PTSD confounds detection of compromised cerebral white matter integrity in military veterans reporting a history of mild traumatic brain injury

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PTSD confounds detection of compromised cerebral white matter integrity in military veterans reporting a history of mild traumatic brain injury

Nicholas D. Davenport 1,2, Greg J. Lamberty 1, Nathaniel W. Nelson 1,3, Kelvin O. Lim 1,2,4, Michael T. Armstrong 1, & Scott R. Sponheim 1,2

1Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA; 2Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA; 3Graduate School of Professional Psychology, University of St. Thomas, Minneapolis, MN, USA, and 4Department of Psychology, University of Minnesota, Minneapolis, MN, USA

Abstract

Primary objective: Based on high comorbidity between mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD) among deployed military service members, this study tested the hypothesis that the presence of PTSD disrupts the association between mTBI and lower white matter integrity identified in non-military samples.

Research design/Methods and procedures: In a sample of 124 recent veterans with a range of mTBI and PTSD history, diffusion tensor imaging (DTI) metrics of white matter integrity in 20 regions were compared using multiple mTBI and PTSD contrasts.

Main outcomes and results: Civilian mTBI was associated with lower global anisotropy, higher global diffusivity and higher diffusivity in 17 of 20 regions. No main effects of deployment mTBI were observed, but an interaction between deployment mTBI and lifetime PTSD on FA was observed globally and in 10 regions. Impact and blast mTBI demonstrated similar but weaker effects to those of civilian and deployment mTBI, respectively, demonstrating the context of mTBI is more relevant to white matter integrity than mechanism of injury.

Conclusions: Overall, a main effect of civilian mTBI indicates long-term disruptions to white matter are likely present, while the interaction between deployment mTBI and PTSD indicates that a history of PTSD alters this relationship.

Introduction

Traumatic brain injury (TBI), especially mild TBI (mTBI), is common among Veterans of Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF) [1–3], affecting an estimated 15–25% of American military service members returning from OIF/OEF deployments [4,5]. Moreover, ~75% of these mTBI events involve exposure to explosive blast (e.g. improvised explosive devices) [6], which may produce different acute and long-term neural effects than traditional impact (i.e. non-blast) mTBI events [7]. In an attempt to identify veterans who may have experienced mTBI during a deployment in one of these recent operations, the Veterans Health Administration (VHA) established a TBI Clinical Reminder screening instrument in 2007 to be administered to any OEF/OIF veteran seeking care at a VHA facility, with positive screens referred to a specialist for a Comprehensive TBI Evaluation (CTBIE) [8]. However, because in-theatre documentation of military mTBI events is rarely available to clinicians at the time of this evaluation, diagnoses rely heavily on retrospective self-report of events that occurred months or years previously and involve potentially traumatic experiences as well as states of confusion, disorientation or loss of consciousness, which may limit a person’s ability to accurately recall details of these events [9]. The difficulty in determining whether these events meet criteria for mTBI is often further complicated by the potential presence of other trauma-related conditions, such as post-traumatic stress disorder (PTSD), that share symptoms with persistent post-concussive syndromes (e.g. sleep disturbance, irritability) and may alter the recollection and reporting of mTBI experiences over time [10,11]. Neuroimaging techniques have provided a means for potentially identifying more objective markers of mTBI, although the role of PTSD in relationships between mTBI and neural disruptions has received less attention. Formal consideration of whether PTSD affects the detection of neuroimaging abnormalities associated with deployment-related mTBI is a key element to establishing their utility as biomarkers.

Based on evidence of diffuse axonal injury in moderate and severe forms of TBI [12], there has been substantial interest in
the use of diffusion tensor imaging (DTI), which quantifies the directional diffusivity of water within each voxel, to investigate white matter integrity disruptions associated with mTBI [13–16]. In general, healthy white matter is composed of directionally organized barriers (e.g. axon membranes, myelin) and is, therefore, characterized by anisotropic (i.e. non-spherical) diffusion [17,18]. The degree of anisotropy and the overall amount of diffusion within each voxel can be quantified by the measures fractional anisotropy (FA) and mean diffusivity (MD), respectively. Healthy white matter is generally characterized by high FA and low MD and studies of civilians generally report that mTBI is associated with lower FA and/or higher MD in the chronic phase (i.e. > 3 months post-injury), consistent with hypotheses of long-term disruptions of white matter integrity [14,19]. Studies of military mTBI using DTI have been somewhat more variable, with some reporting no effect of mTBI on FA or MD [20–22] and some observing effects only when the mTBI event includes loss of consciousness [23–25]. Two studies have reported lower anisotropy associated with mTBI among service members who had been medically evacuated from the OEF/OIF combat theatre for their injuries [26,27], although these cases may not be representative of long-term effects of mTBI in the majority of soldiers. There have also been two reports of military mTBI associated with a greater number of low FA voxels, a measure that allows for spatial variability of disruptions across individuals [28,29]; however, these reports did not account for a statistical bias that may have inflated effects [30,31]. Further investigation of long-term effects of mTBI among Veterans representative of those seen clinically will be important for characterizing neural underpinning of symptoms.

Among the most pressing attributes of military mTBI to address is its comorbidity with PTSD. While the majority of prior reports have acknowledged the confound between PTSD and mTBI, it has been inconsistently considered in study design or statistical testing. Among those that have used linear regression approaches (e.g. covariation), PTSD symptom severity has not been found to have a significant effect on white matter integrity beyond effects of mTBI [23,24,32]. In contrast, a sample of OEF/OIF veterans previously reported that a diagnosis of PTSD was associated with higher anisotropy and lower MD in several white matter regions, while mTBI was associated with fewer high MD regions [33]. This discrepancy highlights the possibility that, among OEF/OIF veterans, the dichotomous diagnosis of PTSD relates to white matter integrity differently than total symptom scores.

Another distinction that may be important to consider in investigations of military mTBI is whether blast forces contribute to the injury mechanism. It is well-documented from simulations and animal models of TBI [7,34–37] that the pressure wave from explosive blast represents a distinct physical experience, both in immediate effects and downstream sequelae, than typical acceleration–deceleration forces involved in non-blast (i.e. impact) mTBI. Given that 75% of mTBI events among OEF/OIF soldiers involve exposure to blast [4,6,38], this influence is likely critical. Moreover, military mTBI events that involve blast (e.g. mortar, improvised explosive device) are likely more psychologically traumatic (e.g. life-threatening, witness death or harm to others) and more disorienting than non-blast mTBI events (e.g. falls, motor vehicle accidents), which could affect how the experiences are recalled and reported months or years later. Alternatively, it is possible that the deployment context itself, instead of or in addition to the mechanism of injury, alters the neural manifestations or later retrospective reporting of mTBI. Given the dependence on retrospective self-report inherent to diagnosis of military mTBI, better understanding of how contextual elements of the index event affect downstream consequences, including the potential for effects on recall and reporting, have substantial clinical relevance.

The primary purpose of the current study was to determine whether the relationships of deployment and civilian mTBI with measures of white matter integrity differ based on the presence or absence of lifetime PTSD within a sample of Veterans with a positive screen on the VA TBI clinical reminder. Based on the hypothesis that PTSD alters recollection of events related to the initial traumatic experience, the relationship between deployment mTBI and white matter integrity is expected to be weaker in the presence than in the absence of PTSD, resulting in an interaction between deployment mTBI and PTSD but not between civilian mTBI and PTSD. A secondary purpose of this study is to determine whether observed effects are better explained by mechanism of injury (Blast vs Impact) than by the deployment context or by a current diagnosis of PTSD rather than by PTSD history.

Methods

Participants

Participants were 124 American military veterans who had been deployed as part of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF), had screened positive for potential mTBI on the VHA TBI Clinical Reminder within the Minneapolis VA Health Care System and had been subsequently referred to the Minneapolis VA Regional Polytrauma Center for evaluation. Exclusion criteria included moderate or severe TBI, other neurological conditions or injuries (e.g. stroke, multiple sclerosis) and contraindications to MRI (e.g. implanted devices).

All participants completed an informed consent process conducted by trained study staff and were provided monetary compensation for their participation after each study procedure. The study protocol was reviewed and approved by the University of Minnesota and Minneapolis Veterans Affairs Health Care System Institutional Review Boards.

Clinical assessment

Participants completed a clinical interview that included the Clinician Administered PTSD Scale (CAPS [39]) to document current and lifetime symptoms of PTSD; the Structured Clinical Interview for DSM-IV-TR (SCID [40]) to assess other DSM-IV-TR diagnoses; and the Minnesota Blast Exposure Screening Tool (MN-BEST [41]) to assess history of potential mTBI events. Interviews were conducted by experienced study staff trained to collect detailed descriptions of events and symptoms. Corroborating information (e.g. medical records) was incorporated when available. Lifetime (i.e. at any point, including currently) DSM-IV-TR diagnoses were determined through consensus review of all available information by doctoral-level
psychologists and advanced graduate students with explicit training in psychopathology diagnosis. Specifically, diagnoses of PTSD were based primarily on information assessed by the CAPS interview and all other DSM-IV diagnoses were based primarily on information from the SCID. Reports of potential head injuries were excluded from the DSM-IV diagnosis review process whenever possible to avoid artificial confounding of PTSD and mTBI experiences.

Potential mTBI events were designated as blast mTBI if exposure to the pressure wave from an explosive blast was reported to be a substantial component of the event, although secondary (e.g. being thrown against the ground or other objects) and tertiary (e.g. being hit by debris) sources of injury were frequently present. Potential mTBI events that did not involve exposure to explosive blast were designated as impact mTBI. The three most severe events of each type, based on duration and intensity of acute symptoms (e.g. alteration or loss of consciousness, post-traumatic amnesia, sensitivity to light, balance problems), from across the participant’s entire lifetime were assessed in detail according to the MN-BEST rating scale. Final determination of likelihood and severity of mTBI events and whether blast exposure represented a substantial component of the injury, was made by consensus review of head injury information by doctoral-level neuropsychologists blind to all other sources of information, including reported PTSD symptoms.

Among the information gathered about each potential mTBI event was whether the participant was deployed at the time. Events that occurred during deployment were designated as deployment mTBI and otherwise as civilian mTBI. While civilian mTBI events occurred primarily in the context of civilian life (e.g. car accidents, sports injuries), events that occurred in a military role outside of deployment (e.g. drills, training) were also placed in this category.

**MRI acquisition and processing**

MRI data were collected on a 3 Tesla Siemens Tim Trio (Erlangen, Germany) scanner using a 32-channel birdcage head coil. Head movements were minimized by placing pads around the participant’s head. The diffusion imaging sequence (TR/TE = 3166/91.4 ms, 66 oblique axial slices, 106 × 106 matrix, 212 mm FOV, 2.0 mm thickness, multi- sequence (TR/TE = 3166/91.4 ms, 66 oblique axial slices, multi-) acquired images in each of 128 non-collinear directions at b = 1500 s mm⁻², along with 17 images with b = 0 evenly distributed throughout the sequence and this sequence was run twice with opposing phase encoding directions (anterior–posterior) to enable retrospective distortion correction.

A field map was estimated using ‘topup’ from the FMRIB Software Library (FSL [42,43]) based on the first non-diffusion weighted (i.e. b = 0) image from each run and distortions due to field inhomogeneity were removed using ‘applytopup’. Residual eddy current distortions were removed using FSL’s ‘eddy_correct’, which registers each diffusion-weighted volume to the first b = 0 image. The diffusion tensor model was fit to voxels and scalars (fractional anisotropy [FA] and mean diffusivity [MD]) were computed using ‘dtifit’ from FSL [44]. Maps of generalized fractional anisotropy (GFA), which provides a more robust measure of anisotropy in regions of crossing fibres, were computed based on the algorithm of Assemllal et al. [45] using custom Matlab (The Mathworks, Inc., Natick, MA) software. To ensure optimal anatomical correspondence across subjects, the tensor maps were aligned to a template using iterative affine and diffeomorphic transformations using the DTI ToolKit (DTI-TK [46]). By incorporating directional information from the entire tensor rather than the intensity of a single scalar, this registration algorithm ensures consistent alignment of individual tracts across subjects. The affine and diffeomorphic transformations were concatenated and applied to each of the scalars (FA, MD, GFA).

To quantify white matter integrity within specific regions of interest (ROIs), the Johns Hopkins University (JHU) White Matter Atlas was non-linearly aligned to the mean FA image using FSL’s Nonlinear Image Registration Tool (FNIRT [47]). A global white matter mask was created that included only voxels in which FA > 0.20 in all subjects and FA > 0.25 in 95% of subjects; this dual-threshold approach was intended to eliminate voxels unlikely to contain white matter, while allowing voxels that had low FA in a small number of participants to be included. In addition to using this mask to compute global measures of white matter integrity, it was used to restrict the ROIs to those voxels most likely to represent white matter. Average FA, GFA and MD were computed for each of the 20 ROIs and for the global mask.

As additional measures of integrity and for comparison to prior publications [29,33,48], the number of voxels with abnormally high values and the number with abnormally low values were quantified within the global mask for each of the scalars. Abnormal integrity was defined within each voxel as a value more than 2 standard deviations higher or lower than the mean across the individuals with no history of PTSD or mTBI (n = 29). The actual thresholds used were 1.946 within this reference group and 2.129 for the remainder of the sample to account for a bias identified in a prior report [29] that has since been addressed by others [30,31]. Voxel counts were log-transformed to normalize the distributions.

**Statistical analyses**

Demographic characteristics were compared between individuals with and without a history of PTSD. Age was compared using an independent samples t-test and the rates of the four types of mTBI (i.e. Blast, Impact, Civilian, Deployment) were compared using Chi-square tests (df = 1). The number of OEF/OIF deployments were compared with a Chi-square test (df = 2) with ‘3 or more’ deployments collapsed into a single category. The total duration of OEF/OIF deployments, months since most recent deployment and months since the most recent of each mTBI type were compared between individuals with and without a history of PTSD using Mann-Whitney U tests to account for the non-normal distributions.

To determine whether the observed relationship between reported mTBI history and white matter integrity differed between samples with and without history of PTSD, a 3-way (Civilian mTBI, Deployment mTBI and Lifetime PTSD) analysis of covariance (ANCOVA) was conducted, with age as a covariate, on each of the DTI scalars (FA, GFA, MD) within each of the regions of interest.
Significance of main effects and interactions within regions of interest was corrected for multiple comparisons using a false discovery rate (FDR) of $q = 0.05$ [49,50]. This ANCOVA was also conducted on the three global measures (i.e. global average across white matter mask, number of high value voxels, number of low value voxels) for each of the DTI scalars and corrected for multiple comparisons. To determine whether mTBI distinctions based on mechanism (i.e. Blast vs Impact), rather than context (i.e. Deployment vs Civilian) result in different observed relationships with white matter integrity, the ANCOVAs described were conducted again with blast and impact mTBI replacing the factors of deployment and civilian mTBI, respectively. Likewise, to determine whether a current diagnosis of PTSD relates to white matter integrity differently than a lifetime diagnosis, ANCOVAs were conducted with current PTSD (i.e. symptoms meeting full diagnostic criteria for PTSD at the time of study) replacing lifetime PTSD.

### Results

#### Sample characteristics

Fifty-six participants (45.2%) met criteria for PTSD at some point in their lives (Table I). In comparison, Hoge et al. [4] reported that 32.7% of soldiers with an injury involving loss or altered consciousness met criteria for PTSD 3–4 months after returning from an OIF deployment. The slightly higher rate seen here is not surprising given that the entire history was taken into account rather than a single time point. Most participants were studied 3–7 years since their most recent deployment. Over half the sample reported an event occurring during deployment that was judged to meet criteria for an mTBI, which is consistent with rates of mTBI diagnosis among positive screens on the VHA TBI clinical reminder reported previously [51]. Additionally, ~40% of participants reported events occurring outside of deployments that were judged to meet mTBI criteria. Overall, 91 participants (73.4%) met criteria for at least one mTBI event. Of the 80 Deployment mTBI events reported, 54 (67.5%) involved explosive blast while the remaining 26 (32.5%) involved only impact forces. Of the 61 civilian mTBI events reported, only one (1.6%) involved explosive blast. Most deployment mTBI events occurred 4–9 years prior to participation, while most civilian mTBI events occurred over a larger time range of 6–18 years prior to participation. No differences in age, number of OEF/OIF deployments, total OEF/OIF deployment duration, months since most recent deployment, frequency of any mTBI type or months since most recent mTBI were observed between participants with and without lifetime PTSD.

### Civilian mTBI

As seen in Table II, civilian mTBI was associated with lower global FA, lower global GFA and higher global MD, consistent with impaired overall white matter integrity. This effect was also manifested as fewer voxels with high FA, high GFA and low MD (i.e. highly constrained diffusion) and more voxels with low FA, low GFA and high MD (i.e. less constrained diffusion). Most effects were medium in size (partial $\eta^2 = 0.061–0.085$) according to traditional guidelines (0.01 small, 0.06 medium, 0.14 large [52,53]), although the effects on low FA voxels (partial $\eta^2 = 0.037$) and low GFA voxels (partial $\eta^2 = 0.039$) were smaller. Effects were substantially diminished when current PTSD was entered into the model instead of lifetime PTSD; however, all effects on MD and the effects on global FA and low FA voxels remained significant. As seen in Table III, impact mTBI demonstrated a similar general pattern to that of civilian mTBI, but only the effects on global MD, low MD voxels and high GFA voxels remained significant and only the effect on low MD voxels was significant when current PTSD was used. Overall, this pattern indicates that civilian mTBI is associated with lower white matter integrity when history of PTSD diagnosis is accounted for. Although civilian mTBI events involved almost exclusively impactful sources of injury, the observation that impact mTBI (i.e. combined across civilian and deployment contexts) demonstrated a similar but weaker effect suggests that this relationship does not generalize to deployment-related impact mTBI events.

Within individual ROIs, civilian mTBI was associated with lower GFA in the left ATR and higher MD in 17 of the 20 regions tested, including bilateral anterior thalamic radiations (ATR), bilateral uncinate fasciculus, bilateral cingulum, bilateral corticospinal tract (CST), bilateral inferior fronto-occipital fasciculus (IFOF), bilateral superior longitudinal fasciculus (SLF), right hippocampal portion of the cingulum, right inferior longitudinal fasciculus (ILF) and forceps minor (Figure 1). Consistent with the global measures, effect sizes were generally medium in size (partial $\eta^2 = 0.040–0.096$). Civilian mTBI was not associated with differences in FA in any individual ROI. When current PTSD was included in the model instead of lifetime PTSD, civilian

### Table I. Participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>No lifetime PTSD ($n = 68$)</th>
<th>Lifetime PTSD ($n = 56$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean (SD)</td>
<td>34.6 (9.1)</td>
<td>33.5 (7.7)</td>
<td>0.473a</td>
</tr>
<tr>
<td>OEF/OIF Deployments1, 1/2/3+</td>
<td>37/21/10</td>
<td>26/25/4</td>
<td>0.173b</td>
</tr>
<tr>
<td>Total OEF/OIF duration, months2, Median (IQR)</td>
<td>14.0 (11, 24)</td>
<td>17.5 (12, 23)</td>
<td>0.234c</td>
</tr>
<tr>
<td>Months since most recent deployment, Median (IQR)</td>
<td>51.5 (35, 82)</td>
<td>49.0 (37, 84)</td>
<td>0.958c</td>
</tr>
<tr>
<td>Deployment mTBI (dTBI) n (%)</td>
<td>35 (51%)</td>
<td>29 (52%)</td>
<td>0.972b</td>
</tr>
<tr>
<td>Months since dTBI, Median (IQR)</td>
<td>87 (59, 103)</td>
<td>77 (48, 103)</td>
<td>0.403c</td>
</tr>
<tr>
<td>Civilian mTBI (cTBI) n (%)</td>
<td>28 (41%)</td>
<td>24 (43%)</td>
<td>0.850b</td>
</tr>
<tr>
<td>Months since cTBI, Median (IQR)</td>
<td>154 (66, 247)</td>
<td>127 (72, 182)</td>
<td>0.557c</td>
</tr>
<tr>
<td>Current PTSD, n (%)</td>
<td></td>
<td>23 (41%)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, Interquartile Range; OEF/OIF, Operation Enduring/Iraqi Freedom; PTSD, post-traumatic stress disorder.

Test statistic: $^a$ Student’s t-test, $^b$ Chi-squared, $^c$ Mann-Whitney U.

Some information was not available for all participants: $^1$ 68 vs 55; $^2$ 66 vs 54; $^3$ 66 vs 55.
mTBI was associated with higher MD in six ROIs (bilateral ATR, bilateral cingulum, right hippocampal cingulum and right CST). Impact mTBI was associated with lower MD in nine ROIs, including bilateral ATR, bilateral CST, left uncinate, right cingulum and hippocampal cingulum, left uncinate and forceps minor. Only the right hippocampal cingulum demonstrated an association between impact mTBI and higher MD when current PTSD was included in the model. Overall, this pattern of effects mirrors that of the global measures, specifically that mTBI classification based on context and lifetime rather than current PTSD provide the strongest effects, with bilateral ATR and right hippocampal cingulum being the most robust across these methodological variations.

### Deployment mTBI and PTSD

The interaction between deployment mTBI and lifetime PTSD had significant effects, after correction for multiple comparisons, on global FA, global GFA, the number of voxels with high FA, the number of voxels with high GFA and mean FA and GFA in 10 ROIs, including bilateral IFOF.

### Table II. Main effects of civilian and deployment mTBI on white matter integrity.

<table>
<thead>
<tr>
<th>Measure</th>
<th>mTBI type</th>
<th>Lifetime PTSD</th>
<th>Current PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$F_{1,115}$</td>
<td>$p$</td>
</tr>
<tr>
<td>Global FA</td>
<td>Civilian</td>
<td>7.53</td>
<td>0.007**</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.07</td>
<td>0.794</td>
</tr>
<tr>
<td>High FA voxels</td>
<td>Civilian</td>
<td>9.15</td>
<td>0.003**</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.68</td>
<td>0.412</td>
</tr>
<tr>
<td>Low FA voxels</td>
<td>Civilian</td>
<td>4.38</td>
<td>0.039**</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.39</td>
<td>0.535</td>
</tr>
<tr>
<td>Global GFA</td>
<td>Civilian</td>
<td>7.74</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.11</td>
<td>0.745</td>
</tr>
<tr>
<td>High GFA voxels</td>
<td>Civilian</td>
<td>10.68</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.89</td>
<td>0.347</td>
</tr>
<tr>
<td>Low GFA voxels</td>
<td>Civilian</td>
<td>4.62</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.12</td>
<td>0.726</td>
</tr>
<tr>
<td>Global MD</td>
<td>Civilian</td>
<td>10.52</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.16</td>
<td>0.691</td>
</tr>
<tr>
<td>High MD voxels</td>
<td>Civilian</td>
<td>8.04</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>0.04</td>
<td>0.844</td>
</tr>
<tr>
<td>Low MD voxels</td>
<td>Civilian</td>
<td>9.91</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Deployment</td>
<td>1.79</td>
<td>0.184</td>
</tr>
</tbody>
</table>

(G)FA, (generalized) fractional anisotropy; MD, mean diffusivity; PTSD, post-traumatic stress disorder.
* $p < 0.05$.
** Survives FDR correction for multiple comparisons.

### Table III. Main effects of impact and blast mTBI on white matter integrity.

<table>
<thead>
<tr>
<th>Measure</th>
<th>mTBI type</th>
<th>Lifetime PTSD</th>
<th>Current PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$F_{1,115}$</td>
<td>$p$</td>
</tr>
<tr>
<td>Global FA</td>
<td>Impact mTBI</td>
<td>4.27</td>
<td>0.041*</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>High FA voxels</td>
<td>Impact mTBI</td>
<td>5.44</td>
<td>0.021*</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>3.23</td>
<td>0.075</td>
</tr>
<tr>
<td>Low FA voxels</td>
<td>Impact mTBI</td>
<td>2.21</td>
<td>0.140</td>
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<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.69</td>
<td>0.408</td>
</tr>
<tr>
<td>Global GFA</td>
<td>Impact mTBI</td>
<td>4.47</td>
<td>0.037*</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.35</td>
<td>0.555</td>
</tr>
<tr>
<td>High GFA voxels</td>
<td>Impact mTBI</td>
<td>6.81</td>
<td>0.010**</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>2.75</td>
<td>0.100</td>
</tr>
<tr>
<td>Low GFA voxels</td>
<td>Impact mTBI</td>
<td>2.28</td>
<td>0.134</td>
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<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.47</td>
<td>0.493</td>
</tr>
<tr>
<td>Global MD</td>
<td>Impact mTBI</td>
<td>6.82</td>
<td>0.010**</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.13</td>
<td>0.723</td>
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<tr>
<td>High MD voxels</td>
<td>Impact mTBI</td>
<td>3.85</td>
<td>0.052</td>
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<tr>
<td></td>
<td>Blast mTBI</td>
<td>0.01</td>
<td>0.909</td>
</tr>
<tr>
<td>Low MD voxels</td>
<td>Impact mTBI</td>
<td>10.51</td>
<td>0.002**</td>
</tr>
<tr>
<td></td>
<td>Blast mTBI</td>
<td>2.14</td>
<td>0.146</td>
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(G)FA, (generalized) fractional anisotropy; MD, mean diffusivity; PTSD, post-traumatic stress disorder.
* $p < 0.05$.
** Survives FDR correction for multiple comparisons.
bilateral superior longitudinal fasciculus (SLF), bilateral temporal portion of the SLF, bilateral ILF, right uncinate and right hippocampal cingulum (Table IV). As seen in Figure 2 and the Supplementary Figure, the specific relationships among the four sub-groups that compose the interaction varied somewhat across tests; however, the effect of deployment mTBI was consistently in the same direction as the main effect of civilian mTBI (i.e. lower anisotropy) in the absence of a history of PTSD, but in the opposite direction when history of PTSD was present. Interestingly, the two groups with highest FA in each region were the individuals with neither deployment nor PTSD and the individuals with both conditions, suggesting that each condition in isolation is associated with lower FA, but the combination is associated with normal or elevated FA.

An interaction between blast mTBI and lifetime PTSD was also observed on FA in six ROIs (left and right IFOF, left ILF, right uncinate, right SLF and right temporal SLF) as well...
as on the number of voxels with high FA and the number of voxels with high GFA. The effect of this interaction on GFA in specific ROIs was similar to that for FA, but did not survive correction for multiple comparisons. No interactions between current PTSD and deployment mTBI or blast mTBI were observed.

Discussion
In a sample of OEF/OIF veterans reporting potential mTBI events during deployment, this study investigated the effects of clinician-determined mTBI and PTSD on measures of white matter integrity. Civilian mTBI was associated with higher diffusivity (i.e. MD) and lower anisotropy (i.e. FA and GFA) on measures summarizing global white matter integrity, suggesting widespread disruption. After correction for multiple comparisons, civilian mTBI was also associated with higher MD in 17 of the 20 individual white matter regions tested. In contrast, while no main effects of lifetime PTSD or deployment mTBI were observed, there was a significant interaction between these factors on FA and GFA in 10 regions, global FA, global GFA and the number of voxels with high FA or GFA. Overall, this pattern of effects suggests a straightforward association between civilian mTBI and disrupted white matter, while the relationships of deployment mTBI and lifetime PTSD with white matter integrity are more complex.

The effects of impact and blast mTBI were similar to those of civilian and deployment mTBI, respectively, but were weaker and less extensive, suggesting that the context of injury is more relevant to white matter integrity than the mechanism. This is a critical observation given unique features of deployment mTBI, relative to civilian mTBI, in terms of the context of the event itself (e.g. prolonged stress and trauma exposure) as well as subsequent experiences (e.g. limited opportunity for rest following injury) and diagnosis (e.g. months or years after injury) and may provide insight into attributes of the deployment context that contribute to long-term outcomes. However, given that many of these differences in context, such as greater stress and delay of medical care, would be expected to be associated with greater severity of injury, it is counterintuitive that civilian mTBI was consistently associated with reduced white matter integrity, while deployment mTBI demonstrated this relationship only in the absence of PTSD. This pattern is consistent with the hypothesis that a history of PTSD, presumably based on deployment experiences, modifies the Veteran’s recollection of other deployment experiences, including mTBI events [54–56]. While such a hypothesis is difficult to test without knowing the ground truth of whether an mTBI occurred, which is rare in the assessment of deployment mTBI, it would be a mechanism by which PTSD could modify observed effects of mTBI on white matter integrity indirectly, without necessarily altering the underlying pathogenesis.

Inherent to the inference that context of injury better explains variability in white matter integrity than mechanism of injury is the conclusion that the long-term neural consequences of blast mTBI are not substantially different than those of impact mTBI, which is contrary to the hypothesis that the presence of explosive blast in an mTBI event results in additional damage beyond the impact sources of injury [32,37]. This is also inconsistent with evidence that close-proximity exposure to blast alone, independent of mTBI symptoms, is associated with alterations of neural function.
[57], but would align with growing neuropsychological evidence that blast and impact mechanisms of injury do not differ in long-term cognitive outcomes [58–60].

The observation that effects were much weaker when current PTSD was included in the model instead of lifetime PTSD may, in part, be due to the relatively low rate of current PTSD in this sample (n = 23), resulting in reduced statistical power. However, effect sizes for the interaction between current PTSD and blast or deployment mTBI were all small (partial η^2 ≤ 0.015), suggesting that a lifetime history of PTSD is indeed a more meaningful classification, with respect to effects on white matter integrity, than whether a person meets criteria at the time of study. Given that lifetime PTSD status is static, this provides evidence that its relationship with mTBI and white matter integrity is also likely to be stable over time, which raises the empirical hypothesis that treatment of PTSD symptoms may not be an effective strategy for altering neural outcomes of mTBI. Moreover, while most studies of military mTBI have only considered current PTSD symptoms [27,28,32,61], the current results indicate that this is insufficient or inappropriate for characterizing relationships with white matter integrity and potentially other outcome measures.

One of the major goals of this analysis was to demonstrate the extent to which observed effects differ under alternative classifications for mTBI and PTSD. Specifically, if this study had followed the conventions of the existing literature by using classifications based on blast vs impact mTBI and on current PTSD, the conclusion would have been that there is little evidence of relationships between mTBI and white matter integrity beyond the main effects of impact mTBI on MD within right hippocampal cingulum and the number of voxels with low MD. If this study had instead classified mTBI based on deployment vs civilian, the interaction between deployment mTBI and PTSD would not have been revealed and if this study conducted the ANCOVA with blast mTBI, impact mTBI and lifetime PTSD the conclusion would have been that the blast mTBI by PTSD interaction was representative of the mechanism of injury rather than the context. Conducting analyses with several variations of the independent variables allowed the observed effects to be more properly characterized and interpreted. A similar approach was recently utilized by Robinson et al. [57] to determine that being in close proximity to an explosive blast was more strongly related to altered functional connectivity than other aspects of potentially traumatic events, such as mTBI symptoms and PTSD. The selection of alternative classifications in the current set of analyses emphasized consideration of mTBI and PTSD experiences across the entire lifespan and the results revealed that doing so provides valuable information, but there are several other aspects that could be considered, including loss of consciousness [23,24,62,63] or the presence of headaches [4,6,60,64,65]. Future studies that conduct and fully report the results of multiple simultaneous, hypothesis-driven strategies to characterizing aspects of military mTBI may provide valuable insight into its short-term and long-term effects.

Strengths and limitations

One of the unique strengths of this study was recruitment of all participants based on positive screens on the TBI clinical reminder, independent of treatment sought or received for conditions related to mTBI or PTSD. This strategy provides higher generalizability to those Veterans for whom clinical differentiation decisions are being made than samples recruited based on established TBI diagnoses. Additionally, an extensive set of measures have been used to characterize multiple aspects of mTBI events and clinical symptoms. These assessments are reinforced by the use of independent consensus review processes for mTBI and psychopathology determinations, which limits spurious confounding of these conditions. Finally, the inclusion of PTSD provides a measure of white matter integrity that has been previously demonstrated to be more sensitive to effects of mTBI and PTSD than FA, despite being highly correlated [33]. The observed effects for GFA and FA were less disparate than in a prior investigation, likely due to the use of a higher b-value, a head coil with more acquisition channels and/or better eddy current compensation.

The major limitation to nearly all studies of military concussion is the dependence on retrospective self-report for assessment of potential mTBI events due to the scarcity of in-theatre documentation. Although this provides an analogue to the clinical environment, increasing the applicability of results to clinical relevance, it has also been shown to introduce a bias in the reporting of mTBI events [10]. The authors have attempted to limit this bias by using a consensus review process conducted by neuropsychologists with extensive experience evaluating mTBI in Veterans. Moreover, mTBI diagnosis was conducted blind to other self-report data, cognitive performance or psychopathology to limit the degree to which determination of the likelihood and severity of past mTBI events is affected by present levels of functioning. While these procedures are not a substitute for in-theatre documentation, this rigorous process ensures that self-reported information is properly evaluated by clinical professionals. It should be noted that, although PTSD diagnoses are also based on self-report and, therefore, not immune to reporting biases, there are several important differences that make this less of a concern than for mTBI diagnosis. Assessment of mTBI requires detailed recollection, on the order of minutes, of events involving altered consciousness and/or amnesia. Symptoms of acute mTBI are largely transient, non-specific and may not be experienced as distressing. In contrast, assessment of index events (i.e. Criterion A) for PTSD requires fewer objective details and weights the subjective experiences more heavily and the diagnostic symptoms (e.g. re-experiencing, avoidance, hypervigilance) persist over an extended period and are, by definition, experienced as distressing or impairing. Moreover, while structured instruments for retrospective assessment of mTBI currently lack rigorous psychometric testing, this study has used a well-established, gold standard clinical instrument for PTSD diagnosis (i.e. CAPS).

An additional limitation is the lack of longitudinal data, which prevents any statements of causality to be drawn from these results. While it is certainly plausible that differences in white matter integrity represent consequences of head injury, it is also possible that they instead represent vulnerability factors, personality traits related to symptom reporting or impulsivity or the effects of related conditions. Longitudinal studies that can establish relationships between mTBI
experiences and changes in white matter integrity over time, especially within the chronic phase, would be valuable to determining whether observed effects are progressive.

Conclusions

Overall, the current analyses provide evidence that civilian mTBI is consistently associated with white matter disruptions, while the effect of deployment mTBI on white matter integrity is contingent on history of PTSD. This interaction may reflect differences in recollection and reporting of mTBI events, but requires further study for additional characterization. Furthermore, this study has demonstrated differential sensitivity of MD and FA to these effects, indicating that different aspects of white matter integrity may be involved. Future studies using diffusion kurtosis imaging (DKI), which provides additional measures of microstructural properties of white matter, may be helpful in further characterizing these differential relationships.

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Declaration of interest

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ORCID

Nicholas Davenport @ http://orcid.org/0000-0002-3441-7256

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