1.14	.07	1.15	.04	1.13	.05	.81	.59	.65
	Post. Cing.	1.04	.05	1.03	.03	1.01	.05	.24	.27	.14
	Ant. IC	1.09	.05	1.12	.04	1.08	.04	.87	.008**	.24
	Post. IC	1.17	.05	1.19	.04	1.13	.05	.63	.002**	.05

mTBI = mild traumatic brain injury, FA = Fractional Anisotropy, RD = Radial Diffusivity, AD = Axial Diffusivity, ROI = Region of Interest, DPFWM = Dorsal Prefrontal White Matter, VPFWM = Ventral Prefrontal White Matter, CC = Corpus Callosum, Ant = Anterior, Post = Posterior, Cing = Cingulum, IC = Internal Capsule.

**False Discovery Rate (FDR) *p*-corrected < .05

*FDR *p*-corrected < .10

Table 3. Means (M) and standard deviations (SD) of neuropsychological tests of executive function (EF) for the control and mild traumatic brain injury (mTBI) groups, and for the mTBI subgroups split by executive function performance

Measure	Control		mTBI		Intact EF		Reduced EF		<i>p</i> values		
									Control vs. mTBI	Intact vs. Reduced EF	Control vs. Reduced EF
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
WCST											
Perseverative Responses											
T-Score	47.1	5.8	49.2	9.6	52.8	9.1	44.2	8.1	0.58	0.004	0.34
D-KEFS											
Category											
Switching SS	12.5	3.2	9.8	3.4	10.8	3.0	8.4	3.5	0.007	0.042	0.002
D-KEFS Trails											
Switching SS	9.9	2.2	8.7	3.5	10.6	1.9	6.1	3.6	0.057	< .001	0.001

WCST = Wisconsin Card Sorting Test, D-KEFS = Delis-Kaplan Executive Function System, SS = scaled score

Figure 1. Atlas-based ROI Placement and Group Comparisons of FA Values

Placement of the TBSS-derived white matter skeleton regions of interest in standard space on a T1 image. FA = Fractional Anisotropy, DPFWM = Dorsal Prefrontal White Matter, VPFWM = ventral prefrontal white matter, PIC = posterior internal capsule, AIC = anterior internal capsule, Ant. Cing. = Anterior cingulum bundle, Post. Cing. = Posterior cingulum bundle, HC = Healthy Controls, EF = Executive Functions. Error bars represent SEM.

****** p -corrected < .05, ***** p -corrected < .10

Figure 2. Ventral Prefrontal White Matter Diffusion Tensor Imaging Indices by LOC/AOC Status in Mild Traumatic Brain Injury Compared to Control Participants

FA = Fractional anisotropy, RD = Radial Diffusivity, AD = Axial Diffusivity, AOC = Alteration of consciousness, LOC = Loss of consciousness. Error bars represent SEM. $*p < .05$

Running head: WHITE MATTER AND EXECUTIVE FUNCTION IN MILD TBI

White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive
Function and Loss of Consciousness

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ABSTRACT

Objective: To investigate using diffusion tensor imaging (DTI) whether white matter integrity accounts for disparate cognitive outcomes in executive function (EF) in post-acute mild TBI (mTBI) and whether injury severity, as measured by loss of consciousness (LOC) versus alterations in consciousness (AOC), is associated with white matter microstructural alterations and neuropsychological outcome.

Participants: Thirty-two Iraq and Afghanistan War era veterans with a history of mTBI and 15 healthy veteran control participants.

Results: There were no significant overall group differences between control and mTBI participants on DTI measures after multiple comparison correction. However, a subgroup of mTBI participants with EF decrements ($n = 13$) demonstrated significantly decreased fractional anisotropy (FA) of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without EF decrements ($n = 19$) and control participants. mTBI participants with LOC were more likely to evidence reduced EF performances and disrupted ventral prefrontal white matter integrity when compared to either mTBI participants without LOC or control participants.

Conclusions: Findings suggest that altered white matter integrity contributes to reduced EF in subgroups of veterans with a history of mTBI and that LOC may be a risk factor for reduced EF as well as associated changes to ventral prefrontal white matter.

Key Words: Traumatic Brain Injury, Executive Functions, Diffusion Tensor Imaging, White Matter

INTRODUCTION

Mild traumatic brain injury (mTBI) is common among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans, with estimated prevalence rates ranging from 15% to 30%^{1,2}. Unfortunately, the long-term neuropsychological consequences of mTBI in this population are not well defined. Although deficits in processing speed, attention, working memory, memory, and executive functions have been frequently demonstrated in the acute phase following mTBI^{3,4}, the prevalence and severity of cognitive deficits in the post-acute phase (i.e., after 3-6 months) are much less clear. Although there are reports showing chronic neuropsychological difficulties following mTBI⁵⁻⁷, meta-analytic studies using unselected and prospective samples report only transient impairments in multiple cognitive domains that tend to return to the normal range by three months post-injury⁸⁻¹¹. However, when studies using clinical samples (i.e., self-referred and/or with persisting cognitive complaints) are included, mTBI has a medium to large effect on neuropsychological functioning in the post-acute phase^{12,13}. Those factors that relate to enduring post-acute symptomatology remain elusive, although some studies have shown associations with injury severity as well as confounding psychiatric conditions such as depression and anxiety^{6,14-16}. Additionally, problems associated with effort and litigation have also been implicated^{12,17}.

As suggested by the aforementioned meta-analyses⁸⁻¹¹, any long-term effects of mTBI, if present, are likely subtle. Given these suggestions coupled with the well documented finding that the structural vulnerability of the frontal lobes in TBI may contribute to impaired executive function (EF) performance¹⁸⁻²⁰, it may be that mTBI preferentially affects specific higher-order cognitive skills such as EF that rely on the integration of multiple component cognitive processes. In support of this possibility, a meta-analysis by Rohling et al.¹⁰ reported that, although the overall effect of mTBI was negligible after three months, a small but significant decrement remained in the working memory domain. In addition, Hartikainen et al.²¹ reported that protracted recovery following mild to moderate TBI was associated with poorer performance measures of EF. Finally, Vanderploeg et al.²² found indications of executive

dysfunction in the form of heightened proactive interference in U.S. military personnel eight years post mTBI, and Nolin²³ has reported deficient encoding strategies in mTBI.

The high prevalence of mTBI in OEF/OIF veterans underscores the need for improved understanding of its possible long-term cognitive consequences, its underlying brain changes, and for enhanced characterization of those factors that may contribute to poorer outcomes. White matter is particularly vulnerable to the effects of the shearing and stretching forces characteristic of neurotrauma and some studies using diffusion tensor imaging (DTI) have found evidence for disrupted white matter integrity following mTBI²⁴⁻³⁰. DTI is a non-invasive neuroimaging method used to investigate and characterize the microstructural integrity of the white matter³¹. This imaging modality is sensitive to the random motion of water molecules within white matter and yields measures such as fractional anisotropy (FA), an index of white matter microstructural integrity gleaned by the intravoxel directional coherence of water molecules in tissue^{32,33}. Thus, higher FA values are indicative of healthy tissue with uniform microstructure, whereas relatively lower values suggest a disruption of microstructure implying tissue damage³². Reductions in FA may result from a decrease in axial diffusivity (AD) (diffusion along the principal diffusion direction [along the axon]), an increase in radial diffusivity (diffusion perpendicular to the primary diffusion direction), or an additive or synergistic effect of the two. Although there is some debate as to the specific meaning of the component diffusion measures^{34,35}, AD has most commonly been interpreted as describing axonal integrity, and radial diffusivity (RD) has been described as a proxy for myelin integrity³⁶.

Injury characteristics such as loss of consciousness (LOC) are used to assign the severity of injury as “mild,” although they have often been shown to be unrelated to cognitive outcomes within mTBI samples³⁷. Among OEF/OIF veterans who have experienced a TBI, the distinction between LOC versus an altered state of consciousness (AOC)—but without LOC—following a head injury has been a focus of recent research^{1,38-40}. However, it remains unclear to what degree these potential differences in severity

within mTBI are associated with outcome, and the neuropsychological consequences of LOC versus AOC in the context of military TBI have not been fully explored.

The goals of the current study were to (1) assess whether OEF/OIF veterans with a history of mTBI demonstrate alterations in white matter microstructure; (2) determine whether our mTBI sample shows executive function decrements; (3) investigate the extent to which executive dysfunction is associated with frontal white matter alterations; and (4), in an exploratory analysis, examine whether injury severity as indexed by LOC is associated with white matter damage and concomitant executive dysfunction. Given prior discrepant findings across studies of chronic mTBI, we did not expect our overall sample of chronic mTBI participants to show gross alterations in white matter microstructure or cognitive dysfunction relative to healthy control participants; however, a subgroup of mTBI participants with evidence suggestive of cognitive dysfunction was expected to show poorer white matter microstructural integrity. We also examined whether and how differences in AD or RD explain any significant subgroup differences in white matter integrity in terms of axonal or myelin compromise. Finally, in an exploratory analysis, we posited that mTBI participants with LOC (versus those with AOC) would evidence poorer white matter integrity, particularly in anterior regions.

METHODS

Participants

Forty-seven OIF/OEF veterans were recruited for the current study (mTBI: $n = 32$; normal controls [NC]: $n = 15$). All mTBI participants were diagnosed with a mild closed head injury during outpatient evaluation of TBI at the Veterans Affairs San Diego Healthcare System (VASDHS). We used the following criteria delineated by the Department of Defense (DoD) and Department of Veterans Affairs Traumatic Brain Injury Task Force⁴¹ for mTBI: (1) AOC or LOC ≤ 30 minutes; (2) an initial Glasgow Coma Scale⁴² (GCS) score between 13-15 (which is often not available in a combat setting); (3) a period of post-traumatic amnesia (PTA) ≤ 24 hours; and (4) no visible lesions on MRI or CT scan.

LOC was not required for a TBI diagnosis, as any AOC lasting less than 24 hours following a head injury event, regardless of mechanism, was sufficient to warrant a diagnosis as defined by the United States DoD⁴³. As is typical of many military and civilian TBI studies, LOC or AOC duration was often determined via self-report given the paucity of patient medical information that is typically available surrounding mTBI events, particularly in combat settings.

No participants included in the current study demonstrated obvious lesions on standard neuroimaging. Exclusion criteria for all mTBI and NC participants included: (1) moderate to severe TBI (LOC > 30 min, PTA > 24 hours, GCS < 12); (2) a history other neurological condition (e.g., multiple sclerosis, seizure disorder); (3) developmental learning disability; (4) current substance or alcohol abuse according to DSM-IV criteria; (5) pre-injury metabolic or other diseases known to affect cognition (e.g., diabetes); (6) history of psychiatric disorder prior to the TBI event; (7) current or pending litigation; (8) any contraindications to MRI scanning (e.g., claustrophobia, shrapnel); or (9) below threshold cut-off scores on effort testing. Participants were, on average, approximately 2-4 years removed from their TBI event or events at the time of testing. All participants provided written informed consent, and all procedures complied with the local UCSD and VA institutional review boards.

Participants' demographic and injury characteristics are presented in Table 1. The normal control and mTBI groups did not significantly differ on any demographic characteristics (e.g., age, education level, sex distribution), although the mTBI group evidenced significantly higher levels of depressive (Beck Depression Inventory-II⁴⁴, BDI-II, $p < .01$) and PTSD-related symptomatology (PTSD Check List – Military Version⁴⁵, PCL-M, $p < .001$). However, the two mTBI subgroups (detailed below) did not differ from one another on either measure of depressive or PTSD-related symptoms, nor did they differ on any of the TBI injury severity characteristics with the exception of LOC percentage ($p = .03$; see Table 1).

[Insert Table 1 here]

Neuropsychological Assessment

Participants were administered a battery of neuropsychological tests selected for its sensitivity to TBI. The following tasks were used to evaluate executive functions: the Wisconsin Card Sorting-Task 64-Card Version^{46,47} and the Delis-Kaplan Executive Functioning System⁴⁸ Trail Making and Verbal Fluency Switching tests. Participants were also administered the Wide Range Achievement Test-4⁴⁹ (WRAT-4) Reading subtest as a measure of premorbid intellectual functioning. Demographically-adjusted *T*-scores⁴⁷ and scaled scores⁴⁸ were used for all analyses. Participants were also administered the PLC-M and the BDI-II. Administration time for the entire neuropsychological battery was approximately 2.5 hours.

Reduced Executive Function Subgroup Criteria. Participants were classified as having reduced executive function performances if any of the following criteria were met: *T*-score less than 40 for WCST Perseverative Responses (PR) or a Scaled Score less than 7 for D-KEFS Verbal Fluency Category Switching Total Correct or Trails Letter-Number Switching. Of the 13 mTBI participants identified with reduced executive function performances, 6 demonstrated impairment on the WCST-PR, 5 on Category Fluency Switching and 7 on Letter-Number Switching. Nine of the 13 had impaired scores on only one of the three executive function measures; 3 had impaired scores on two of the measures; and 1 was impaired on all three measures.

Symptom Validity Test Measures. The Test of Memory Malingering⁵⁰ (TOMM) and the Forced-Choice Recognition Trial of the California Verbal Learning Test-II⁵¹ (CVLT-II) were used to assess effort. Cut-off scores for identifying inadequate effort (TOMM Trial 2 < 45 and CVLT-II Forced-Choice Recognition Trial < 15) were based on recommendations from Tombaugh⁵⁰ and Moore & Donders⁵², respectively.

Brain Imaging

All participants underwent structural MRI and DTI on 3T General Electric (GE) MRI scanners housed within the UCSD Functional Magnetic Resonance Imaging (fMRI) Center on the UCSD La Jolla campus. Thirty-seven participants were scanned on with the scanner equipped with the Excite HDx

platform and, following the FMRI Center's scanner upgrade, data on 10 subjects were acquired with the scanner running the MR750 platform. There were no significant differences in regional FA values between those 10 participants scanned on the MR750 platform and 10 randomly selected age-matched participants scanned on the Excite HDx platform (p 's = .21 - .99 for all regions of interest).

Structural Scanning: A sagittally-acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: FOV 24 cm, 256 x 256 x 192 matrix, 0.94 x 0.94 x 1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms; flip angle 12°, scan time was roughly 7 minutes.

Diffusion Tensor Imaging: DTI images were collected with a dual spin echo EPI acquisition⁵³ with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 X 128, in-plane resolution = 1.875 x 1.875, TR = 10900 ms, TE = 93 ms. The ten scans from the MR750 platform used identical scanning parameters though TR was shortened to 8000 ms to reduce scan time without affecting image quality. Across scanners, thirty-four slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model⁵⁴ and a b-value of 1500 s/mm², as well as one T2 image with no diffusion weighting (b = 0). Two field maps with the same spatial parameters as those of the DTI scan were collected in order to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12-16 minutes.

DTI Data Processing: The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Package⁵⁵ (FSL) was used for image processing. The two field maps were used to unwarp the EPI acquisitions. Images were then corrected for motion and eddy currents using the *eddy correct* FSL command. Each image was visually inspected for quality and data from three participants did not meet quality standards and therefore were removed from analyses. The FSL program *bet* removed non-brain voxels from the analysis. The FSL program *dtifit* fit a diffusion tensor model at each voxel to provide DTI variables such as fractional anisotropy and eigenvalues on a voxel-by-voxel basis. Per Song et al.³⁶, axial diffusivity was defined by the principal eigenvalue (i.e., AD = L1), and radial diffusivity (RD) was defined as the average of the second and third eigenvalues: RD = (L2 + L3)/2.

Semi-Automated Regions of Interest: Region of Interest (ROI) placement was guided by a multi-step process, and all ROIs were placed in MNI standard space as shown in Figure 1. First, the Tract-based Spatial Statistics (TBSS) algorithm was used to align all FA images to a standard space, as well as to identify those fiber tracts common to all participants (see Smith et al.⁵⁶ for a complete description). An FA threshold of .20 was used to restrict the white matter skeleton to voxels comprising only white matter and to reduce partial voluming effects. Next, ROIs were placed in the genu, body, and splenium subsections of the corpus callosum (CC), and bilaterally in the cingulum bundles and the anterior and posterior internal capsules (AIC, PIC) following the ICBM-DTI-81 white matter labels atlas available within FSL⁵⁷. The cingulum bundle was segmented into posterior and anterior components wherein anterior cingulum was defined as those voxels anterior to the CC body and CC genu division, and posterior cingulum was defined as those voxels posterior to the CC body and CC splenium division. Two additional ROIs were placed in the prefrontal white matter identified as the dorsal prefrontal white matter (DPWM) and ventral prefrontal white matter (VPWM). Prefrontal white matter was defined as all skeleton voxels anterior to the genu of the CC. The ventral/dorsal boundary was defined by a parasagittal line connecting the anterior and posterior commissures⁵⁸. Mean FA, RD and AD values for each ROI were extracted for each subject and exported to SPSS 18 for statistical analyses.

Statistical Analyses

Group comparisons were conducted using analysis of variance (ANOVA) followed by contrast testing (t-tests), including comparisons of the executive function subgroup status and AOC vs. LOC group comparisons of the DTI metrics. Effect size statistics (Cohen's *d*) for the significant *p*-values for each of the group comparisons were also calculated. Categorical data were analyzed using likelihood-ratio chi-square tests (e.g., LOC by executive function subgroups) due to the relatively small sample size. Multiple comparison corrections were conducted using false discovery rate (FDR) methodology⁵⁹ for the primary DTI analysis between reduced and intact EF subgroups and control participants with FDR set at .05. Multiple comparison corrections were not performed on the LOC vs. AOC analyses due to their

exploratory nature.

RESULTS

Mild TBI vs. Normal Control Group Comparisons

As shown in Table 2, comparisons of the regional DTI values between the mTBI and NC groups revealed significantly lower FA in the anterior (Cohen's $d = .57, p = .01$) and posterior cingulum (Cohen's $d = .51, p = .003$), although these group differences of medium effect sizes did not survive FDR correction for multiple comparisons (p -corrected $> .10$). Group comparisons between healthy control and mTBI participants in all other DTI regions of interest did not reach significance ($p > .10$).

As shown in Table 3, the mTBI group performed significantly worse than the NC participants on category fluency switching (Cohen's $d = .80, p = .002$). Importantly, a post-hoc analysis of co-variance (ANCOVA) adjusting for BDI-II and PCL-M scores found that the lower score on category fluency switching remained significant, suggesting that co-morbid psychiatric disturbance did not account for the lower scores observed in the mTBI sample.

[Tables 2 and 3 about here]

Reduced vs. Intact Executive Function mTBI Subgroup Comparisons

Approximately 41% percent (13/32) of the mTBI sample demonstrated reductions on executive function (EF) measures based on the criteria described above. As shown in Table 1, there were no significant differences on demographic characteristics or psychiatric symptomatology between the two subgroups. Of the injury characteristics, LOC status significantly differed between subgroups, with higher rates of LOC in the reduced EF subgroup ($p = .03$). Additionally, the number of months since the most recent mTBI significantly differed between subgroups. Specifically, the reduced EF subgroup had more recently experienced an mTBI event ($p = .03$), with a mean time since injury of roughly two years for the reduced EF subgroup versus four years for the intact EF subgroup. However, mTBI subgroups did not differ in frequency of blast exposure or total number of mTBI events (all p -values $> .70$).

[Figure 1 about here]

Executive Function mTBI Subgroup Differences by DTI Indices of White Matter Integrity

Table 2 lists the means, standard deviations, and results of comparisons of the control group and two mTBI subgroups on the DTI measures across each of the regions of interest. The group FA comparisons for each ROI are further illustrated in Figure 1. It is important to note that the intact EF mTBI subgroup did not significantly differ from control participants on any DTI measure (including all fractional anisotropy and radial and axial diffusivity measures) across all ROIs (all p -values $> .10$). However, as can be seen in Figure 1, statistically significant (p -corrected $< .05$) FA reductions with large effect-sizes were found for the reduced EF mTBI subgroup when compared to the intact EF subgroup in the DPFWM (Cohen's $d = 1.05$), VPFWM (Cohen's $d = .96$), CC genu (Cohen's $d = .98$), CC body (Cohen's $d = 1.07$), CC splenium (Cohen's $d = .99$), the posterior cingulum (Cohen's $d = 1.28$), and with a trend toward significance (p -corrected $< .10$) in the anterior cingulum (Cohen's $d = .76$). These findings were unchanged after adjusting for months since injury in analyses of co-variance (ANCOVA). All other FA ROIs (i.e., AIC and PIC) did not reach significance (all p -values $> .10$). When compared to control participants, the reduced EF mTBI subgroup showed significantly lowered (p -corrected $< .05$) FA values in the VPFWM (Cohen's $d = .98$), the anterior cingulum (Cohen's $d = .97$) and the posterior cingulum (Cohen's $d = 1.28$) with trends in this direction for the CC genu (Cohen's $d = .79$) and CC splenium (Cohen's $d = .73$).

The reduced EF mTBI subgroup showed significantly higher (p -corrected $< .05$) radial diffusivity (RD) than the intact EF subgroup within the VPFWM (Cohen's $d = 1.02$), the CC body (Cohen's $d = .94$), and the posterior cingulum (Cohen's $d = .94$), with trends (p -corrected $< .10$) in the CC genu (Cohen's $d = .75$) and splenium (Cohen's $d = .74$). Compared to NCs, there was a trend (p -corrected $< .10$) toward higher RD in both the VPFWM (Cohen's $d = .98$) and posterior cingulum (Cohen's $d = .88$) in the reduced mTBI subgroup. Regarding axial diffusivity (AD), the reduced EF mTBI subgroup showed significantly lower (p -corrected $< .05$) AD values within the AIC (Cohen's $d = 1.10$) and the PIC (Cohen's $d = 1.26$) relative the intact EF subgroup. All other AD ROIs did not reach significance, and there were no significant differences between the control and reduced EF mTBI groups.

[Figure 2 about here]

Exploratory Group Comparisons by LOC vs. AOC

Since the reduced EF subgroup demonstrated a higher percentage of participants with LOC compared to the intact EF subgroup (see Table 1), exploratory analyses were conducted to investigate the associations among LOC, cognition, and white matter integrity. The mTBI sample as separated by LOC/AOC status [LOC ($n = 20$) versus AOC ($n = 12$)] did not significantly differ in terms of age, education, WRAT-Reading scores, or injury and psychiatric characteristics (p values $> .05$). Group comparisons of AOC vs. LOC on the individual executive function scaled scores and T -scores were not significantly different (p values $> .05$). However, the LOC subgroup was found to have significantly lower D-KEFS Category Fluency Switching Total Correct scaled score compared to NCs ($M_{\text{Control}} = 12.5$, $SD_{\text{Control}} = 3.2$, $M_{\text{LOC}} = 10.0$, $SD_{\text{LOC}} = 3.3$, $p = .04$, Cohen's $d = .77$).

An analysis of the regional DTI values did reveal significant group differences in white matter integrity. As can be seen in Figure 2, the LOC subgroup evidenced significantly higher RD in the VPFWM than the AOC subgroup (RD $\times 10^{-3}$ mm²/sec: $M_{\text{AOC}} = 0.54$, $SD_{\text{AOC}} = 0.02$, $M_{\text{LOC}} = 0.57$, $SD_{\text{LOC}} = 0.04$, $p = .02$, Cohen's $d = .87$) with a trend toward higher VPFWM AD (AD $\times 10^{-3}$ mm²/sec: $M_{\text{AOC}} = 1.07$, $SD_{\text{AOC}} = 0.03$, $M_{\text{LOC}} = 1.09$, $SD_{\text{LOC}} = 0.03$, $p = .08$, Cohen's $d = .65$). Similarly, when compared with control participants, VPFWM RD was significantly higher in the LOC subgroup ($M_{\text{Control}} = 0.54$, $SD_{\text{Control}} = 0.03$, $M_{\text{LOC}} = 0.57$, $SD_{\text{LOC}} = 0.04$, $p = .03$, Cohen's $d = .73$) with a trend toward lower FA values ($M_{\text{Control}} = 0.42$, $SD_{\text{Control}} = 0.02$, $M_{\text{LOC}} = 0.41$, $SD_{\text{LOC}} = 0.03$, $p = .06$, Cohen's $d = .63$). The LOC subgroup also significantly differed from the normal control group in the anterior cingulum FA ($M_{\text{Control}} = 0.48$, $SD_{\text{Control}} = 0.03$, $M_{\text{LOC}} = 0.46$, $SD_{\text{LOC}} = 0.03$, $p = .05$, Cohen's $d = .71$). Comparisons of other ROIs did not approach significance (p 's $> .10$).

DISCUSSION

Our finding that reduced EF performance may be present in a subgroup of OEF/OIF veterans with a history of mTBI is consistent with other reports showing chronic neuropsychological difficulties

1 following mTBI⁵⁻⁷. Results further revealed that this subgroup of mTBI participants demonstrated
 2 significantly lower white matter integrity (FA) when compared to either mTBI participants with intact EF
 3 or healthy control participants within prefrontal, commissural, and posterior association tracts, and
 4 findings are consistent with other reports showing lower white matter integrity in a mTBI subgroup with
 5 protracted recovery^{21,30}. In addition, the RD analysis suggests that compromised myelin integrity may
 6 contribute to the lower white matter integrity within frontal white matter, the corpus callosum, and
 7 posterior cingulum within this reduced EF subgroup. These findings were in contrast to the mTBI group
 8 as a whole, which did not significantly differ from our normal control group in terms of white matter
 9 integrity. Taken together, our results demonstrate that (1) executive dysfunction is strongly associated
 10 with white matter integrity in a subgroup of OEF/OIF veterans with mTBI across frontal and more
 11 posterior regions, and (2) further suggest that the observed impairment in executive functioning, in some
 12 cases, may be a result of persisting neuronal damage from mild TBI.

13 The exploratory LOC analyses offer some provisional support to the notion that the observed EF
 14 reductions and concomitant white matter compromise in our sample of mTBI participants are perhaps
 15 related to neurotrauma history and are not solely due to normal variation in EF scores. First, LOC was
 16 associated with higher rates of impaired EF scores when compared to those reporting AOC (without
 17 LOC). This distinction is generally consistent with some mTBI studies that have tied LOC to poorer
 18 health outcomes and a more prolonged recovery^{1,39,40}. However, the effect of LOC in these studies was
 19 significantly attenuated after accounting for psychiatric symptomatology such as PTSD symptom
 20 severity. Moreover, Belanger et al.³⁸ reported that PTSD symptom severity, but not LOC, was associated
 21 with increased reporting of post-concussive symptoms. In contrast, in our sample, LOC was not
 22 associated with higher levels of psychiatric distress when compared to those who did not lose
 23 consciousness.

24 Additionally, the DTI findings show that LOC was associated with ventral prefrontal white matter
 25 integrity degradation, as indicated by RD and AD. The specificity of these findings suggests potential

1 differences in frontal myelin and neural integrity in terms of injury severity (indexed by LOC vs. AOC).
2 The injury severity findings are further consistent with other recent studies indicating persisting white
3 matter damage associated with mTBI in OEF/OIF samples^{60,61}, though they contrast with the results
4 reported by Levin and colleagues⁶² wherein no main effect or graded severity effect (mild vs. moderate)
5 of TBI was found. However, it is important to note that Levin and colleagues⁶² examined only blast-
6 related mild to moderate TBI, whereas most of our mTBI sample (56%) reported a mixed history of both
7 blunt and blast force mTBI and multiple mTBI events. Recently, Goldstein et al.⁶³ found
8 neuropathologic evidence for persistent chronic traumatic encephalopathy (CTE) in the brains of military
9 veterans with blast exposure and/or blunt concussive injury, suggesting that TBI induced by different
10 insults under different conditions can trigger common pathogenic mechanisms leading to similar
11 neuropathology and sequelae. Notably, within the small autopsy sample they examined, the effects of
12 blast exposure, blunt concussive injury, and mixed trauma were indistinguishable. Note too that Belanger
13 et al.⁶⁴ failed to show neuropsychological differences between blast vs. blunt trauma TBI subgroups.
14 Given the high prevalence of blast and/or blunt concussive exposures among OEF/OIF veterans, the
15 chronic effects of TBI and potential for long-term CTE-linked neuropathologic changes among our retired
16 warfighters warrants further investigation.

17 The elevated psychiatric symptom ratings (i.e., PTSD-related or depressive symptom ratings) in
18 the mTBI group relative to control participants are consistent with other reports that self-reported
19 neurotrauma, in general, and psychiatric distress are highly co-morbid among OEF/OIF veterans^{1,65,66}.
20 However, our executive function subgroups did not significantly differ in PTSD-related or depressive
21 symptom ratings, suggesting that psychiatric distress alone cannot account for the observed group
22 differences in white matter integrity. In addition, the intact executive function (EF) mTBI subgroup did
23 not differ from normal control participants on any of the DTI or cognitive comparisons, despite their
24 higher levels of PTSD-related and depressive symptom ratings, further supporting the notion that
25 psychiatric distress did not contribute to the regional white matter differences.

1 Our finding of worse performance on a speeded test of category fluency switching in the mTBI
2 group relative to control participants, even after statistically adjusting for the higher rates of depression
3 and PTSD symptom severity scores, somewhat contrasts with the results of meta-analytic studies that
4 generally show no or very mild effects of mTBI⁸⁻¹². However, the clinical significance of this finding is
5 limited as the mean performance of the mTBI group, as a whole, falls within the average range. Category
6 fluency is thought to rely on both frontal and temporal regions, and the added switching component may
7 draw more heavily on frontally-mediated attentional and executive function processes⁶⁷. Indeed,
8 Zakzanis and colleagues⁶⁸ report that switching within category fluency tasks may be especially sensitive
9 to frontal brain dysfunction. It is possible then that the observed damage to frontal and posterior
10 association tracts in the reduced EF subgroup relative to control participants may collectively disrupt the
11 concerted integration of the many cognitive subprocesses responsible for optimal performance on this
12 task.

13 Our findings are derived from one of the few investigations of cognitive dysfunction as it relates
14 to white matter integrity in a sample of OEF/OIF veterans. None of the participants in the current sample
15 were involved in litigation and none of the 47 participants on whom the analyses were performed
16 evidenced performances below expectations on symptom validity testing. Our exclusion criterion based
17 on symptom validity testing may, in part, explain some of the differences between the results of our study
18 and those of other studies where it was not conducted or reported (e.g., Levin et al.⁶², Hoge et al.¹). It
19 is noteworthy that the study by Levin et al.⁶², which did not show DTI differences between OEF/OIF
20 veterans with blast TBI and controls, did not report effort testing in their sample. If some participants
21 with insufficient effort were included in their sample, one might expect to see cognitive test score
22 differences but no DTI differences, and inconsistent or non-significant correlations of DTI variables with
23 symptom measures, all of which were demonstrated in their study. Our finding of comparable PTSD- and
24 depressive-symptom severities across subgroups, combined with formal effort testing, further supports the

1 notion that psychiatric distress or insufficient effort were not contributors to the cognitive test score
 2 findings or regional white matter differences in our reduced mTBI subgroup.

3 There are limitations to this study that warrant discussion. First, our data are cross-sectional, and
 4 it is possible that the observed differences in FA and neuropsychological performance may reflect
 5 premorbid differences that are perhaps unrelated to the mTBI. However, the groups were comparable on
 6 educational attainment and reading level. Second, the generalizability of our findings to single-event
 7 mTBIs is limited as most of our mTBI participants endorsed having sustained more than one TBI. Third,
 8 a little more than 40% of our clinical sample showed reductions on tests of executive function, although
 9 the impairment criteria described above were designed to be liberal in order to increase our sensitivity to
 10 detect possible impairment for the research purposes specific to this study. They are not meant to
 11 represent the basis for a clinical diagnosis of a cognitive disorder. Fourth, insufficient sample size limited
 12 our ability to study the effects of blast only ($n = 5$) vs. blunt only ($n = 9$) injury mechanisms, though as
 13 noted the presence of any blast injury was not associated with EF impairment or LOC. Moreover, at
 14 present, those investigations comparing blast only and blunt only mTBI in OEF/OIF veterans have found
 15 no strong evidence of disparate outcomes whether in post-concussive symptom reporting or
 16 neuropsychological performance^{38,64}. Finally, the tensor model of diffusion-weighted is limited in
 17 regions with more complex architecture (e.g., where crossing fibers exist within a single voxel), and thus
 18 the measured FA may be attenuated in some regions⁶⁹. Although this possibility may have altered the FA
 19 measures to some degree, this effect is assumed to be consistent across the groups such that differences in
 20 diffusivity measures, while imprecise, continue to signify altered white matter integrity.

22 CONCLUSION

23 Although direct main effects of mTBI were limited, we identified a subgroup of OEF/OIF
 24 veterans with mild, but demonstrable, executive function reductions and concomitant brain changes
 25 associated with their history of mTBI, suggesting that neuronal and cognitive recovery may be protracted

1 in some cases, especially in patients who experienced a loss of consciousness. Given the lack of
2 differences between those with and without executive function decrements on PTSD-related or depressive
3 symptom severities, it is less likely that psychiatric symptomatology can fully explain the pattern of
4 cognitive and brain findings. Clearly, additional research within this population is warranted to better
5 understand the cognitive and neurostructural effects of mild TBI and to better identify veterans who may
6 continue to struggle cognitively (and potentially psychiatrically) in the aftermath of their brain injuries.

7

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1 Table 1. Demographic, TBI severity, and psychiatric characteristics of control participants and mTBI
 2 subgroups (unimpaired and impaired executive function [EF])

	Control	Intact EF	Reduced EF	<i>p</i>
<i>n</i>	15	19	13	-
Age (years)	32.9 (8.2)	29.3 (7.7)	32.8 (10.8)	.41
Years of Education	14.3 (1.8)	13.6 (1.6)	13.3 (0.9)	.19
WRAT-4 Reading (SS)	105.7 (9.0)	106.2 (10.7)	104.0 (13.1)	.85
% Male	73%	90%	85%	.46
% Caucasian	73%	63%	46%	.33
Months Since mTBI	-	52.3 (34.3)	28.2 (19.1)	.03
Mean Number of mTBIs	-	2.9 (2.4)	3.1 (2.4)	.81
% > 1 mTBI	-	74%	69%	.78
% Combat mTBI	-	58%	69%	.51
% Reporting Any LOC at TBI	-	47%	85%	.03
% Reporting Blast Related mTBI	-	74%	69%	.78
BDI-II *	5.1 (10.1)	16.1 (9.5)	17.5 (5.4)	< .01
PCL-M *	22.8 (14.5)	41.5 (14.5)	41.0 (18.6)	< .001

* Reduced and Intact mTBI subgroups did not significantly differ ($p > .50$).

Notes. mTBI = mild traumatic brain injury; SS = scaled score; LOC = loss of consciousness; WRAT-4 = Wide Range Achievement Test, Fourth Edition; BDI-II = Beck Depression Inventory-2; PCL-M = Post-traumatic Stress Disorder Check List- Military Version.

1

Table 2. Means (M), standard deviations (SD), and group comparisons of regional values on diffusion tensor imaging in control participants and mTBI subgroups (intact and reduced executive function [EF])

	ROI	Control		Intact EF		Reduced EF		<i>p</i> values		
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	Control vs. TBI	Intact vs. Reduced EF	Control vs. Reduced EF
FA	DPFWM	.40	.02	.40	.01	.39	.02	.35	.01**	.05
	VPFWM	.42	.02	.42	.02	.40	.02	.09	.009**	.009**
	CC Genu	.67	.04	.67	.03	.64	.03	.22	.02**	.03*
	CC Body	.66	.04	.68	.03	.64	.05	.80	.006**	.12
	CC Splenium	.76	.02	.76	.02	.73	.04	.27	.006**	.03*
	Ant. Cing.	.48	.03	.47	.03	.45	.03	.05	.04*	.01**
	Post. Cing.	.50	.03	.50	.02	.47	.02	.04	.004**	.003**
	Ant. IC	.57	.02	.57	.02	.56	.02	.61	.21	.31
	Post. IC	.68	.02	.67	.02	.67	.02	.51	.58	.42
RD x 10⁻³ mm²/s	DPFWM	.55	.03	.55	.02	.56	.03	.33	.16	.14
	VPFWM	.54	.03	.54	.03	.57	.04	.11	.006**	.009*
	CC Genu	.39	.04	.39	.03	.42	.05	.23	.05*	.05
	CC Body	.40	.05	.38	.04	.43	.07	.70	.009**	.11
	CC Splenium	.29	.02	.29	.01	.31	.04	.39	.03*	.09
	Ant. Cing.	.51	.04	.52	.03	.54	.04	.13	.10	.04
	Post. Cing.	.45	.02	.44	.02	.47	.02	.22	.005**	.02*
	Ant. IC	.40	.02	.41	.02	.40	.03	.67	.84	.79
	Post. IC	.33	.02	.33	.02	.32	.02	.80	.22	.71
AD x 10⁻³ mm²/s	DPFWM	1.02	.03	1.03	.03	1.03	.03	.51	.48	.83
	VPFWM	1.07	.04	1.07	.04	1.09	.03	.61	.38	.40
	CC Genu	1.39	.07	1.40	.05	1.39	.06	.69	.60	.94
	CC Body	1.40	.05	1.42	.05	1.40	.06	.52	.54	.81
	CC Splenium	1.40	.05	1.41	.06	1.37	.05	.74	.04	.20
	Ant. Cing.	1.14	.07	1.15	.04	1.13	.05	.81	.59	.65
	Post. Cing.	1.04	.05	1.03	.03	1.01	.05	.24	.27	.14
	Ant. IC	1.09	.05	1.12	.04	1.08	.04	.87	.008**	.24
	Post. IC	1.17	.05	1.19	.04	1.13	.05	.63	.002**	.05

mTBI = mild traumatic brain injury, FA = Fractional Anisotropy, RD = Radial Diffusivity, AD = Axial Diffusivity, ROI = Region of Interest, DPFWM = Dorsal Prefrontal White Matter, VPFWM = Ventral Prefrontal White Matter, CC = Corpus Callosum, Ant = Anterior, Post = Posterior, Cing = Cingulum, IC = Internal Capsule.

**False Discovery Rate (FDR) *p*-corrected < .05

*FDR *p*-corrected < .10

Table 3. Means (M) and standard deviations (SD) of neuropsychological tests of executive function (EF) for the control and mild traumatic brain injury (mTBI) groups, and for the mTBI subgroups split by executive function performance

Measure	Control		mTBI		Intact EF		Reduced EF		<i>p</i> values		
									Control vs. mTBI	Intact vs. Reduced EF	Control vs. Reduced EF
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
WCST											
Perseverative Responses											
T-Score	47.1	5.8	49.2	9.6	52.8	9.1	44.2	8.1	0.58	0.004	0.34
D-KEFS											
Category											
Switching SS	12.5	3.2	9.8	3.4	10.8	3.0	8.4	3.5	0.007	0.042	0.002
D-KEFS Trails											
Switching SS	9.9	2.2	8.7	3.5	10.6	1.9	6.1	3.6	0.057	< .001	0.001

WCST = Wisconsin Card Sorting Test, D-KEFS = Delis-Kaplan Executive Function System, SS = scaled score

Figure 1. Atlas-based ROI Placement and Group Comparisons of FA Values

Placement of the TBSS-derived white matter skeleton regions of interest in standard space on a T1 image. FA = Fractional Anisotropy, DPFWM = Dorsal Prefrontal White Matter, VPFWM = ventral prefrontal white matter, PIC = posterior internal capsule, AIC = anterior internal capsule, Ant. Cing. = Anterior cingulum bundle, Post. Cing. = Posterior cingulum bundle, HC = Healthy Controls, EF = Executive Functions. Error bars represent SEM.

****** p -corrected < .05, ***** p -corrected < .10

Figure 2. Ventral Prefrontal White Matter Diffusion Tensor Imaging Indices by LOC/AOC Status in Mild Traumatic Brain Injury Compared to Control Participants

FA = Fractional anisotropy, RD = Radial Diffusivity, AD = Axial Diffusivity, AOC = Alteration of consciousness, LOC = Loss of consciousness. Error bars represent SEM. $*p < .05$

Figure1
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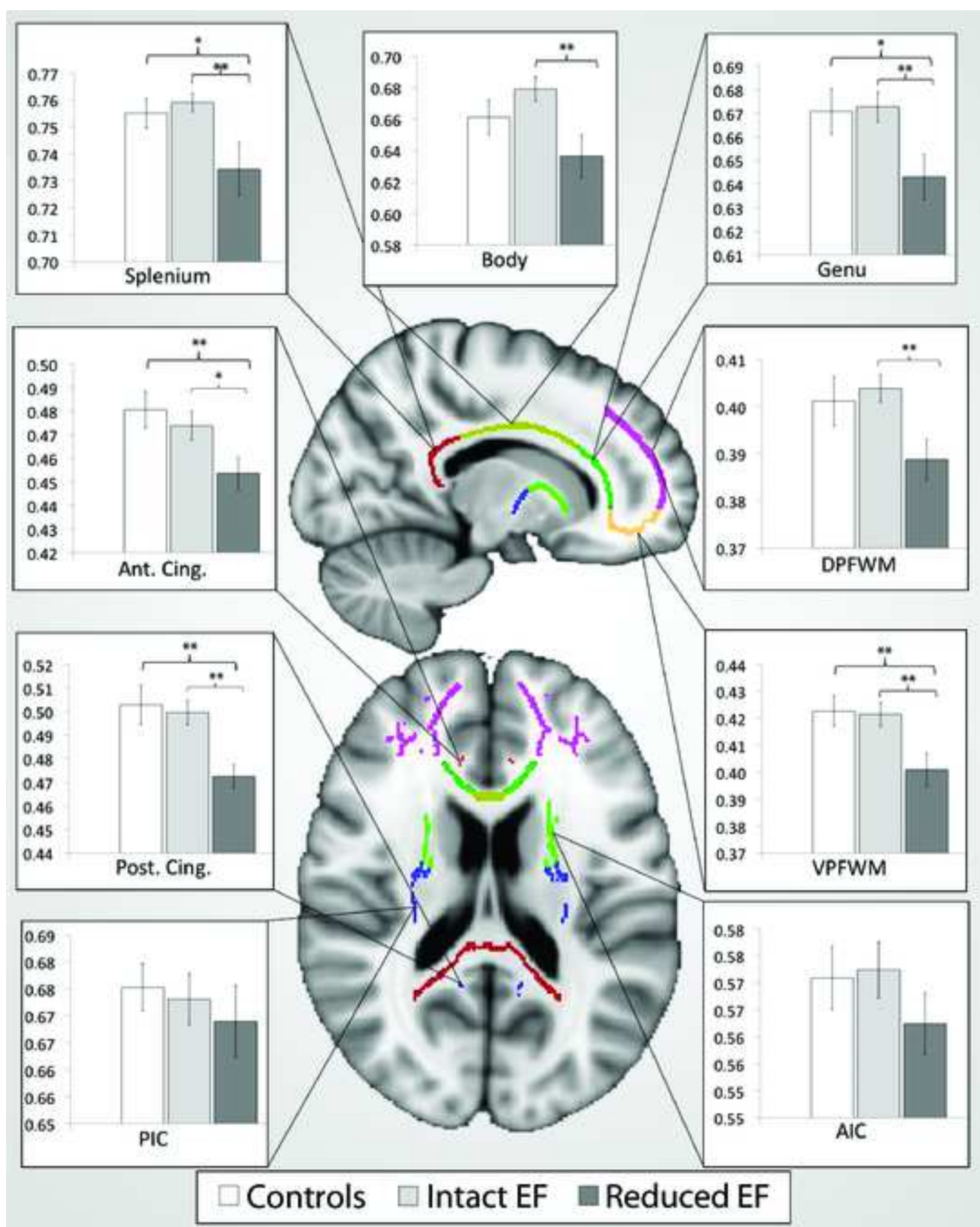


Figure2
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