White Matter Abnormalities are Associated With Chronic Postconcussion Symptoms in Blast-Related Mild Traumatic Brain Injury

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Abstract: Blast-related mild traumatic brain injury (mTBI) is a common injury among Iraq and Afghanistan military veterans due to the frequent use of improvised explosive devices. A significant minority of individuals with mTBI report chronic postconcussion symptoms (PCS), which include physical, emotional, and cognitive complaints. However, chronic PCS are nonspecific and are also associated with mental health disorders such as posttraumatic stress disorder (PTSD). Identifying the mechanisms that contribute to chronic PCS is particularly challenging in blast-related mTBI, where the incidence of comorbid PTSD is high. In this study, we examined whether blast-related mTBI is associated with diffuse white matter changes, and whether these neural changes are associated with chronic PCS. Ninety Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans were assigned to one of three groups including a blast-exposed no − TBI group, a blast-related mTBI without loss of consciousness (LOC) group (mTBI − LOC), and a blast-related mTBI with LOC group (mTBI + LOC). PCS were measured with the Rivermead Postconcussion Questionnaire. Results showed that participants in the mTBI + LOC group had more spatially heterogeneous white matter abnormalities than those in the no − TBI group. These white matter abnormalities were significantly associated with physical PCS severity even after accounting for PTSD symptoms, but not with cognitive or emotional PCS severity. A mediation analysis revealed that mTBI + LOC significantly influenced physical PCS severity through its effect on white matter integrity. These results suggest that white matter abnormalities are associated with chronic PCS independent of

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PTSD symptom severity and that these abnormalities are an important mechanism explaining the relationship between mTBI and chronic physical PCS. *Hum Brain Mapp 00:000–000, 2015.*

Key words: diffusion tensor imaging; OEF/OIF; PTSD; loss of consciousness

INTRODUCTION

Due to the frequent use of explosive devices in modern warfare, mild traumatic brain injury (mTBI) is a common occurrence in the Iraq and Afghanistan Wars. Estimates suggest that 15% of individuals deployed in support of the Wars in Iraq and Afghanistan screen positive for mTBI [Hoge et al., 2008]. While the majority of individuals with mTBI recover to preinjury functioning, a minority suffer from chronic postconcussion symptoms (PCS), which include physical (e.g., dizziness, headaches), cognitive (e.g., slowed thinking, difficulties with concentration), and emotional (e.g., irritability, anxiety) complaints [Carroll et al., 2004]. Whereas PCS in the acute phase reflect the transient effects of mTBI, psychological and motivational factors are thought to play an important role in the persistence of these symptoms [McCrea, 2008]. PCS are nonspecific and are also associated with chronic pain and a variety of mental health disorders [Bigler, 2008; Donnell et al., 2012; Smith-Seemiller et al., 2003], thus complicating efforts to disentangle the direct contribution of mTBI vs comorbid factors to chronic PCS.

The nonspecificity of PCS poses particular diagnostic difficulty in veterans who sustained mTBI during deployment, given the high rate of comorbid psychiatric conditions in this population [Fear et al., 2009; Hoge et al., 2008]. Despite evidence that some symptoms in the chronic stage may be associated with mTBI-related neuropathology [Bigler and Maxwell, 2012], recent behavioral studies of veterans with self-reported mTBI suggest that PCS symptoms are linked primarily to mental health symptoms [Belanger et al., 2010; Hoge et al., 2008; Lippa et al., 2010; Schneiderman et al., 2008; Verfaellie et al., 2013]. However, it is possible that in vivo characterization of traumatic axonal injury, as is possible with diffusion tensor imaging (DTI), may provide a more sensitive means to assess whether chronic PCS relate to neuropathology associated with mTBI.

Consistent with the notion that chronic PCS may be linked to mTBI-related traumatic axonal injury, recent studies of civilian mTBI have found that DTI metrics (e.g., fractional anisotropy-FA) in both white [Bartnik-Olson et al., 2014; Messe et al., 2012] and gray [Bouix et al., 2013] matter are associated with PCS in the chronic stage of injury, and that reductions in white matter abnormalities over time are associated with reductions in PCS severity [Ling et al., 2012]. However, these findings may not generalize to war-exposed veteran samples, which are likely to include individuals with higher rates of trauma exposure and mental health disorders than civilians.

In a recent study that examined the contribution of microstructural white matter abnormalities to chronic PCS in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with blast-related mTBI, Petrie et al. (2014) found no association between white matter integrity and PCS. However, two other studies examining PCS in OEF/OIF veterans did find a significant association with white matter [Levin et al., 2010; Yeh et al., 2014], although Levin et al.'s (2010) findings varied depending on the method of imaging analysis used. One potential factor contributing to these mixed findings is that these studies used techniques that focused on white matter alterations that were spatially consistent across subjects. Recently, our group and others have shown that white matter abnormalities in blast-related mTBI are spatially heterogeneous [Davenport et al., 2011; Hayes et al., 2015; Jorge et al., 2012]. These studies raise the possibility that methods that capture diffuse and spatially nonoverlapping white matter abnormalities may be better suited to assess the relationship with PCS. Consistent with this notion, the only longitudinal study to find an association between changes in PCS severity and white matter integrity in civilians used a methodology that captured the spatial heterogeneity of mTBI [Ling et al., 2012].

In this study, we used voxel-wise cluster-based methods that have been shown to be sensitive to white matter abnormalities in blast-related mTBI [Jorge et al., 2012] to examine the relationship between white matter integrity and chronic PCS in a large cohort of OEF/OIF veterans with and without mTBI. The goals of this study are (1) to examine the presence of white matter abnormalities in blast-related mTBI; (2) to assess the association between these white matter abnormalities and the severity of PCS, after accounting for traumatic stress; and (3) to examine whether white matter integrity mediates the relationship between mTBI and PCS, after accounting for traumatic stress symptoms.

MATERIALS AND METHODS

Participants

Participants were 90 OEF/OIF veterans who reported exposure to blast within 100 m. Individuals were recruited through the VA Boston Polytrauma Network and through flyers and outreach events in the community. Participants were part of a larger neuroimaging study evaluating white matter changes associated with blast-related mTBI

TABLE I. Demographic and Clinical Characteristics

	no - TBI (n = 37)	mTBI − LOC (n = 29)	mTBI + LOC (n = 24)	Group comparison
Age in years, *M (SD)*	30.2 (6.3)	28.8 (7.0)	28.2 (4.3)	$F(2,87) = 0.88$, $P = 0.42$
Males, *no. (%)*	35 (94.6)	28 (96.6)	24 (100.0)	$\chi^2(2) = 1.32$, $P = 0.52$
Education in years, *M (SD)*	13.8 (2.1)	13.0 (1.6)	12.8 (2.0)	$F(2,87) = 2.74$, $P = 0.07$
WTAR, *M (SD)*	0.3 (0.8)	0.6 (0.7)	0.2 (0.8)	$F(2,87) = 1.26$, $P = 0.30$
Blast exposures, *M (SD)*	8.4 (11.7)	12.2 (12.3)	5.1 (7.2)	$F(2,87) = 2.85$, $P = 0.06$
Injury to scan interval in months, *M (SD)*	49.8 (36.3)	44.7 (27.9)	58.2 (24.4)	$F(2,87) = 1.81$, $P = 0.17$
Current alcoholic drinks per week, *M (SD)*	4.6 (6.4)	3.5 (4.8)	3.9 (6.9)	$F(2,87) = 0.46$, $P = 0.63$
CAPS total, *M (SD)*	48.8 (27.8)	58.2 (24.7)	59.7 (22.0)	$F(2, 87) = 1.76$, $P = 0.18$
PCS physical, *M (SD)*	0.9 (0.7)*	1.5 (0.8)	1.4 (0.7)	$F(2, 87) = 7.10$, $P = 0.001$
PCS emotional, *M (SD)*	1.4 (1.2)	1.8 (1.2)	2.0 (1.2)	$F(2,87) = 1.79$, $P = 0.17$
PCS cognitive, *M (SD)*	1.6 (1.4)	2.1 (1.3)	2.1 (0.9)	$F(2,87) = 1.57$, $P = 0.21$

Note: For ease of interpretation, mean (*M*) and standard deviation (SD) reflect nontransformed data for non-normal variables. WTAR is listed as average *z*-score. * = significantly different from other groups. mTBI = mild traumatic brain injury; LOC = loss of consciousness; WTAR = Wechsler Test of Adult Reading; CAPS = Clinician-Administered PTSD Scale; PCS = postconcussion symptoms.

[Hayes et al., 2015]. Exclusion criteria for the study were a history of predeployment TBI with loss of consciousness (LOC) or with symptoms persisting longer than three months post injury, high levels of current alcohol use (>25 drinks per week), questionable effort with raw scores below 45 on the retention trial of the Test of Memory Malingering (TOMM; Tombaugh and Tombaugh, 1996), and structural brain abnormalities (e.g., hemorrhages, hematomas, skull fractures, tumors, excessive hyperintensities, hemispheric asymmetries) on FLAIR, SWI, or T1 sequences as determined by a board-certified neuroradiologist. Participants were also excluded if more than 10 weeks had elapsed between their behavioral assessment and neuroimaging.

Individuals were further subdivided into three groups (no − TBI, mTBI without LOC [mTBI − LOC], and mTBI with LOC [mTBI + LOC]) using the definition of mTBI put forth by the American Congress of Rehabilitation Medicine (1993). Evaluation of TBI was based on an extensive clinical interview, which is described in detail in Verfaellie et al. (2013). Briefly, participants were questioned about their blast exposure(s) to determine the index event, which was the most severe exposure. Then, individuals were asked for an in-depth description of the index event including their memory for events preceding, during, and subsequent to the blast in order to infer the presence and duration of posttraumatic amnesia and LOC. Participants were also questioned about the presence of neurological symptoms immediately after the blast. Last, we inquired whether TBI could be corroborated by medical examination or witness reports. For individuals in the mTBI + LOC group, in all but two cases, information regarding the presence and duration of LOC was based on information the participant obtained from a medic or combat peers who had witnessed the event. Interviews were transcribed and evaluated by two investigators who sought consensus as to whether a minimal biomechanical threshold for mTBI had been met as well as any reported disorientation was the result of mTBI rather than situational chaos and confusion.

Of the 90 blast-exposed veterans, 37 were in the no − TBI group, 29 in the mTBI − LOC group, and 24 in the mTBI + LOC group. The no − TBI group consisted of individuals who had been exposed to deployment-related blast but reported no subsequent symptoms suggestive of TBI. Individuals were excluded from this group if they reported TBI from any other mechanism of injury during their deployment. Furthermore, because the goal of this study was to examine blast-related mTBI, participants with mTBI not associated with blast during their deployment were excluded from the mTBI − LOC and mTBI + LOC groups. A subset of mTBI participants (n = 16) reported having tertiary injuries (e.g., being thrown against an object). Thus, any reference to blast-related injuries in this study refers to blast mechanisms with the inclusion of additional tertiary injury in some cases. Groups did not significantly differ in gender, age, education, premorbid IQ (as assessed by the Wechsler Test of Adult Reading [WTAR]; Wechsler, 2001), number of alcoholic drinks per week, number of blast exposures, or interval between time of injury and MRI scan. A summary of the demographic characteristics can be found in Table I.

An additional 14 OEF/OIF veterans (age, mean [standard deviation] = 30.2 [7.4]) without a history of blast exposure or deployment-related TBI, who did not meet diagnostic criteria for posttraumatic stress disorder (PTSD) as assessed by the Clinician-Administered PTSD scale (CAPS) for DSM-IV [Blake et al., 1995], were also scanned and formed the reference group for the purpose of neuroimaging analyses. Of these 14 reference-group participants, 10 were male.

Behavioral and Neuropsychiatric Assessments

Assessments were administered by a trained licensed clinical neuropsychologist. PCS were evaluated in the blast

exposed sample using the Rivermead Postconcussion Questionnaire (RPQ; King et al., 1995). The RPQ is a 16-item checklist that requires participants to rate the severity of their current physical, emotional, and cognitive symptoms in comparison to preinjury functioning. Participants rated severity for each item on a scale from 0 to 4. An average score for each domain (physical, emotional, and cognitive) was calculated.

PTSD was assessed using the CAPS for DSM-IV [Blake et al., 1995]. CAPS scores were used as a measure of PTSD symptom severity.

Image Acquisition and Processing

Data were acquired on a 3-T Siemens Trio whole-body MRI scanner located at the VA Boston Healthcare System, Jamaica Plain campus. Two T1-weighted scans were collected for each participant. The first 22 participants had T1 weighted anatomical scans collected with the following parameters: FOV = 256, Matrix = 240 × 256, 160 slices, 1 × 1 × 1.2 mm voxels, TR = 2,300 ms, TE = 2.98 ms, flip angle = 9°, and thereafter, a slightly modified sequence was used: FOV = 256, Matrix = 256 × 256, 176 slices, 1 × 1 × 1 mm voxels, TR = 2,530 ms, TE = 3.32 ms, flip angle = 7°. DTI scan parameters for the first 22 participants consisted of two acquisitions of 30 directions averaged for a total of 60 diffusion weighted images, FOV = 256, Matrix = 128 × 128, TR = 8,000 ms, TE = 83 ms, 2 × 2 × 2 mm voxels, b value = 700 s/mm^2. Thereafter, a slightly modified DTI sequence was used consisting of one acquisition of 60 directions, FOV = 256, Matrix = 128 × 128, TR = 10,000 ms, TE = 103 ms, 2 × 2 × 2 mm voxels, b value = 700 s/mm^2. The sequences were modified in order to align them with the pulse sequence of a separate study protocol for data sharing. Eight of the 14 reference group participants were scanned with both DTI sequences and all analyses were corrected by sequence (see below) to account for any potential sequence differences.

Imaging data were analyzed using the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) FSL software package (http://www.fmrib.ox.ac.uk/fsl). Images were first corrected for motion and eddy currents and then brain-extracted using BET to remove nonbrain voxels from the analysis [Smith, 2002]. Using Freesurfer, FA images were created by fitting a tensor model using linear least squares to the raw diffusion data. Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) was used to align all FA images to a standard space. A FA threshold of 0.20 was used to restrict the white matter skeleton to voxels comprising only white matter and to reduce partial volume effects.

To identify clusters of abnormal FA, we used a procedure similar to White et al. (2009), in which the FA standard space skeletonized images produced by TBSS were used to calculate z-score maps. First, average and standard deviation values for each voxel were created using the FA skeletonized images of the reference group. Next, the statistical images were used to generate a z-score map for each individual, in which each voxel of the skeletonized image was converted into a z-score. To correct for potential sequence differences, z-score maps for individuals scanned with the original DTI sequence were based on reference-group participants who were scanned with the original sequence (n = 8), and z-score maps for individuals scanned with the modified sequence were based on reference group participants who were scanned with the modified sequence (n = 14). To find clusters with reduced FA relative to the reference group, z-score maps were thresholded at $z = -3.0$. Next, Freesurfer's *mri_volcluster* was used to find clusters of z-scores of $z = -3.0$ in at least 5 contiguous voxels. The total number of clusters for each individual was calculated.

Statistical Analysis

Statistical analyses were performed using SPSS, version 19 (IBM Corp., Armonk, NY). Age and total number of clusters were square root transformed to account for the positive skew of the data before entering into group analyses.

To examine whether blast-related mTBI was associated with the number of clusters with reduced FA, a hierarchical linear regression analysis was performed, in which number of clusters with reduced FA was the dependent variable. Age was added as a covariate in the first step of the model and mTBI group status (no − TBI, mTBI − LOC, and mTBI + LOC coded as dummy variables) was added in the second step. To examine the contribution of PTSD to clusters with reduced FA, CAPS total score was added in the third step.

To examine the association between number of clusters with reduced FA and PCS, a multivariate analysis was performed in which the three PCS domains (physical, emotional, and cognitive) were the dependent variables. Age was added as a covariate. CAPS scores were added into the model to account for traumatic stress symptoms and number of clusters was added to determine whether white matter abnormalities accounted for additional variance in PCS severity. In order to determine which particular domain of PCS was most associated with white matter abnormalities, follow-up univariate hierarchical linear regression analyses were performed for each PCS domain (physical, emotional, and cognitive).

Finally, a mediation analysis was performed to examine whether the number of clusters with reduced FA influenced the relationship between mTBI and PCS. In simple mediation models, the independent variable (mTBI group status) can exert an indirect effect on the dependent variable (PCS severity) through an intermediate variable (number of clusters with reduced FA). Age and CAPS

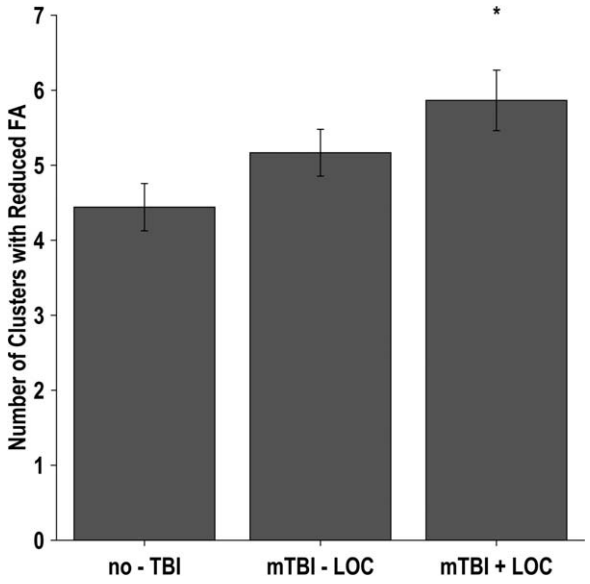

Figure 1.

Mean number of clusters with reduced FA for each group. *Note*: figure displays number of clusters with reduced FA that have been square root transformed. * = significant group difference from the no - TBI group, $P = 0.011$. Error bars refer to standard error of the mean. FA = fractional anisotropy; mTBI = mild traumatic brain injury; LOC = loss of consciousness.

were included as covariates. Groups were compared with simple indicator coding, in which the no − TBI group was the reference group. Direct and indirect effects were examined with the Mediate macro for SPSS [Hayes and Preacher, 2014]. Bootstrapping was used to estimate the sampling distribution ($n = 5000$) and 95% confidence intervals for the indirect effect. Because only severity of physical PCS was significantly associated with the number of clusters with reduced FA, a mediation analysis was performed for physical PCS only.

RESULTS

Groups did not significantly differ in PTSD symptom severity. Individuals in the no − TBI group had significantly fewer physical PCS than individuals in the mTBI − LOC and mTBI + LOC groups, but there were no group differences in emotional or cognitive PCS (Table I).

Hierarchal linear regression showed an effect of group on the number of clusters with reduced FA, with a significant overall model ($R^2 = 0.10$, $F(3,86) = 3.22$, $P = 0.03$) and a significant change in the model when group was added ($\Delta R^2 = 0.08$, $\Delta F(2,86) = 3.58$, $P = 0.03$). Compared to the no − TBI group, the mTBI + LOC group had a greater number of clusters with reduced FA ($\beta = 0.30$, $P = 0.01$; see Fig. 1), suggesting that mTBI, and in particular LOC, has an effect on white matter integrity. The no − TBI and mTBI − LOC groups did not significantly differ from each other ($\beta = 0.19$, $P = 0.11$). PTSD symptom severity had no effect on clusters with reduced FA ($\Delta R^2 = 0.02$, $\Delta F(1,85) = 1.97$, $P = 0.16$). The spatial distribution of clusters with reduced FA in each group is shown in Figure 2, demonstrating that the abnormalities are dispersed throughout the brain and are not constrained to any particular location across individuals.

Visual inspection of the data revealed a multivariate outlier in the mTBI + LOC group for number of clusters with reduced FA and physical PCS. Examination of Cook's distance (Cook's $D > 0.04$) confirmed that this subject was a statistical outlier and was thereby removed from all further analyses. Results revealed an effect of clusters with reduced FA on PCS severity, even after accounting for traumatic stress, with a significant multivariate model ($F(3,83) = 3.00$, $P = 0.04$, Wilks' $\Lambda = 0.90$, partial $\eta^2 = 0.10$). Follow-up analyses revealed that as expected, CAPS had a significant effect on all three symptom domains (physical: $\Delta R^2 = 0.27$, $\Delta F(1,86) = 32.18$, $\beta = 0.52$, $P < 0.001$; emotional: $\Delta R^2 = 0.32$, $\Delta F(1,86) = 41.32$, $\beta = 0.57$, $P < 0.001$, cognitive: $\Delta R^2 = 0.34$, $\Delta F(1,86) = 44.20$, $\beta = 0.58$, $P < 0.001$). Adding number of clusters with reduced FA to the model accounted for significant variance in physical PCS, with a significant overall model ($R^2 = 0.34$, $F(3,85) = 14.64$, $P < 0.001$) and a significant change in the model when number of clusters was added ($\Delta R^2 = 0.07$, $\Delta F(1,85) = 8.80$, $\beta = 0.27$, $P = 0.004$). However, there was no significant change in the model when number of clusters was added for emotional ($\Delta R^2 = 0.01$, $\Delta F(1,85) = 1.37$, $\beta = 0.10$, $P = 0.25$) or cognitive ($\Delta R^2 = 0.003$, $\Delta F(1,85) = 0.39$, $\beta = 0.06$, $P = 0.53$) symptoms. The association of physical PCS severity with number of clusters with reduced FA is shown in Figure 3.

A mediation analysis was performed to determine if the number of abnormal white matter clusters mediates the relationship between mTBI and PCS after accounting for PTSD symptom severity. This analysis revealed that the number of clusters with reduced FA was a significant mediator between mTBI + LOC and physical PCS severity (see Fig. 4). Individuals in the mTBI + LOC group had a greater number of abnormal white matter clusters ($a = 1.05$, $P = 0.02$), which in turn was associated with increased physical PCS severity ($b = 0.10$, $P = 0.02$). A bias-corrected bootstrap confidence interval for the indirect effect for PCS severity did not encompass zero for number of clusters ($ab = 0.10$; 95% CI [0.01, 0.28]). As expected, number of clusters with reduced FA was not a significant mediator for the mTBI − LOC group. These results suggest that the association between mTBI that resulted in LOC and physical PCS complaints is mediated in part by the degree to which individuals have alterations in white matter.

DISCUSSION

We used a voxel-wise cluster-based technique to examine the association between white matter integrity, chronic

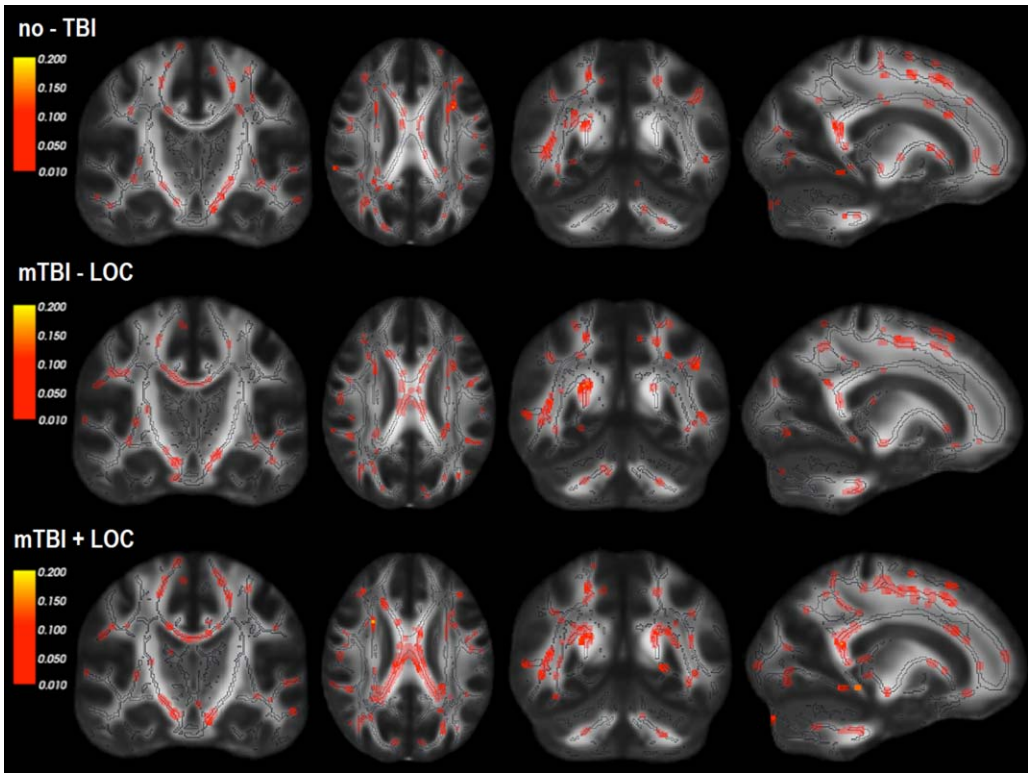

Figure 2.
Distribution of clusters with reduced FA within groups. Scale represents the proportion of individuals within each group that have a cluster of reduced FA in the area marked. FA = fractional anisotropy; mTBI = mild traumatic brain injury; LOC = loss of consciousness.

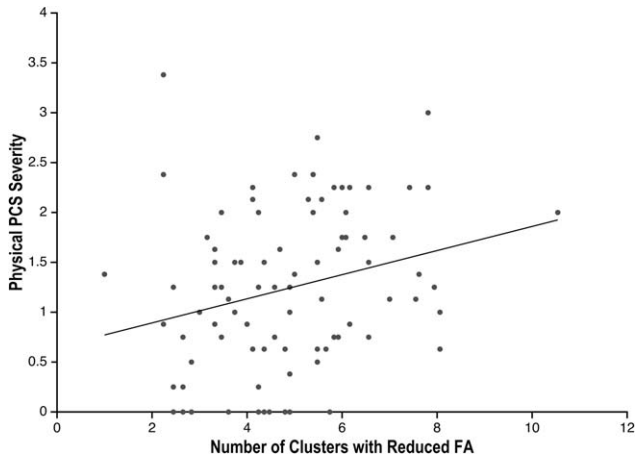

Figure 3.
Physical postconcussion symptoms are associated with the number of clusters with reduced FA. Individuals with a greater number of clusters with reduced FA had more physical PCS. *Note*: PCS represents mean score (range 0–4) and number of clusters with reduced FA is square root transformed. FA = fractional anisotropy; PCS = postconcussion symptoms.

PCS severity, and blast-related mTBI in a large sample of OEF/OIF veterans. Blast-related mTBI with LOC was associated with more extensive white matter abnormalities than blast exposure without mTBI. These white matter abnormalities were spatially heterogeneous, with very little overlap in the distribution of clusters across individuals. Further, we found that white matter abnormalities were associated with physical PCS severity, even after accounting for traumatic stress symptoms. Finally, we found that for individuals who suffered LOC, these white matter abnormalities mediated the relationship between mTBI and physical PCS severity.

Our results add to an emerging literature pointing to the importance of LOC in white matter abnormalities across varying methodologies [Hayes et al., 2015; Jorge et al., 2012; Matthews et al., 2012; Sorg et al., 2013]. One possibility for these results is that LOC may represent a more significant white matter injury than mTBI without LOC. LOC is thought to result from more widespread brain disruption, and thus may be more likely to lead to disconnection of cortical and subcortical structures from deeper structures such as the brainstem [Ommaya and Gennarelli, 1974]. Additionally, LOC may be a more

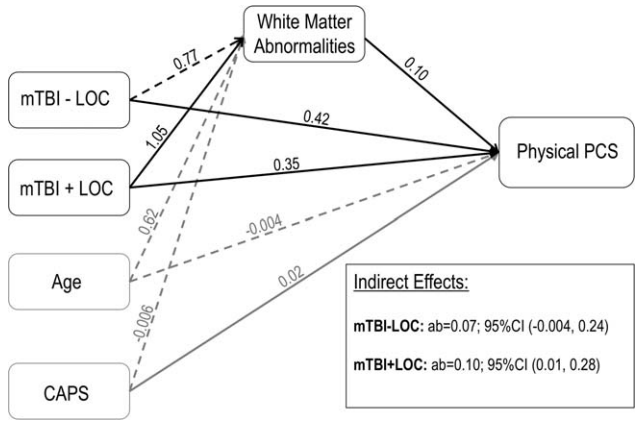

Figure 4.

The number of clusters with reduced FA mediates the relationship between mTBI + LOC and physical PCS. Individuals in the mTBI + LOC group had a greater number of clusters with reduced FA, which in turn was associated with greater physical PCS severity. Numbers shown represent unstandardized coefficients. Solid lines indicate significance ($P < 0.05$). Gray indicates covariates in the model. FA = fractional anisotropy; PCS = postconcussion symptoms; mTBI = mild traumatic brain injury; LOC = loss of consciousness; CAPS = Clinician-Administered PTSD Scale.

reliable indicator of the presence of mTBI than other alterations in consciousness such as posttraumatic amnesia and confusion, which may also occur in the context of a psychologically traumatic event.

The finding that LOC was a marker for white matter abnormalities contradicts the claim by Xydakis et al. (2012) that retrospective self-report of LOC may not be a useful indicator of TBI-related neuropathology. Their conclusion was based on the fact that in their study, individuals with LOC had fewer neuroimaging abnormalities on CT or MRI than those without LOC. The discrepancy in findings may be due to the fact that white matter disruptions are a more sensitive marker of TBI-related brain abnormalities than clinical abnormalities found on CT and MRI [Borg et al., 2004; Lee et al., 2008; Niogi and Mukherjee, 2010]. Additionally, there were important differences in study population. While participants in our study were evaluated following completion of deployment, Xydakis et al.'s (2012) findings pertained to individuals with extensive injury requiring immediate stateside evacuation. In the latter case, LOC may be more likely to reflect a neurophysiologic response to extracranial bodily injuries.

We found that in blast-exposed OEF/OIF veterans, physical PCS severity was associated with the number of white matter abnormalities even after accounting for PTSD symptom severity. These findings support and extend those of two previous studies investigating the association between white matter integrity and chronic PCS following blast exposure [Levin et al., 2010; Yeh et al., 2014]. While these studies did not take into account the contribution of mental health symptoms, our results demonstrate that the link between white matter abnormalities and physical PCS is independent of PTSD symptom severity. Furthermore, our findings suggest a specific relationship between mTBI-related white matter abnormalities and physical symptoms. Physical symptoms include complaints that may be more directly linked to traumatic axonal injury (e.g., blurred vision, light sensitivity) than cognitive and emotional symptoms and thus, may be more likely to be associated with diffuse white matter alterations [Landre et al., 2006]. A recent longitudinal study in civilians similarly found that recovery from white matter injury was associated selectively with a reduction in physical symptoms [Ling et al., 2012].

For the first time, we demonstrated that the number of white matter abnormalities mediates the relationship between blast-related mTBI with LOC and physical PCS severity, even after accounting for traumatic stress symptoms. Thus, our results suggest that spatially heterogeneous white matter abnormalities may constitute an independent mechanism accounting for chronic PCS in mTBI. It is well established that mTBI transiently disrupts neural function, and as such, contributes to acute PCS [Bazarian et al., 2007; Bigler, 2008; Macciocchi et al., 1996; McCrea et al., 2003]. Here, we demonstrate that even in the chronic stage, residual mTBI-related white matter alterations continue to be associated with physical symptoms.

Our findings should not overshadow the fact that mental health factors including PTSD have an important role in the maintenance of chronic PCS. In this study, PTSD symptom severity was significantly associated with PCS severity in all three domains, a finding that has been observed in a number of other studies [Belanger et al., 2010; Lippa et al., 2010; Verfaellie et al., 2013]. However, PTSD symptom severity was not associated with white matter alterations. Several other studies have reported similar negative findings [Jorge et al., 2012; Morey et al., 2012; Taber et al., 2015] although two studies using different diffusion metrics suggest white matter involvement in PTSD [Bazarian et al., 2012; Davenport et al., 2015]. Nonetheless, PTSD-related neuropathology appears to be associated primarily with changes in gray matter volume [Bremner et al., 1995; Corbo et al., 2005; Kasai et al., 2008; O'Doherty et al., 2015; Smith, 2005] and functional alterations [Bremner et al., 1999; Daniels et al., 2010; Hayes et al., 2011; Milad et al., 2009; Sadeh et al., 2015; Shin and Liberzon, 2010; Shin et al., 2004; St Jacques et al., 2013; van Wingen et al., 2012]. Further research is needed to determine if PTSD-related neuropathology independently mediates the relationship between PTSD and PCS severity. These open questions notwithstanding, our findings reinforce the notion that chronic PCS are multidetermined and reflect at least in part TBI-associated axonal injury.

These results should be considered within the context of the limitation that mTBI group assignment was dependent on retrospective self-reports long after the injury occurred.

Therefore, these reports are potentially subject to misremembering or reporting bias. However, mTBI assessment was conducted using a guided in-depth structured interview, which is currently the gold standard for diagnosis [Corrigan and Bogner, 2007]. Another limitation is the small sample size of the reference group used for the purposes of neuroimaging analyses. Difficulty enrolling participants in this group reflects the strict inclusion criteria, which required absence not only of blast exposure but also of deployment-related TBI or current PTSD. Future studies would benefit from a larger reference group.

CONCLUSION

In summary, we report spatially heterogeneous white matter abnormalities in individuals with a history of blast-related mTBI, particularly when accompanied by LOC. While multiple factors contribute to chronic PCS, the current findings provide evidence for a direct association between white matter abnormalities and reports of physical symptoms such as headaches, nausea, dizziness, and fatigue. PTSD symptom severity was not related to white matter abnormalities, but it was highly associated with severity of PCS in all three domains. These results suggest that white matter abnormalities are an additional, unique mechanism for chronic physical PCS in blast-related mTBI with LOC. It will be important to validate these findings with other measures that are equally sensitive to spatially heterogeneous white matter abnormalities in mTBI. Furthermore, it will be of interest to determine in longitudinal studies whether changes in white matter integrity are associated with changes in PCS.

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