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

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Abstract

Objective—We investigated using diffusion tensor imaging (DTI) and the association between white matter integrity and executive function (EF) performance in postacute mild traumatic brain injury (mTBI). In addition, we examined whether injury severity, as measured by loss of consciousness (LOC) versus alterations in consciousness (AOC), is related to white matter microstructural alterations and neuropsychological outcome.

Participants—Thirty 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. However, a subgroup of mTBI participants with EF decrements ($n = 13$) demonstrated significantly decreased fractional anisotropy of prefrontal white matter, corpus callosum, and cingulum bundle structures compared with mTBI participants without EF decrements ($n = 17$) and control participants. Participants having mTBI with LOC were more likely to evidence reduced EF performances and disrupted ventral prefrontal white matter integrity when compared with 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.

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Keywords

diffusion tensor imaging; executive functions; traumatic brain injury; white matter

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} Despite these high rates, the long-term neuropsychological consequences of mTBI in this population are not well defined. Deficits in processing speed, attention, working memory, memory, and executive functions (EFs) have been frequently demonstrated in the acute phase following mTBI^{3,4}; however, the prevalence and severity of cognitive deficits in the postacute phase (ie, after 3–6 months) are much less clear. Although there are reports showing chronic neuropsychological difficulties following mTBI,^{5–7} 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 3 months postinjury.^{8–11} However, when studies using clinical samples (ie, self-referred and/or with persisting cognitive complaints) are included, mTBI has a medium to large effect on neuropsychological functioning in the postacute phase.^{12,13} Those factors that relate to enduring postacute 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} In addition, problems associated with effort and litigation have also been implicated.^{12,17}

As suggested by the aforementioned meta-analyses,^{8–11} 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 EF performance,^{18–20} it may be that mTBI preferentially affect 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 al¹⁰ reported that, although the overall effect of mTBI was negligible after 3 months, a small but significant decrement remained in the working memory domain. In addition, Hartikainen et al²¹ reported that protracted recovery following mild to moderate TBI was associated with poorer performance measures of EF. Finally, Vanderploeg et al²² found indications of executive dysfunction in the form of heightened proactive interference in US military personnel 8 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 mTBI.^{24–30} Diffusion tensor imaging is a noninvasive neuroimaging method used to investigate and characterize the microstructural integrity of the white matter.³¹ Specifically, DTI allows for in vivo examination of the orientation of the white matter by reflecting the

degree of intravoxel diffusion anisotropy, most commonly represented as fractional anisotropy (FA).^{32,33}

Importantly, a decrease in FA within a structure suggests a disruption of the microstructure and possible tissue damage.³² Such 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 integrity.³⁶

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 samples.³⁷ 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 EF 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 (vs those with AOC) would evidence poorer white matter integrity, particularly in anterior regions.

METHODS

Participants

Forty-five OIF/OEF veterans were recruited for the current study (mTBI: $n = 30$; 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. We used the following criteria delineated by the Department of Defense and Department of Veterans Affairs Traumatic Brain Injury Task Force⁴¹ for mTBI: (1) AOC or LOC ≤ 30 minutes; (2) an initial Glasgow Coma Scale⁴² score between 13 and 15 (which is often not

available in a combat setting); (3) a period of post-traumatic amnesia of 24 hours or less; and (4) no visible lesions on magnetic resonance imaging (MRI) or computed tomographic scan. Loss of consciousness 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 Department of Defense.⁴³ 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.

A clinical neuropsychologist and radiologic technologist with more than 30 years of expertise (M.J.M.) in neuroimaging processing and analysis reviewed each scan to ensure no obvious lesions on structural images. In addition, an on-call clinical neuroradiologist reads any scans where there is a questionable abnormality determined by M.J.M. on participant's structural scans. No participants included in the current study demonstrated obvious lesions on standard neuroimaging. Exclusion criteria for all mTBI and NC participants included the following: (1) moderate to severe TBI (LOC > 30 minutes, posttraumatic amnesia > 24 hours, Glasgow Coma Scale score < 12); (2) a history of other neurological condition (eg, multiple sclerosis, seizure disorder); (3) developmental learning disability; (4) current substance or alcohol abuse according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)- criteria; (5) preinjury metabolic or other diseases known to affect cognition (eg, diabetes); (6) history of psychiatric disorder prior to the TBI event; (7) current or pending litigation; (8) any contraindications to MRI scanning (eg, claustrophobia, shrapnel); or (9) below threshold cutoff scores on effort testing. Participants were, on average, approximately 2 to 4 years removed from their TBI event or events at the time of testing. Two additional participants were recruited but were later identified as outliers with respect to time since injury due to their TBI events occurring 8 and 12 years prior to testing. To equate group on this variable (time since injury), these outliers were excluded from all analyses; however, removal of those 2 participants did not change the results described later. All participants provided written informed consent, and all procedures complied with the local University of California San Diego (UCSD) and Veterans Affairs institutional review boards.

Neuropsychological Assessment

Participants were administered a battery of neuropsychological tests selected for its sensitivity to TBI in addition to the Beck Depression Inventory-II⁴⁴ (BDI-II) and the posttraumatic stress disorder (PTSD) checklist—military version (PCL-M).⁴⁵ The following tasks were used to evaluate EFs: 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, Fourth Edition⁴⁹ (WRAT-4) Reading subtest as a measure of premorbid intellectual functioning. Demographically adjusted *T* scores⁴⁷ and scaled scores⁴⁸ were used for all analyses. Administration time for the entire neuropsychological battery was approximately 2.5 hours.

Reduced EF subgroup criteria—Participants were classified as having reduced EF 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 EF 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 EF 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 and the Forced-Choice Recognition Trial of the California Verbal Learning Test-II⁵¹ were used to assess effort. Cutoff scores for identifying inadequate effort (Test of Memory Malingering Trial 2 < 45 and California Verbal Learning Test-II Forced-Choice Recognition Trial < 15) were based on recommendations from Tombaugh⁵⁰ and Moore and Donders,⁵² respectively.

Brain Imaging

All participants underwent structural MRI and DTI on 3T General Electric MRI scanners housed within the UCSD Functional Magnetic Resonance Imaging (fMRI) Center on the UCSD La Jolla campus. Thirty-five participants (78%) were scanned with the scanner running 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. Several studies support the reproducibility and robustness of FA across platforms.^{53,54} Importantly, the gradients system and application were not changed during the upgrade, and the postprocessing and analysis software techniques were consistent across the data. Specifically, we used the same *b* value (1500 s/mm²) and number of diffusion gradients (61) and vector definitions, and all diffusion parameters (described later) were consistent before and after the scanner upgrade.

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

Diffusion tensor imaging—Diffusion tensor imaging images were collected with a dual spin echo EPI acquisition⁵⁵ with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 × 128, in-plane resolution = 1.875 × 1.875, TR = 10 900 ms, TE = 93 ms. The 10 scans from the MR750 platform used identical scanning parameters though TR was shortened to 8000 ms to reduce scan time without affecting image quality. Specifically, given that the previous TR was much longer than necessary for accommodating the number of slices needed, the excess time in TR was reduced while holding all other parameters constant. This change is not expected to affect image SNR and contrast since, even at 8 seconds, the TR is still many times greater (> five times) than the T1 value of the brain tissue. Indeed, a simulation of the DTI signal equation in Matlab conducted by our lead neurophysicist (K.L.) showed that, assuming T1 of white matter at 3T is 840 ms (see Gelman et al⁵⁶), the SNR difference in white matter between TR 8000 ms and TR 10 900 ms

is only 0.007%. Across scanners, 24 slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model⁵⁷ and a b value of 1500 s/mm², as well as 1 T2 image with no diffusion weighting ($\beta = 0$). Two field maps with the same spatial parameters as those of the DTI scan were collected to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12 to 16 minutes.

Diffusion tensor imaging data processing—The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library⁵⁸ (FSL) was used for image processing. The 2 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 3 participants did not meet quality standards and therefore were removed from analyses. The FSL program *bet* removed nonbrain voxels from the analysis. The FSL program *dtifit* fit a diffusion tensor model at each voxel to provide DTI variables such as FA and eigenvalues on a voxel-by-voxel basis. Per Song et al,³⁶ AD was defined by the principal eigenvalue (ie, AD = L1), and RD was defined as the average of the second and third eigenvalues: RD = (L2 + L3)/2.

Semiautomated regions of interest—Region of interest (ROI) placement was guided by a multistep process, and all ROIs were placed in MNI standard space as shown in Figure 1. First, the tract-based spatial statistics 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 al⁵⁹ for a complete description). An FA threshold of 0.20 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 (anterior internal capsule [AIC], posterior internal capsule [PIC]) following the International Consortium for Brain Mapping (ICBM-DTI-81) white matter labels' atlas available within FSL.⁶⁰ 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 and ventral prefrontal white matter. 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 commissures.⁶¹ Mean FA, RD, and AD values for each ROI were extracted for each subject and exported to SPSS Statistics 18, 2009 (SPSS Inc, Chicago, Illinois) for statistical analyses.

Statistical Analyses

Group comparisons were conducted using analysis of variance followed by contrast testing (*t* tests), including comparisons of the EF subgroup status and AOC versus LOC group comparisons of the DTI metrics. Effect size statistics (Cohen *d*) for the significant *P* for each of the group comparisons were also calculated. Categorical data were analyzed using likelihood-ratio chi-square tests (eg, LOC by EF subgroups) because of the relatively small

sample size. Multiple comparison corrections were conducted using false discovery rate methodology⁶² for the primary DTI analysis between reduced and intact EF subgroups and control participants with false discovery rate set at 0.05. Multiple comparison corrections were not performed on the LOC versus AOC analyses because of their exploratory nature.

RESULTS

TBI and NC Group Demographic and Clinical Characteristics

Participants' demographic and injury characteristics are presented in Table 1. Although the TBI group demonstrated 1 year less education on average, their estimated premorbid intellectual functioning as measured by the WRAT-4 did not differ between groups, and the groups did not significantly differ on age or sex distribution. As expected, however, the mTBI group evidenced significantly higher levels of depressive (BDI-II, $P < .01$) and PTSD-related symptomatology (PCL-M, $P < .001$). However, the 2 mTBI subgroups 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 ($P = .02$; see Table 1).

Mild TBI Versus NC Group Comparisons

As shown in Table 2, comparisons of the regional DTI values between the mTBI and NC groups did not reach significance ($P > .10$). In terms of neuropsychological performance, the mTBI group performed significantly worse than the NC participants on category fluency switching (Cohen $d = 0.80$, $P = .002$) (see Table 3). Importantly, a post hoc analysis of covariance adjusting for BDI-II and PCL-M scores found that the lower score on category fluency switching remained significant, suggesting that comorbid psychiatric disturbance did not account for the lower scores observed in the mTBI sample.

Reduced Versus Intact EF mTBI Subgroup Comparisons

Approximately 43% (13/30) of the mTBI sample demonstrated reductions on EF measures based on the criteria described previously. As shown in Table 1, there were no significant differences on demographic characteristics or psychiatric symptomatology between the 2 subgroups. Of the injury characteristics, LOC status significantly differed between subgroups, with higher rates of LOC in the reduced EF subgroup ($P = .02$). The number of months since the most recent mTBI did not significantly differ between subgroups ($P = .06$), nor was there a statistically significant difference in the proportion of participants whose most recent mTBI was within the past 2 years. In addition, mTBI subgroups did not differ in frequency of blast exposure or total number of mTBI events (all $P > .40$).

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 2 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 FA and radial and AD measures) across all ROIs (all $P > .10$). 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 with the intact EF subgroup in the dorsal prefrontal white matter (Cohen $d = 1.07$), ventral prefrontal white matter (VPFWM) (Cohen $d = .99$), CC genu (Cohen $d = 1.08$), CC body (Cohen $d = 1.11$), CC splenium (Cohen $d = 1.00$), the posterior cingulum (Cohen $d = 1.37$), and with a trend toward significance (P corrected $< .10$) in the anterior cingulum (Cohen $d = .81$). These findings were unchanged after adjusting for months since injury in analyses of covariance. All other FA ROIs (ie, AIC and PIC) did not reach significance (all $P > .10$). When compared with control participants, the reduced EF mTBI subgroup showed significantly lowered (P corrected $< .05$) FA values in the VPFWM (Cohen $d = .98$), the anterior cingulum (Cohen $d = .97$), and the posterior cingulum (Cohen $d = 1.28$) with trends in this direction for the CC genu (Cohen $d = .79$) and CC splenium (Cohen $d = .73$).

The reduced EF mTBI subgroup showed significantly higher (P corrected $< .05$) RD than the intact EF subgroup within the posterior cingulum (Cohen $d = 1.21$), with trends (P corrected $< .10$) in the VPFWM (Cohen $d = 1.00$), the CC body (Cohen $d = .92$), and the CC genu (Cohen $d = .77$). Compared to NCs, there was a trend (P corrected $< .10$) toward higher RD in both the VPFWM (Cohen $d = .98$) and posterior cingulum (Cohen $d = .88$) in the reduced mTBI subgroup. Regarding AD, the reduced EF mTBI subgroup showed significantly lower (P corrected $< .05$) AD values within the AIC (Cohen $d = 1.19$) and the PIC (Cohen $d = 1.21$) relative to 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.

Exploratory Group Comparisons by LOC Versus AOC

Because the reduced EF subgroup demonstrated a higher percentage of participants with LOC compared with 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 [$n = 18$] vs AOC [$n = 12$]) did not significantly differ in terms of age, education, WRAT-Reading scores, or injury and psychiatric characteristics ($P > .05$). Group comparisons of AOC versus LOC on the individual EF scaled scores, and T scores were not significantly different ($P > .05$). However, compared with NCs, the LOC subgroup was found to have significantly lower scaled scores on both the D-KEFS Category Fluency Switching Total Correct ($M_{\text{Control}} = 12.5$, $SD_{\text{Control}} = 3.2$, $M_{\text{LOC}} = 9.2$, $SD_{\text{LOC}} = 2.6$, $P = .01$, Cohen $d = 0.99$) and D-KEFS Trails Letter-Number Switching ($M_{\text{Control}} = 9.9$, $SD_{\text{Control}} = 2.2$, $M_{\text{LOC}} = 7.7$, $SD_{\text{LOC}} = 3.8$, $P = .046$, Cohen $d = 0.74$).

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 $RD \times 10^{-3} \text{ mm}^2/\text{s}$ ($M_{\text{AOC}} = 0.54$, $SD_{\text{AOC}} = 0.02$, $M_{\text{LOC}} = 0.57$, $SD_{\text{LOC}} = 0.04$, $P = .02$, Cohen $d = .89$) with a trend toward lower VPFWM FA ($M_{\text{AOC}} = 0.42$, $SD_{\text{AOC}} = 0.02$, $M_{\text{LOC}} = 0.41$, $SD_{\text{LOC}} = 0.02$, $P = .07$, Cohen $d = .71$). 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 $d = .84$) and VPFWM FA was significantly lower in the LOC subgroup ($M_{\text{Control}} = 0.42$, $SD_{\text{Control}} = 0.02$, $M_{\text{LOC}} = 0.41$, $SD_{\text{LOC}} = 0.02$, $P = .04$, Cohen $d = .85$).

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

The exploratory LOC analyses offer some provisional support to the notion that the observed EF reductions and concomitant white matter compromise in our sample of mTBI participants are perhaps related to neurotrauma history and are not solely because of normal variation in EF scores. First, LOC was associated with higher rates of impaired EF scores when compared with those reporting AOC (without LOC). This distinction is generally consistent with some mTBI studies that have tied LOC to poorer health outcomes and a more prolonged recovery.^{1,39,40} However, the effect of LOC in these studies was significantly attenuated after accounting for psychiatric symptomatology such as PTSD symptom severity. Moreover, Belanger et al³⁸ reported that PTSD symptom severity, but not LOC, was associated with increased reporting of post-concussive symptoms. In contrast, in our sample, LOC was not associated with higher levels of psychiatric distress when compared with those who did not lose consciousness.

In addition, the DTI findings show that LOC was associated with ventral prefrontal white matter integrity degradation, as indicated by RD and AD. The specificity of these findings suggests potential differences in frontal myelin and neural integrity in terms of injury severity (indexed by LOC vs AOC). The injury severity findings are further consistent with other recent studies indicating persisting white matter damage associated with mTBI in OEF/OIF samples,^{63,64} though they contrast with the results reported by Levin et al⁶⁵ wherein no main effect or graded severity effect (mild vs moderate) of TBI was found. This difference in study findings may be related to differences in sensitivity of the DTI sequence employed (eg, our data were acquired using a 61- vs 32-direction sequence); however, it is important to note that Levin et al⁶⁵ examined only blast-related mild to moderate TBI, whereas most of our mTBI sample (56%) reported a mixed history of both blunt and blast

force mTBI and multiple mTBI events. Recently, Goldstein et al⁶⁶ found neuropathologic evidence for persistent chronic traumatic encephalopathy in the brains of military veterans with blast exposure and/or blunt concussive injury, suggesting that TBI induced by different insults under different conditions can trigger common pathogenic mechanisms leading to similar neuropathology and sequelae. Notably, within the small autopsy sample they examined, the effects of blast exposure, blunt concussive injury, and mixed trauma were indistinguishable. Note too that Belanger et al⁶⁷ failed to show neuropsychological differences between blast versus blunt trauma TBI subgroups. Given the high prevalence of blast and/or blunt concussive exposures among OEF/OIF veterans, the chronic effects of TBI and potential for long-term chronic traumatic encephalopathy–linked neuropathologic changes among our retired veterans warrants further investigation.

The elevated psychiatric symptom ratings (ie, PTSD-related or depressive symptom ratings) in the mTBI group relative to control participants are consistent with other reports that self-reported neurotrauma, in general, and psychiatric distress are highly comorbid among OEF/OIF veterans.^{1,65,68} However, our EF subgroups did not significantly differ in PTSD-related or depressive symptom ratings, suggesting that psychiatric distress alone cannot account for the observed group differences in white matter integrity. In addition, the *intact* EF mTBI subgroup did not differ from NC participants on any of the DTI or cognitive comparisons, despite their higher levels of PTSD-related and depressive symptom ratings, further supporting the notion that psychiatric distress did not contribute to the regional white matter differences.

Our finding of worse performance on a speeded test of category fluency switching in the mTBI group relative to control participants, even after statistically adjusting for the higher rates of depression and PTSD symptom severity scores, somewhat contrasts with the results of meta-analytic studies that generally show no or very mild effects of mTBI.^{8–12} However, the clinical significance of this finding is limited as the mean performance of the mTBI group, as a whole, falls within the average range. Category fluency is thought to rely on both frontal and temporal regions, and the added switching component may draw more heavily on frontally mediated attentional and EF processes.⁶⁹ Indeed, Zakzanis et al⁷⁰ report that switching within category fluency tasks may be especially sensitive to frontal brain dysfunction. It is possible then that the observed damage to frontal and posterior association tracts in the reduced EF subgroup relative to control participants may collectively disrupt the concerted integration of the many cognitive subprocesses responsible for optimal performance on this task.

Our findings are derived from one of the few investigations of cognitive dysfunction as it relates to white matter integrity in a sample of OEF/OIF veterans. None of the participants in the current sample were involved in litigation, and none of the 45 participants on whom the analyses were performed evidenced performances below expectations on symptom validity testing. Our exclusion criterion based on symptom validity testing may, in part, explain some of the differences between the results of our study and those of other studies where it was not conducted or reported (eg, Levin et al,⁶⁵ Hoge et al¹). It is noteworthy that the study by Levin et al,⁶⁵ which did not show DTI differences between OEF/OIF veterans with blast TBI and controls, did not report effort testing in their sample. If some participants

with insufficient effort were included in their sample, one might expect to see cognitive test score differences but no DTI differences, and inconsistent or nonsignificant correlations of DTI variables with symptom measures, all of which were demonstrated in their study. Our finding of comparable PTSD- and depressive-symptom severities across subgroups, combined with formal effort testing, further supports the notion that psychiatric distress or insufficient effort were not contributors to the cognitive test score findings or regional white matter differences in our reduced mTBI subgroup.

There are limitations to this study that warrant discussion. First, our data are cross-sectional and injury characteristics (e.g., LOC and AOC) were largely gleaned from self-report, and thus it is possible that the observed differences in FA and neuropsychological performance may reflect premorbid differences that are perhaps unrelated to the mTBI. However, the groups were comparable on educational attainment and reading level. Second, the generalizability of our findings to single-event mTBIs is limited as most of our mTBI participants endorsed having sustained more than 1 TBI. Third, a little more than 40% of our clinical sample showed reductions on tests of EF, although the impairment criteria described earlier were designed to be liberal to increase our sensitivity to detect possible impairment for the research purposes specific to this study. They are not meant to represent the basis for a clinical diagnosis of a cognitive disorder. Fourth, insufficient sample size limited our ability to study the effects of blast-only ($n = 5$) versus blunt-only ($n = 9$) injury mechanisms, though as noted the *presence* of any blast injury was not associated with EF impairment or LOC. Moreover, at present, those investigations comparing blast-only and blunt-only mTBI in OEF/OIF veterans have found no strong evidence of disparate outcomes whether in postconcussive symptom reporting or neuropsychological performance.^{38,67} Finally, the tensor model of diffusion-weighted imaging is limited in regions with more complex architecture (eg, where crossing fibers exist within a single voxel), and thus the measured FA may be attenuated in some regions.³⁴ Although this possibility may have altered the FA measures to some degree, this effect is assumed to be consistent across the groups such that differences in diffusivity measures, while imprecise, continue to signify altered white matter integrity.

CONCLUSIONS

Although there were no direct main effects of mTBI demonstrated in the context of this study, we identified a subgroup of OEF/OIF veterans with mild, but demonstrable, EF reductions and concomitant brain changes associated with their history of mTBI, suggesting that neuronal and cognitive recovery may be protracted in some cases, especially in patients who experienced an LOC. Given the lack of differences between those with and without EF decrements on PTSD-related or depressive symptom severities, it is less likely that psychiatric symptomatology can fully explain the pattern of cognitive and brain findings. Clearly, additional research within this population is warranted to better understand the cognitive and neurostructural effects of mild TBI and to better identify veterans who may continue to struggle cognitively (and potentially psychiatrically) in the aftermath of their brain injuries.

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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. AIC indicates anterior internal capsule; Ant Cing, anterior cingulum bundle; DPFWM, dorsal prefrontal white matter; EF, executive functions; FA, fractional anisotropy; HC, healthy controls; PIC, posterior internal capsule; Post Cing, posterior cingulum bundle; ROI, region of interest; TBSS, tract-based spatial statistics; VPFWM, ventral prefrontal white matter. Error bars represent SEM. ^a*P* corrected < .10, ^b*P* corrected < .05.

Figure 2.

Ventral prefrontal white matter diffusion tensor imaging indices by LOC/AOC status in mild traumatic brain injury compared to control participants. AD indicates axial diffusivity; AOC, alteration of consciousness; FA, fractional anisotropy; LOC, loss of consciousness; RD, radial diffusivity. Error bars represent SEM. ^a $P < .05$.

TABLE 1

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

	Control	TBI	P	Intact EF	Reduced EF	P
<i>n</i>	15	30	...	17	13	...
Age, y	32.9 (8.2)	30.7 (9.3)	.42	28.9 (8.0)	32.8 (10.8)	.27
Years of education	14.3 (1.8)	13.3 (1.3)	.04	13.4 (1.5)	13.3 (0.9)	.93
WRAT-4 reading (SS)	105.7 (9.0)	104.2 (10.8)	.63	104.3 (9.2)	104.0 (13.1)	.94
% Male	73%	87%	.27	88%	85%	.77
% Caucasian	73%	57%	.28	65%	46%	.31
BDI-II	5.1 (10.1)	17.5 (11.6)	.001	16.4 (8.7)	17.5 (5.4)	.56
PCL-M	22.8 (14.5)	42.0 (15.6)	<.001	43.1 (14.2)	41.0 (18.6)	.66
Mean number of mTBIs	...	...	...	2.9 (2.5)	3.1 (2.4)	.90
Months since mTBI	...	...	...	43.5 (21.8)	28.2 (19.1)	.06
% mTBI within past 2 y	...	...	...	24%	46%	.19
% > 1 mTBI	...	...	...	76%	69%	.66
% Combat mTBI	...	...	...	65%	69%	.79
% Reporting any LOC at TBI	...	...	...	41%	85%	.02
% Reporting blast related mTBI	...	...	...	82%	69%	.40

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

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			P		
	M	SD		M	SD		M	SD		Control vs TBI	Intact vs Reduced EF	Control vs Reduced EF
FA	DPFWM	0.40	0.02	0.40	0.01	0.39	0.02			.46	.007 ^a	.05
	VPFWM	0.42	0.02	0.42	0.02	0.40	0.02			.15	.01 ^a	.009 ^a
	CC genu	0.67	0.04	0.67	0.02	0.64	0.03			.35	.007 ^a	.03 ^b
	CC body	0.66	0.04	0.68	0.03	0.64	0.05			.99	.006 ^a	.12
	CC splenium	0.76	0.02	0.76	0.01	0.73	0.04			.61	.01 ^a	.03 ^b
	Ant Cing	0.48	0.03	0.47	0.03	0.45	0.03			.09	.04 ^b	.01 ^a
	Post Cing	0.50	0.03	0.50	0.02	0.47	0.02			.08	.001 ^a	.003 ^a
	Ant IC	0.57	0.02	0.57	0.02	0.56	0.02			.59	.31	.31
	Post IC	0.68	0.02	0.67	0.02	0.67	0.02			.55	.62	.42
	DPFWM	0.55	0.03	0.55	0.02	0.56	0.03			.33	.23	.14
RD × 10 ⁻³ mm ² /s	VPFWM	0.54	0.03	0.54	0.03	0.57	0.04			.21	.012 ^b	.009 ^b
	CC genu	0.39	0.04	0.37	0.03	0.42	0.05			.34	.04 ^b	.05
	CC body	0.40	0.05	0.38	0.04	0.43	0.07			.83	.02 ^b	.11
	CC splenium	0.29	0.02	0.29	0.01	0.31	0.04			.53	.06	.09
	Ant. Cing.	0.51	0.04	0.52	0.03	0.54	0.04			.18	.11	.04
	Post. Cing.	0.45	0.02	0.44	0.01	0.47	0.02			.35	.003 ^a	.02 ^b
	Ant. IC	0.40	0.02	0.41	0.02	0.40	0.03			.56	.67	.79
	Post. IC	0.33	0.02	0.33	0.02	0.32	0.02			.75	.29	.71
	DPFWM	1.02	0.03	1.04	0.03	1.03	0.03			.39	.39	.83
	VPFWM	1.07	0.04	1.07	0.04	1.09	0.03			.71	.33	.40
AD × 10 ⁻³ mm ² /s	CC genu	1.39	0.07	1.40	0.05	1.39	0.06			.64	.37	.94
	CC body	1.40	0.05	1.42	0.04	1.40	0.06			.33	.29	.81
	CC splenium	1.40	0.05	1.42	0.06	1.37	0.05			.95	.04	.20
	Ant Cing	1.14	0.07	1.15	0.04	1.13	0.05			.85	.48	.65

ROI	Control		Intact EF		Reduced EF		P		
	M	SD	M	SD	M	SD	Control vs TBI	Intact vs Reduced EF	Control vs Reduced EF
Post Cing	1.04	0.05	1.03	0.03	1.01	0.05	.30	.23	.14
Ant IC	1.09	0.05	1.12	0.04	1.08	0.04	.71	.003 ^a	.24
Post IC	1.17	0.05	1.19	0.04	1.13	0.05	.81	.003 ^a	.05

Abbreviations: AD, axial diffusivity; Ant, anterior; CC, corpus callosum; Cing, cingulum; DPFWM, dorsal prefrontal white matter; FA, fractional anisotropy; FDR, false discovery rate; IC, internal capsule; mTBI, mild traumatic brain injury; Post, posterior; RD, radial diffusivity; ROI, region of interest; VPFWM, ventral prefrontal white matter.

^aFDR *P* corrected < .05
^bFDR *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		P		
	M	SD	M	SD	M	SD	M	SD	Control vs mTBI	Intact vs Reduced EF	Control vs Reduced EF
WCST Perseverative Responses T-Score	47.1	5.8	48.6	8.7	52.2	7.7	44.2	8.1	.56	.01	.34
D-KEFS Category Switching SS	12.5	3.2	9.4	3.0	10.2	2.5	8.4	3.5	.003	.12	.002
D-KEFS Trails Switching SS	9.9	2.2	8.5	3.5	10.4	1.9	6.1	3.6	.15	<.001	.001

Abbreviations: D-KEFS, Delis-Kaplan executive function system; SS, scaled score; WCST, Wisconsin Card Sorting Test.