Diffuse and spatially variable white matter disruptions are associated with blast-related mild traumatic brain injury

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A B S T R A C T

Mild traumatic brain injury (mTBI) due to explosive blast is common among military service members and often associated with long term psychological and cognitive disruptions. Little is known about the neurological effects of blast-related mTBI and whether they differ from those of civilian, non-blast mTBI. Given that brain damage from blasts may be diffuse and heterogeneous, we tested the hypothesis that blast mTBI is associated with subtle white matter disruptions in the brain that are spatially inconsistent across individuals. We used diffusion tensor imaging to examine white matter integrity, as quantified by fractional anisotropy (FA), in a group of American military service members with (n=25) or without (n=33) blast-related mTBI who had been deployed as part of Operation Iraqi Freedom or Operation Enduring Freedom. History of civilian non-blast mTBI was equally common across groups, which enabled testing of both blast and non-blast mTBI effects on measures sensitive to (1) concentrated, spatially consistent (average FA within a ROIs with low average FA), and (3) diffuse (number of voxels with low FA) disruptions of white matter integrity. Blast mTBI was associated with a diffuse, global pattern of lower white matter integrity, and this pattern was not affected by previous civilian mTBI. Neither type of mTBI had an effect on the measures sensitive to more concentrated and spatially consistent white matter disruptions. Additionally, individuals with more than one blast mTBI tended to have a larger number of low FA voxels than individuals with a single blast injury. These results indicate that blast mTBI is associated with disrupted integrity of several white matter tracts, and that these disruptions are diluted by averaging across the large number of voxels within an ROI. The reported pattern of effects supports the conclusion that the neurological effects of blast mTBI are diffuse, widespread, and spatially variable.

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Introduction

One of the most common injuries to military service members in recent conflicts is mild traumatic brain injury (mTBI) from explosive blast (Taber et al., 2006; Warden, 2006). Approximately 15–25% of American service members deployed to Iraq or Afghanistan reported mTBI (i.e. concussion), and explosive blast was involved in approximately 75% of these incidents (Hoge et al., 2008; Terrio et al., 2009; Wilk et al., 2010). The brain damage associated with mTBI has traditionally been believed to be minimal and temporary, supported by the relatively rapid reduction of symptoms and lack of gross abnormalities on structural neuroimaging scans like computed tomography (CT) and magnetic resonance imaging (MRI) (Niogi and Mukherjee, 2010). However, evidence of white matter disruptions in moderate and severe forms of TBI (Kasahara et al., 2010; Kinnunen et al., 2010; Levin et al., 2008; Oni et al., 2010; Sidaros et al., 2008), along with reports of persistent post-concussive symptoms in up to 30% of cases (Schneiderman et al., 2008), raises the possibility of long-term neurological effects that may not be evident using traditional clinical and neuropsychological instruments.

Diffusion tensor imaging (DTI), an MRI technique used to assess microstructural properties of white matter, has generally demonstrated lower integrity of white matter tracts in frontal and temporal regions in individuals with mTBI relative to a healthy control group (for full review, see Niogi and Mukherjee, 2010). However, given that the directions of forces involved in the initial injury differ across cases (e.g. the orientation of the head relative to the impact), so too may the locations of injury within the brain. Consistent with multiple and varied areas of white matter being affected in mTBI, two studies have shown that the number of regions with “abnormally” low
white matter integrity (i.e. fractional anisotropy [FA]) several standard deviations below a control group mean) correlated with measures of trauma severity and cognitive function (Levin et al., 2008; Ptak et al., 2003). Because the specific regions with compromised white matter integrity varied across individuals in these studies it may be the number of areas with affected white matter, rather than the magnitude of damage within any single region, that is the most relevant aspect of the brain damage associated with mTBI (Ptak et al., 2003). Additionally, studies with data at multiple time points have failed to find an effect of time since injury on FA, suggesting that long-term neurological effects of mTBI may be present shortly after the injury (Inglese et al., 2005; Rutgers et al., 2008). Other DTI measures, such as mean diffusivity (MD), have also been used to test effects of mTBI on white matter integrity and have generally demonstrated effects analogous to those of FA (Niogi and Mukherjee, 2010), though some studies have demonstrated an effect of mTBI on MD but not FA (e.g., Cubon et al., 2011) or on FA but not MD (e.g., Smits et al., 2011), suggesting potential differential sensitivity among measures.

Blast and non-blast mTBI are qualitatively different in their origins and may carry different consequences for the structural and functional connectivity of the brain. For instance, most non-blast mTBI is due to impact injuries, such as automobile and sports-related collisions, that involve acceleration-deceleration forces, whereas explosive blast involves a series of pressure waves with compressive and tensile components (Moore and Jaffee, 2010; Taber et al., 2006). The first published comparison of FA between individuals with blast mTBI and healthy controls failed to find effects in any region of interest (ROI) or using voxelwise comparisons (Levin et al., 2010); however, a more recent report found that a subset of service members with blast mTBI had FA abnormalities in a greater number of ROIs than would be expected by chance (MacDonald et al., 2011). Our own previous work has demonstrated that in soldiers who experienced blast mTBI, but not in soldiers without blast mTBI, the FA of frontal tracts correlated with electroencephalography (EEG) measures of functional connectivity between brain regions (Sponheim et al., 2010). Therefore, it is likely that neurological effects of blast injury are present, though their characterization may require different techniques than those used in civilian, non-blast mTBI.

In the current study, we examined United States military service members deployed to Operation Enduring Freedom or Operation Iraqi Freedom to investigate effects of exposure to explosive blasts on the white matter of the brain. We hypothesized that the nature of blast creates a diffuse and widespread pattern of white matter damage characterized by focal reductions in integrity that are diluted when averaged at the level of tracts and that are spatially heterogeneous across individuals. Therefore, we predicted that traditional methods that average measures of white matter integrity within a region or across individuals would be less sensitive to these effects than a method based on voxelwise z-scores that does not have strict spatial constraints. Specifically, we predicted that blast mTBI would be associated with a greater number of voxels with low FA (i.e. more points of compromised white matter integrity) but would not affect average FA within individual regions of interest.

Materials and Methods

Participants

Participants consisted of 25 veterans of Operation Enduring Freedom and Operation Iraqi Freedom who had been exposed during deployment to an explosive blast followed shortly thereafter by symptoms indicative of mTBI, and 33 veterans who had not experienced an explosive blast or symptoms of blast-related mTBI. Subjects were recruited from an existing sample of National Guard soldiers, Minneapolis Veterans Affairs Medical Center patient rosters, and by word of mouth from other participants or service providers.

Symptoms of mTBI were assessed by self-report and included altered consciousness (e.g. confusion, disorientation), loss of consciousness (LOC) less than 30 minutes, post-traumatic amnesia (PTA) up to 24 h, and neurological symptoms (e.g. headache, tinnitus, nausea, sensitivity to light or noise) immediately after the event. Blast injuries occurred 2–5 years prior to involvement in the study. Table 1 summarizes demographic and clinical characteristics of the groups.

Clinical Assessment

All participants underwent a clinical interview that included the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002), Clinician-Administered Post-Traumatic Stress Disorder (PTSD) Scale (CAPS; Blake et al., 1995), and the Minnesota Blast Exposure Screening Tool (MN-BEST; Nelson et al., 2011), a TBI rating scale developed for the project. Exclusionary criteria included native language other than English, current or pre-deployment unstable medical condition that would affect brain function (e.g. anoxic episode greater than 10 s, stroke, seizures, multiple sclerosis, etc.), uncorrected visual or auditory disturbances, moderate or severe TBI not due to blast, any pre-deployment DSM-IV Axis I condition requiring treatment, and contraindications to MRI (e.g. metallic implants, shrapnel, claustrophobia). In addition, individuals with a diagnosis of current PTSD according to the CAPS were excluded to limit potential confounds of combat-related stress conditions; however, individuals with past PTSD or who endorsed several PTSD symptoms without meeting full diagnostic criteria were included to maximize generalizability of results.

As a measure of re-experiencing of traumatic events (including explosive blasts), each of the five Criterion B symptoms for PTSD was assessed using the CAPS by summing 5 point scales (0–4) of intensity and frequency for total possible CAPS B scores ranging between 0 and 40. Using the MN-BEST we assessed the 3 most significant blast-related and impact-related head injuries, each of which received a severity score ranging from 0 (no concussion) to a potential maximum of 30 (severe TBI), though no score was higher than 4 (LOC 5–30 min or PTA>12 h) in the current sample. Blast-related injuries were defined as those in which the individual felt a blast wave and attributed the resultant concussion to its effects, though secondary and tertiary effects, such as being thrown against the ground or being hit by a projectile, were acceptable. Non-blast injuries, including civilian injuries (e.g., high school sports concussions) and non-blast deployment injuries (e.g. falling off a wall or vehicle), were assessed on the same scale. Over 90% of the non-blast injuries occurred in a civilian setting prior to the most recent deployment; therefore, the term “civilian” mTBI will be used hereafter. TBI ratings were completed by doctoral-level neuropsychologists based on

Table 1

Demographic and clinical characteristics of the sample.

<table>
<thead>
<tr>
<th></th>
<th>Blast</th>
<th>No blast</th>
<th>Statistical tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>33</td>
<td>ns</td>
</tr>
<tr>
<td>Percent female</td>
<td>4%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Percent with civilian mTBI</td>
<td>56%</td>
<td>58%</td>
<td>ns</td>
</tr>
<tr>
<td>Percent with past PTSD</td>
<td>20%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Age in years: mean (SD)</td>
<td>36.0 (8.9)</td>
<td>32.5 (8.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Range</td>
<td>24–55</td>
<td>22–52</td>
<td></td>
</tr>
<tr>
<td>CAPS B total (median)</td>
<td>5</td>
<td>0</td>
<td>z = −2.61, p = .009</td>
</tr>
<tr>
<td>Range</td>
<td>0–18</td>
<td>0–17</td>
<td></td>
</tr>
<tr>
<td>Blast TBI Index (median)</td>
<td>2</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Range</td>
<td>0–6</td>
<td>1–6</td>
<td></td>
</tr>
<tr>
<td>Civilian TBI Index (median)</td>
<td>2</td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Range</td>
<td>0–9</td>
<td>0–7</td>
<td></td>
</tr>
</tbody>
</table>

TBI = traumatic brain injury. mTBI = mild TBI. CAPS B total = total of severity and frequency ratings of PTSD Criterion B symptoms from the CAPS. Blast and Civilian TBI Indexes represent summed severity scores of the 3 most significant injuries of each type according to the MN-BEST. ns = not significant.
descriptions of events secured by study interviewers. DSM diagnoses, including PTSD, were finalized by advanced doctoral students whose work was supervised and reviewed by doctoral-level licensed psychologists.

Participants completed an informed consent process that included complete description of the study, and participants were provided with monetary compensation for their participation after each study procedure. The study was approved by the University of Minnesota and Minneapolis Veterans Affairs Medical Center Institutional Review Boards.

**Image Acquisition and Processing**

Images were acquired on a 3 Tesla Siemens Trio (Erlagen, Germany) scanner using a 12-channel birdcage head coil. Head movements were minimized by placing pads around the participant’s head. Localizers were acquired for orientation and prescription of subsequent scans. A high resolution MP-RAGE structural image (repetition time [TR] = 2,530 ms, echo time [TE] = 3.65 ms, 240 coro-

nal slices, 256 × 256 matrix, 256 mm field of view [FOV], 1.0 mm thickness) was collected for anatomical alignment and visualization. Two sets of diffusion weighted images aligned to the plane including the anterior and posterior commissures were collected in each of 30 noncollinear directions at b = 800 s/mm², along with 10 images collected with no diffusion weighting evenly distributed throughout the sequence. Other parameters included TR/TE = 9000/84 ms, 72 oblique axial slices, 128 × 128 matrix, 256 mm FOV, 2.0 mm thickness. A field map of the DTI space was collected immediately following the DTI sequence.

We used the FMRIB software library (FSL: Smith et al., 2004; Woolrich et al., 2009) tools to co-register the diffusion-weighted images to remove small movements that may have occurred during the sequence, remove eddy currents, and correct field inhomogeneity artifacts using the field map. Fractional anisotropy (FA) values were computed at each brain voxel (Basser and Pierpaoli, 1996; Basser et al., 1994).

**Statistical Analyses**

**Demographic and Clinical Characteristics**

Gender, history of civilian mTBI, and lifetime diagnosis of PTSD were compared across groups using chi-squared statistics. Age was compared across groups with a t-test, and total scores on the Criterion B items of the CAPS (i.e. total CAPS B scores) and on the civilian portion of the MN-BEST were compared across groups with Mann-Whitney U tests to account for the non-normal distribution.

**Average FA within Regions of Interest (ROI)**

To determine whether the FA of specific tracts was affected by mTBI, a set of 20 standard probabilistic tractography-based ROIs (Mori et al., 2005) were thresholded at 25% probability in standard space, as shown in Fig. 1, and registered to each subject’s DTI space using nonlinear transformations (FNIRT: Andersson et al., 2007a,b). These ROIs were selected because they encompass major subcortical white matter tracts. For each ROI, FA was averaged across all voxels in which FA > 0.20 (i.e. non-white matter was excluded) and compared across groups using t-tests. Since a history of civilian mTBI and compared in the same manner.

**Number of Voxel with Low Average FA**

Both preceding methods assume that mTBI affects entire tracts, or at least affects substantial enough portions of tracts to create a detectable effect on the average. To determine whether small regions, rather than entire tracts, were affected by mTBI, we compared the number of voxels with abnormally low FA with minimal spatial constraints across subjects. Each subject’s FA map was registered to standard space by inverting the nonlinear transformation computed in 2.4.2 to align the ROIs to native space. Images of the mean and standard deviation at each voxel were created based on the 14 non-TBI participants (i.e. participants who had neither blast nor civilian mTBI), and each participant’s average FA scores were converted to z-scores by subtracting the mean and dividing by the standard deviation of the respective ROIs. For each individual we then determined the number of ROIs out of 20 with FA more than 2.0 standard deviations below the “healthy” mean (i.e. z < −2.0). The tallies of ROIs with abnormally low FA were converted to ranks to account for their non-normal distribution and compared across groups using a t-test and 2-way ANOVA as described above.

**Number of Voxel with Low Average FA**

Given the heterogeneous nature of blast-related head injury, it is possible that a different set of white matter tracts is affected in each individual. In this case, each ROI would only be affected in a subset of individuals, which would reduce the likelihood of detecting an effect in any single ROI. To determine whether the specific tracts affected by mTBI varied across individuals, we compared the number of ROIs with “low” average FA without requiring the same regions to be abnormal across participants. The mean and standard deviation of the average FA measures in each ROI were computed across the 14 non-TBI participants (i.e. participants who had neither blast nor civilian mTBI), and each participant’s average FA scores were converted to z-scores by subtracting the mean and dividing by the standard deviation of the respective ROIs. For each individual we then determined the number of ROIs out of 20 with FA more than 2.0 standard deviations below the “healthy” mean (i.e. z < −2.0). The tallies of ROIs with abnormally low FA were converted to ranks to account for their non-normal distribution and compared across groups using a t-test and 2-way ANOVA as described above.

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To test the hypothesis that effects are spatially variable across individuals, we determined the number of voxels across the entire white matter mask in which the median $z$-score across individuals with blast mTBI was less than $-2.0$ as these would indicate locations at which a majority of participants had abnormally low FA.

### Results

#### Demographic and Clinical Characteristics

As seen in Table 1, groups did not differ on gender composition, age, percentage of participants with a history of civilian mTBI or past PTSD, or civilian head injury scores (all $p > 0.05$). For reference, Table 2 presents the distribution of prior civilian mTBI across groups. Individuals with blast mTBI had somewhat higher scores on the Criterion B items of the CAPS than those without blast mTBI ($z = -2.61$, $p = .009$), indicating higher re-experiencing of trauma, though none of the subjects met diagnostic criteria for PTSD at the time of study. This difference is expected given that the blast exposure constituted a traumatic experience for many individuals. Additional information about the rates of current and lifetime DSM-IV diagnoses are provided in Supplemental Tables 1 and 2, respectively.

### Number of Voxels with Low FA

According to t-tests, blast mTBI was associated with a greater number of voxels with low FA (i.e. low white matter integrity) in 10 of the 20 ROIs after correcting for multiple comparisons. Regions demonstrating this effect included the forceps major and minor, bilateral anterior thalamic radiations, right corticospinal tract, bilateral inferior frontal occipital fasciculus (IFOF), bilateral inferior longitudinal fasciculus (ILF), and left superior longitudinal fasciculus (SLF). Table 3 summarizes these effects, and Figs. 2 and 3 demonstrate properties of the underlying histograms. Blast mTBI was also associated with a greater number of low FA voxels across the entire white matter mask ($t_{56} = -3.94$, $p < 0.001$), indicating that blast injury was associated with a greater frequency of voxels with low white matter integrity, although the particular locations within and across ROIs varied across individuals. Supplemental Figure 2 demonstrates the distribution of aberrant voxels in two representative participants.

When prior civilian mTBI was accounted for by using an ANOVA approach, the effect of blast mTBI was significant in the right SLF and right cingulum as well as the 10 previously mentioned regions, but no main effect of prior civilian mTBI or interaction term survived correction for multiple comparisons. When the total number of low FA voxels across the entire white matter mask was compared, both main effects (blast: $F_{1,54} = 20.99$, $p < .001$; civilian: $F_{1,54} = 5.10$,

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**Table 2**

<table>
<thead>
<tr>
<th>History of civilian mTBI</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blast mTBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Both (n=14)</td>
<td>Blast Only (n=11)</td>
</tr>
<tr>
<td>No</td>
<td>Civilian Only (n=19)</td>
<td>No TBI (n=14)</td>
</tr>
<tr>
<td></td>
<td>Civilian (n=33)</td>
<td>No Civilian (n=25)</td>
</tr>
</tbody>
</table>

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Based on the observation that a subset (n = 7) of the blast mTBI group had experienced more than one blast mTBI event, we conducted an unplanned follow-up analysis to determine whether additional blast mTBI events were associated with a greater degree of white matter integrity disruption. Specifically, we used a one-way ANOVA to compare the log-transformed total number of low FA voxels across all ROIs among the three groups, defined as no blast (n = 33), single blast (n = 18), and multiple blasts (n = 7). As expected, the effect of group was significant (F2,55 = 8.60, p = .001), and Tukey post hoc statistics indicated that both blast groups had larger numbers of low FA voxels than the no blast group (p = .027 and .001 for single and multiple blast groups, respectively). In addition, the group with multiple blast mTBI events had a higher number of low FA voxels than the single blast group (Fig. 4), though this difference did not reach significance according to Tukey post hoc statistics (p = .20).

Discussion

We used a combination of analysis strategies to assess the long-term effects of blast mTBI on white matter integrity in a sample of American military service members. Blast mTBI was associated with a greater number of low FA voxels in a majority of a priori defined brain regions and in total white matter, while traditional ROI methods failed to reveal effects of either type of injury. Furthermore, the number of low FA voxels was especially high in individuals with multiple blast mTBI events. This suggests that the long-term effects of blast mTBI on white matter integrity consist of subtle, widespread disruptions rather than damage to specific tracts that is consistent across individuals. Additionally, there were virtually no voxels in which a majority of participants with blast mTBI demonstrated abnormally low FA, indicating a high degree of spatial heterogeneity across individuals. Prior civilian (i.e. non-blast) mTBI did not change this pattern and generally did not demonstrate an independent effect, suggesting that a history of civilian mTBI is a minimal consideration in this population. However, given that the results involving civilian mTBI were not wholly negative, future studies may benefit from consideration of such injuries.

In light of recent literature suggesting that mean diffusivity (MD) may be more sensitive than FA to effects of mTBI (Cubon et al., 2011), we conducted an analogous set of comparisons to determine whether blast mTBI was associated with a greater number of high MD voxels or ROIs. No effects were detected for any comparison (all p > .05, corrected for multiple comparisons), indicating greater sensitivity to effects for FA than MD. Furthermore, in contrast to recent literature demonstrating that loss versus alteration of consciousness in blast-related injuries is an important distinction in terms of somatic complaints (Belanger et al., 2011; Wilk, et al, 2010) and brain function (Matthews et al., 2011), we found no difference in the number of low FA voxels, suggesting that this distinction may be less critical to structural connectivity measures, though additional subjects with loss of consciousness would be beneficial to testing this effect further (see Supplemental Analysis B).

Evidence of FA abnormalities years after the injury is important given the controversy over how persistent post-concussive symptoms should be interpreted and treated in a military setting (Vasterling et al., 2011). To date, the overlap of mTBI and PTSD symptomatology has made it difficult to determine the relative contributions of each condition to the impairments of returning service members and to determine the appropriate treatment. The current results indicate that blast mTBI is indeed associated with long-term white matter disruption, perhaps uniquely as compared to PTSD (Sponheim et al., 2010). Further research is required to determine how to best use this information on an individual case basis.

Table 3

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>No blast % median</th>
<th>Blast % median</th>
<th>t</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Interhemispheric tracts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceps major</td>
<td>1.21 (0.2–26.4)</td>
<td>4.08 (0.5–21.8)</td>
<td>−3.72* &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Forceps minor</td>
<td>1.21 (0.1–10.0)</td>
<td>2.80 (0.4–10.2)</td>
<td>−2.80* .007</td>
<td></td>
</tr>
<tr>
<td>Subcortical–cortical tracts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior thalamic radiations</td>
<td>1.44 (0.2–5.3)</td>
<td>2.84 (0.4–13.7)</td>
<td>−3.20* .002</td>
<td></td>
</tr>
<tr>
<td>Right anterior thalamic radiations</td>
<td>1.26 (0.1–6.7)</td>
<td>2.59 (0.3–11.5)</td>
<td>−3.24* .002</td>
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<tr>
<td>Left corticospinal tract</td>
<td>2.09 (0.0–10.6)</td>
<td>2.98 (0.0–15.5)</td>
<td>−0.81 .421</td>
<td></td>
</tr>
<tr>
<td>Right corticospinal tract</td>
<td>1.73 (0.0–10.2)</td>
<td>3.54 (0.3–14.1)</td>
<td>−2.87* .006</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe tracts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left IFOF</td>
<td>1.03 (0.1–6.7)</td>
<td>2.82 (0.4–8.4)</td>
<td>−3.99* &lt;.001</td>
<td></td>
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<tr>
<td>Right IFOF</td>
<td>0.83 (0.1–5.9)</td>
<td>2.19 (0.1–11.0)</td>
<td>−2.73* .008</td>
<td></td>
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<tr>
<td>Left ILF</td>
<td>1.39 (0.0–6.3)</td>
<td>2.98 (0.5–12.3)</td>
<td>−3.64* .001</td>
<td></td>
</tr>
<tr>
<td>Right ILF</td>
<td>1.24 (0.0–8.3)</td>
<td>3.27 (0.1–10.5)</td>
<td>−2.50* .015</td>
<td></td>
</tr>
<tr>
<td>Left temporal SLF</td>
<td>0.00 (0.0–17.6)</td>
<td>2.94 (0.0–23.5)</td>
<td>−1.91 .061</td>
<td></td>
</tr>
<tr>
<td>Right temporal SLF</td>
<td>0.68 (0.0–38.6)</td>
<td>2.03 (0.0–18.0)</td>
<td>−2.09 .041</td>
<td></td>
</tr>
<tr>
<td>Left uncinate</td>
<td>0.98 (0.0–12.5)</td>
<td>1.71 (0.0–28.9)</td>
<td>−1.64 .107</td>
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<tr>
<td>Right uncinate</td>
<td>0.63 (0.0–19.2)</td>
<td>1.05 (0.0–11.2)</td>
<td>−1.26 .214</td>
<td></td>
</tr>
<tr>
<td>Left cingulum/hippocampus</td>
<td>0.26 (0.0–5.9)</td>
<td>0.26 (0.0–5.2)</td>
<td>−1.18 .243</td>
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<tr>
<td>Right cingulum/hippocampus</td>
<td>0.40 (0.0–4.6)</td>
<td>1.00 (0.0–10.4)</td>
<td>−1.74 .087</td>
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<tr>
<td>Fronto-parietal tracts</td>
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<td></td>
</tr>
<tr>
<td>Left cingulum</td>
<td>1.66 (0.1–29.4)</td>
<td>3.98 (0.0–15.8)</td>
<td>−1.86 .068</td>
<td></td>
</tr>
<tr>
<td>Right cingulum</td>
<td>1.88 (0.0–44.0)</td>
<td>3.50 (0.4–26.5)</td>
<td>−2.17* .034</td>
<td></td>
</tr>
<tr>
<td>Left SLF</td>
<td>1.75 (0.1–10.8)</td>
<td>2.97 (0.2–8.1)</td>
<td>−2.81* .007</td>
<td></td>
</tr>
<tr>
<td>Right SLF</td>
<td>2.09 (0.1–15.6)</td>
<td>3.74 (0.3–13.5)</td>
<td>−1.86* .068</td>
<td></td>
</tr>
<tr>
<td>Summary measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total of white matter mask</td>
<td>1.69 (0.5–8.6)</td>
<td>3.40 (0.9–10.8)</td>
<td>−3.94* &lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Voxel counts converted to percentages of total volume of each region of interest (ROI). Estimates of t and p are based on t-test comparisons of log-transformed voxel counts. Bold values represent regions in which participants with blast mTBI had significantly higher number of abnormally low FA voxels than participants without blast mTBI, corrected for multiple comparisons (α = .05, FDR q = .05). * Regions in which the main effect of blast TBI was significant in the 2-way ANOVA, corrected for multiple comparisons (α = .05, FDR q = .05).

p = .028) and the interaction (F1,54 = 5.26, p = .026) were significant. The interaction indicated that a history of civilian mTBI was only associated with a greater number of low FA voxels in the absence of blast mTBI (Supplemental Figure 3).

Eight voxels out of the 382,194 included in the white matter mask had a median z-score less than −2.0, indicating locations in which the majority of individuals in the blast mTBI group had low FA. Based on the rates of low FA voxels in this group that ranged between 0.9–10.8% (Table 3), no voxels would be expected to be identified purely by chance (i.e., if effects were randomly distributed across individuals); therefore, this represents a highly significant effect (γ2 > 1000, p < .001). However, given that the median number of low FA voxels within this group was 13,000 this is a very small region of overlap.

Average FA within Regions of Interest and Number of Regions with Aberrantly Low Average FA

When FA was averaged across voxels within an ROI, rather than tallying the number of low FA voxels, no ROIs revealed an effect of blast mTBI, civilian mTBI, or an interaction for either test. Likewise, the number of ROIs with low average FA failed to differ between groups. Thus, averaging FA across multiple voxels within an ROI did not reveal any white matter abnormalities associated with blast mTBI regardless of whether the effects of prior civilian mTBI were accounted for. Removal of the FA threshold used to exclude non-white matter did not change the results of these tests.

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The use of a military control population in the present study helped to control for the potential physical and psychological effects of deployment, as well as personality characteristics and other features common among members of the military. Thus, the design substantially reduces extraneous differences between groups. The similar rates of past PTSD and prior civilian mTBI across groups support this equivalence. However, the observation that rates of PTSD symptoms below the diagnostic threshold, as evidenced by CAPS B total scores and the “sub-threshold PTSD” category of Supplemental Tables 1 and 2, were higher in individuals with blast mTBI suggests that extraneous differences may indeed exist. This raises the concern that the observed effects may be attributable to differences in factors such as combat-related stress rather than the blast mTBI itself. In an attempt to address this concern, we compared the Military Occupational

Fig. 3. Histograms of voxelwise z-scores. Histograms of voxelwise z-scores across all voxels within the white matter mask (top), the difference between group histograms (middle), and the differences from the histogram of the No TBI group (bottom).
military roles involve varying levels of combat exposure and, compared to 15% of those without blast mTBI. It is likely that different individuals with blast mTBI had an Infantry or Health Care MOS Specialty (MOS) designations among the 43 individuals (74% of the total sample) for whom this information was available. This revealed that 50% of the 26 service members without blast mTBI had an MOS relating to Information Technology, Intelligence, Mechanical, Logistics, or Civil Affairs, whereas only 1 of the 17 service members with blast mTBI had an MOS from these categories. In contrast, 59% of the individuals with blast mTBI had an Infantry or Health Care MOS compared to 15% of those without blast mTBI. It is likely that different military roles involve varying levels of combat exposure and, therefore, relative risk of injury. Future studies would benefit from more directly addressing the potential effects of combat exposure, deployment stress, and risk of harm to separate these from those due to the mTBI itself.

Limitations

A major limitation of virtually all investigations of blast-related mTBI is the absence of symptom documentation at the time of injury, which creates a reliance on retrospective self-report. We have used a measure (MN-BEST) specifically designed for retrospective reports of blast-related experiences in military populations, and ratings were assigned based on consensus review by psychologists with substantial experience evaluating service members exposed to explosive blasts. Although absolute determination of the nature of a blast event is impossible based solely on retrospective information, we have used a method that maximizes our ability to make the most accurate determination possible.

A second common limitation to studies of blast-related mTBI is its comorbidity with psychopathology in general, as demonstrated in Supplemental Tables 1–2, raising the possibility that the observed effects are related to these conditions rather than to the presence of mTBI. In Supplemental Analysis A, we have attempted to account for potential effects of depressive and post-traumatic symptomatology through statistical covariation and failed to find any marked impact on the reported effects. It is therefore likely that the higher number of low FA voxels is better explained by the presence of mTBI than by these other conditions.

One difficulty of using z-scores as a dependent variable is that the results are only as reliable as the estimates of means and standard deviations on which they are based. In particular, poor estimation of the mean of low FA voxels is better explained by the presence of mTBI than by any marked impact from the NMR spin echo. J. Magn. Reson. B 103, 247–254. Belanger, H.G., Proctor-Weber, Z., Kretzmer, T., Kim, M., French, L.M., Vanderploeg, R.D., 2011. Symptom complaints following reports of blast versus non-blast mild TBI: does mechanism of injury matter? Clin. Neuropsychol. 25 (5), 702–715. Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gussman, F.D., Charney, D.S., et al., 1995. The development of a Clinician-Administered PTSD Scale. J. Trauma. Stress 8 (1), 75–90. Cubon, V.A., Putikian, M., Boyer, C., Dettwiler, A., 2011. A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. J. Neurotrauma 28, 189–201. First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV–TR Axis I Disorders, Research Version, Patient Edition. Biometrics Research, New York State Psychiatric Institute, New York. SCID-I/P. Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15 (4), 870–878. Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C., Castro, C.A., 2008. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N. Engl. J. Med. 358 (5), 453–463. possible that the number of aberrant voxels in the affected groups was somewhat inflated by this bias. However, to include subjects who are hypothesized to have “abnormal” FA in at least a subset of voxels in the estimation of the distribution would introduce its own bias. In an attempt to address this, we conducted a supplemental analysis (see Supplemental Figures 4–6) that included each voxel’s immediate neighbors in the estimation of its mean and standard deviation and thus used seven times the data. This process provided more stable estimates of the mean by reducing Gaussian measurement error at the expense of an increased standard deviation due to spatial heterogeneity. The results using this method were similar to those of the primary study in that blast mTBI was associated with a greater number of low FA voxels in 11 regions and overall (see Supplemental Table 4) and that prior civilian mTBI had an effect only in the left anterior thalamic radiations and when all voxels were considered. Although this provides evidence that the results are not an artifact of poor distribution estimation, a larger healthy population would be the optimal method of addressing this concern.

Conclusions

Our analyses demonstrated widespread white matter disruptions associated with blast-related mTBI to which standard ROI methods were insensitive. In contrast, a history of civilian (i.e., non-blast) mTBI failed to be associated with white matter disruption, perhaps indicating a difference in the mechanism of action between the types of mTBI. It will be important in the future to obtain longitudinal data and to explore the functional consequences of blast-induced white matter disruptions.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2011.10.050.

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References


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