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Diffusion tensor imaging evidence of white matter disruption associated with loss versus alteration of consciousness in warfighters exposed to combat in Operations Enduring and Iraqi Freedom

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1. Introduction

The majority of combat injuries sustained by warfighters in Operations Enduring (OEF) and Iraqi (OIF) Freedom are caused by improvised explosive devices, blasts, landmines, and explosive fragments(1). These blast injuries result commonly in neurotrauma, such as mild traumatic brain injury (mTBI), which is defined as a blow or jolt to the head that disrupts brain function(1, 2) resulting in a brief (i.e., maximum of 20 mins) loss (LOC) or alteration (AOC) of consciousness. It has been estimated that approximately 196,000 cases of blast-related TBI occurred among OIF-OEF warriors between 2000 and 2010, approximately 150,000 of which were of mild severity(3, 4). Although neurotrauma that results in LOC >20 minutes (i.e., moderate/severe TBI) often produces brain damage that is detectable with clinical neuroimaging techniques(5), individuals who have experienced mTBI often have normal scans. Little is known about the neuroanatomical effects of blast-related mTBI on the human brain.

Although the mechanism is unknown, individuals who sustain mTBI frequently develop major psychiatric illnesses, such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD)(1, 6, 7). Prior research has shown that 30% of a brigade of warriors exposed to OIF combat subsequently experienced MDD and/or PTSD(7). Related evidence from a group of individuals who sustained blunt force neurotrauma showed that depression severity was related to structural changes in brain regions involved in emotion processing (8). Functional neuroimaging research has revealed that among OIF-OEF veterans who experienced blast-related mTBI, functional activation of emotion processing circuitry was dependent on whether or not the subjects had experienced LOC(9). Additionally, individuals who developed MDD after blast-related mTBI versus those who did not, reported higher rates of LOC and appeared to show disruption in white matter tracts such as the superior longitudinal fasciculus (SLF), (10). Taken together, this evidence suggests the possibility that LOC may be uniquely associated with brain changes that may increase risk of developing psychiatric symptoms or mental illness after neurotrauma.

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The primary aim of the current study was to build on prior work suggesting that LOC may be associated with maladaptive brain changes that may increase risk of psychiatric symptoms and mental illness(9, 10), by using diffusion tensor imaging (DTI) to examine the effect of LOC, MDD and PTSD on white matter integrity in OEF-OIF veterans who sustained blast-related mTBI. We hypothesized that LOC would be associated with significant disruption, above and beyond putative effects of MDD and PTSD, of white matter tracts such as the SLF and corpus callosum. Support for this hypothesis would increase understanding of the effects of LOC on the human brain and suggest a brain basis for psychiatric symptoms and mental illness after mTBI.

2. Materials and Methods

2.1. Study Design

Forty-six male subjects with a reported history of blast-related mTBI during OEF-OIF combat completed this cross sectional study, which was approved by the local Human Research Protection Program. During session one, subjects: (a) provided written informed consent; (b) completed a semi-structured interview based on the DSM-IV(11); (c) completed the Combat Exposure Scale (CES)(12), Beck Depression Inventory-2 (BDI-2)(13), Patient Health Questionnaire-15 (PHQ-15)(14) and the Clinician Administered PTSD Scale (CAPS) (15) to quantify the severity of combat exposure, depressive, somatic and PTSD symptoms, respectively, and; (d) completed the Defense and Veterans Brain Injury Center TBI Screening Tool, i.e., the Brief Traumatic Brain Injury Screen (BTBIS) (16), and an additional TBI questionnaire to obtain data regarding how many concussions they had experienced, whether the most severe concussion resulted in AOC (i.e., “being dazed or confused” or “seeing stars”) or LOC for a maximum of 20 minutes, the source of injury (e.g. blast vs blunt) and the duration of any physical or mental sequelae (e.g., nausea, disorientation). During session two, subjects underwent DTI scanning.

2.2. Subjects

All subjects indicated on their responses on the BTBIS that they had experienced LOC or AOC for a maximum of 20 minutes related to blast exposure, which is consistent with blast-related concussion(17–20). For any case when the AOC/LOC distinction was ambiguous, the subject was classified as having experienced AOC. All subjects denied a history of concussion or other head injury prior to combat. Exclusion criteria for all subjects included a reported history of LOC or AOC > 20 minutes (i.e., moderate/ severe TBI), alcohol/ substance dependence or abuse within 30 days of scannning, and/or lifetime history of attention deficit hyperactivity disorder, psychotic, bipolar or chronic pain disorder, active medical problems or claustrophobia. Subjects were also excluded if they endorsed a history of head injury prior to combat or if they had been diagnosed with MDD, PTSD or any other psychiatric illness prior to military service.

2.3. Diffusion Tensor Imaging Data Acquisition and Analysis

Participants were imaged in a 3T General Electric Excite scanner with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). High angular resolution diffusion images (HARDI) (21) were collected along 61 noncollinear directions determined by the electrostatic repulsion model which minimizes bias in measurements by sampling with approximately uniform distribution on a sphere(22), in addition to a reference image with no diffusion weighting (b = 0). The diffusion encoding scheme consisted of a single-shot dual spin echo excitation optimized for minimum TE and reduction of eddy current artifacts (23). The following sequence parameters were applied; TE/TR = 93.1/13,900 ms, FOV = 240 mm, matrix = 128 × 128, 43 contiguous slices, 3 mm slice thickness, b-value = 1500 s/mm2, one average. Two field maps were collected for

unwarping to correct for signal loss and geometric distortion due to B0 field inhomogeneities (24, 25).

Data were preprocessed and subjected to tensor decomposition. This included corrections for head motion, eddy current distortion, and signal loss using FSL tools (FMRIB Software Library, Oxford, United Kingdom)(26). Fractional anisotropy (FA) was computed in native coordinate space using AFNI's diffusion routine, 3dDWItoDT, and data were analyzed with Tract-Based Spatial Statistics (TBSS)(27). For the TBSS analysis, FA maps were registered to an averaged FA template (FMRIB-58) in MNI-152 standard space using an affine-only registration. This was followed by a non-linear transformation into 1-mm cubic voxel dimensions using FNIRT, FMRIB's Non-linear Registration Tool. Data were examined for laterality, orientation, and cross-subject anatomical alignment. Next, transformed images were averaged across subjects to create a mean FA image, from which a white matter skeleton was derived, representing tracts common to the group of subjects who completed the study. Individually transformed FA images were then projected onto the skeleton. To minimize partial volume effects and areas of high inter-subject variability, values were thresholded at FA>0.2. FA values from individuals' nearest relevant tract center were assigned to the skeleton via a perpendicular search for the maximum FA value within the local skeleton structure. This process accounted for misalignments between subjects that may have remained after the initial registration, thereby minimizing systematic differences in tract location between groups. Data from each point on the skeleton formed the basis of voxelwise statistical comparisons(26–28).

Group analysis of FA was conducted in R using AFNI's linear mixed effects model (3dLME) with three grouping variables (LOC/AOC, MDD/non-MDD, and PTSD/non-PTSD) entered as fixed factors and subject number entered as a random factor predicting the voxel-based FA value. Although multiple analytic approaches are available, we used a linear mixed effects model because this validated approach (29) does not assume independence of data. Based on prior studies (30) and Monte-Carlo calculations (3dClustsim based on the skeleton mask), a voxel-based threshold was set at $p<0.01$ and a cluster threshold at $p<0.01$ resulting in significant clusters of more than 203 μl. Average FA values were then extracted from each individual subject's data using the group functional mask that survived this threshold/cluster method. To investigate the degree to which hypothesized differences in white matter integrity between the LOC and AOC subgroups may have been associated with severity of MDD and/or PTSD, Spearman's rho post-hoc correlations were computed between FA in regions that were different between the LOC and AOC subgroups and scores on the BDI-2, PHQ-15 and CAPS. To reduce the probability of false positives, correlations were considered significant at an alpha of $p<.01$.

3. Results

3.1. Clinical

All subjects reported a history of concussion (i.e., LOC or AOC for a maximum of 20 minutes) related to blast exposure. Within the total sample (n=46), 23 subjects met DSM-IV criteria for current MDD, 28 subjects met DSM-IV criteria for current PTSD and 22 reported a history of LOC (Table 1). Because several regions of FA difference were observed between the LOC and AOC subgroups, we compared these subgroups on demographic and clinical characteristics (Table 1). LOC versus AOC individuals had a higher prevalence of MDD and PTSD, reported significantly more intense combat exposure, and reported more severe MDD and PTSD symptoms (Table 1). The LOC and AOC groups were not significantly different in estimated lifetime number of concussions, time since most severe concussion, prevalence of current or past medication use (i.e., mood stabilizers,

typical or atypical antipsychotics, antidepressants or benzodiazepines), or socio-demographic characteristics such as age, ethnicity and education (Table 1).

3.2. Diffusion Tensor Imaging

The LOC versus AOC contrast revealed 14 regions within the brainstem, corpus callosum, cingulate gyrus, inferior and superior longitudinal fasciculus, inferior frontal occipital fasciculus, anterior limb of the internal capsule, anterior thalamic radiation, and anterior corona radiata, where FA was significantly lower in the LOC compared to the AOC group (Table 2). Post-hoc correlations between FA and clinical symptoms showed that within the LOC group, no significant associations were observed between FA in any of the regions that were different between the LOC and AOC groups and scores on the CAPS, BDI-2, or PHQ15 (Table 3). Conversely, there was a pattern of significant post-hoc correlations between FA and clinical symptom severity within the AOC group. Higher FA in the callosal body/cingulum [rho(22) =.63, p=.001] and the left SLF [rho(22)=.51, p=.01] was related to more depressive symptoms, and higher FA in the bilateral cingulum and callosal body [rho(20)=.52, p=.01; rho(20)=.60, p=.003] was related to more somatic symptoms (Table 3).

The remaining contrasts between the PTSD versus non-PTSD, and MDD versus non-MDD groups revealed no regions of significant FA difference. Finally, there were no significant clusters found for the 2-way (MDDxPTSD, MDDxLOC, LOCxPTSD) or 3-way (MDDxPTSDxLOC) interactions.

Discussion

The main goal of this study was to examine the effects of LOC, MDD and PTSD on white matter integrity in OEF-OIF warfighters with a history of mTBI. Three main findings were observed. First, LOC versus AOC individuals showed significant disruption of white matter, as indicated by lower FA in several regions, which included the bilateral brainstem, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, body of the corpus callosum, cingulum, superior longitudinal fasciculus (SLF), and anterior thalamic radiations. Second, PTSD versus non-PTSD individuals showed no significant differences in white matter integrity. Third, MDD versus non-MDD individuals also showed no significant differences in white matter integrity.

Prior work has shown that lesions of white matter tracts that link cortical areas with each other and with subcortical structures in order to subserve sensorimotor function, intellect, or emotion may disrupt the interconnectivity of the brain(31). In particular, the SLF is a large white matter tract connecting the prefrontal cortex with the parietal, occipital and temporal lobes(32), forming a heteromodal neural network that is necessary for core processes such as attention, memory, language and emotion processing and modulation(33). In prior work, without controlling for PTSD or LOC, we observed lower FA in the SLF in individuals who developed MDD after blast-related mTBI relative to individuals who had experienced comparable mTBI events but did not develop MDD(10). Related research has shown that otherwise healthy individuals with current MDD compared to healthy non-depressed volunteers also demonstrated lower FA in the SLF(34), suggesting that lesions to this structure may be related to the development of depression. However, we did not observe differences in the integrity of the SLF between the MDD and non-MDD individuals in the current study, indicating that the role of the SLF in depression requires further investigation. We also observed that individuals with LOC had lower FA in the cingulate and corpus callosum. Microstructural alterations in these regions have been implicated in late-life depression(35) and cognitive impairment(36) and, like the SLF, these structures provide connections between brain regions that are necessary for emotion processing(37). Taken together, our findings, though preliminary, suggest that a history of LOC may be a crucial,

and underappreciated, variable in predicting the trajectory of psychopathology following mTBI.

Recent studies examining white matter integrity of combat exposed OEF-OIF veterans with PTSD have reported reductions of FA in regions of the frontal lobe, including the anterior cingulate cortex, posterior angular gyrus(38), and cingulum bundle (39, 40). These findings are in line with the current results in that we also identified clusters in prefrontal white matter, although these regions of disruption were related to LOC and not PTSD. Due to the frequent comorbidity between TBI and PTSD, future studies should further examine the unique and overlapping effects of PTSD and LOC on on white matter integrity.

Consistent with prior research by Hoge and colleagues(41), the LOC relative to AOC subjects in the current study showed a higher prevalence of current MDD and PTSD and more severe depressive and PTSD symptoms. However, despite the fact that the LOC subjects were experiencing more psychopathology, no significant correlations were observed within the LOC group between FA in the regions that differed between the LOC and AOC groups and scores on the CAPS, BDI-2, or PHQ15. Conversely, we observed significant relationships between more FA in the callosal body, cingulum, and the SLF and greater severity of depressive and somatic symptoms within the AOC group. These relationships represent post-hoc findings that require replication before they can be meaningfully interpreted.

Prior research investigating white matter integrity in individuals with a reported history of concussion from blast exposure relative to individuals with no history of concussion or blast exposure showed no differences in FA or apparent diffusion coefficients (42, 43). The current work builds on this research by providing specific evidence that a history of LOC rather than history of concussion with AOC, may reflect underlying alterations in brain microstructure as measured by DTI. Importantly, in our sample, we observed no differences between the LOC and AOC groups either in number of reported concussions or time since most severe concussion, which further suggests that the observed group differences in brain microstructure may relate primarily to the presence or absence of LOC. Although still preliminary, these findings suggest that a reported history of LOC may increase the likelihood that a given individual has experienced trauma-associated disruption of white matter.

There were several important limitations of this study. First, information about blast exposure and TBI (including whether an individual had experienced AOC or LOC) was obtained retrospectively via each participant’s subjective report. Although this is a widely used method for determining concussion history, corroborating information from medical records or other sources, which was not available for the subjects in this study, would have been preferred. Therefore, we cannot rule out the possibility of recall bias related to head injury, which could have affected the reported findings. Second, we cannot infer causality from the results of this cross sectional study. However, all subjects denied a history of psychiatric illness prior to military service, suggesting that that these findings are not due to premorbid differences. Longitudinal studies are needed to determine whether LOC may have caused the observed differences in brain microstructure. Third, the LOC individuals in this study reported significantly more severe combat exposure, suggesting that LOC may also mark more traumatic combat experiences, potentially making PTSD and MDD more likely. Additional research is needed to clarify this issue. Future studies should also examine whether these findings generalize to females and/or to individuals who have experienced concussion from non-blast injuries. Finally, it should be emphasized that the characteristics of blast exposure (i.e., proximity to the explosion, direction of blast wind, etc.) likely relate directly to brain effects (i.e., location and degree of white matter disruption), which may

partially explain discrepancies between studies in terms of the putative effects of blasts on the human brain. Despite these limitations, this study provides evidence of microstructural alterations in individuals with a history of LOC, and may suggest a brain basis for psychiatric symptoms and mental illness following mTBI.

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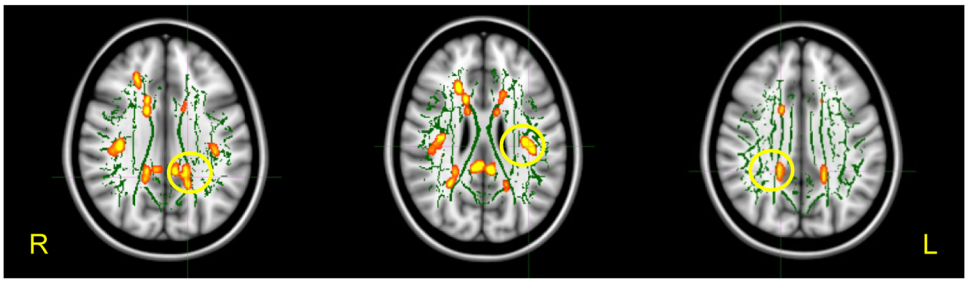

Figure 1. Group differences in fractional anisotropy

Individuals who experienced loss of consciousness versus alteration of consciousness showed less fractional anisotropy in several white matter areas, including the left cingulate gyrus/callosal body (LEFT PANEL), the left superior longitudinal fasciculus (MIDDLE PANEL) and the right cingulate gyrus and body of the corpus callosum (RIGHT PANEL).

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Table 1

Sociodemographic subject characteristics

	LOC			AOC				
	Mean	**S.D.**	**n**	**Mean**	**S.D.**	**n**	**F-value /χ^2**	**p-value**
Age	29.13	6.07	22	26.59	4.92	24	2.39	0.13
Ethnicity								
White			12			13		
Non-White			10			11	<0.01	0.61
Education (years)	13.32	1.3		13.92	1.82		1.76	0.19
Years since most	3.52	1.46		3.61	1.43		0.04	0.84
severe concussion								
Number of	14.43	28.49		5.27	6.14		2.37	0.13
concussions (lifetime)								
Current MDD			16			7	8.71	<0.01**
Current PTSD			17			11	4.76	0.03*
Current medications			10			9	0.18	0.68
Prior medications			6			5	0.25	0.62
BDI-2	20.00	11.77	20	12.83	10.27	23	4.56	0.04*
CAPS	80.77	24.25	22	58.67	29.23	24	7.71	0.01**
PHQ15	10.00	5.50	17	8.76	4.81	21	0.55	0.46
CES	29.50	6.60	20	20.38	7.22	21	17.77	<0.01**

* p≤.05,

** p≤.01**,

MDD= major depressive disorder, PTSD= posttraumatic stress disorder, BDI-2= Beck Depression Inventory-2, CAPS= Clinician Administered PTSD Scale, CES= Combat Exposure Scale.

Table 2

Group differences in fractional anisotropy

Cluster size (μl)*	x	y	z	Brain regions**
1,257	−2	−30	−8	Bilateral brainstem
1,243	−40	−30	−6	Inferior longitidinal fasciculus and inferior fronto-occipital fasciculus (L)
666	41	−25	−8	Inferior longitudinal fasciculus and inferior front-occipital fasciculus (R)
550	−14	16	23	Body of corpus callosum
409	17	−41	34	Cingulate gyrus (R); body of the corpus callosum
332	−18	18	−2	Anterior thalamic radiation (L)
315	39	−50	9	Inferior and superior longitudinal fasiculus and inferior fronto-occipital fasciculus (R)
310	−17	−46	30	Cingulate gyrus (L); body of the corpus callosum
297	22	2	14	Anterior limb of the internal capsule (L)
272	15	12	28	Body of corpus callosum
252	26	−47	23	Inferior fronto-occipital fasciculus; inferior longitudinal fasciculus (R); body of the corpus callosum
247	39	−21	28	Superior longitudinal fasciculus (R)
241	−37	−22	26	Superior longitudinal fasciculus (L)
206	22	26	27	Anterior corona radiata (R)

* All clusters were > 203 μl, p<.01

** In all regions, fractional anisotropy was lower in the group that had experienced loss of consciousness versus the group that had experienced alteration of consciousness.

Table 3

Spearman's rho correlations between fractional anisotropy and clinical symptoms

	Loss of Consciousness Group			Alteration of Consciousness Group		
Brain region (L/R hemisphere)	**BDI-2**	**CAPS**	**PHQ-15**	**BDI-2**	**CAPS**	**PHQ-15**
Bilateral brainstem	0.04	−0.10	0.02	0.23	0.20	0.25
Inferior longitidinal fasciculus and inferior fronto-occipital fasciculus (L)	0.20	−0.07	−0.25	0.37	0.01	0.34
Inferior longitudinal fasciculus and inferior front-occipital fasciculus (R)	0.13	−0.10	−0.08	0.37	0.09	0.15
Body of corpus callosum	0.23	−0.13	−0.12	0.48*	−0.08	0.26
Cingulate gyrus (R); body of the corpus callosum	0.13	−0.08	−0.14	0.46*	0.15	0.52**
Anterior thalamic radiation (L)	0.15	−0.10	−0.09	0.03	−0.08	−0.04
Inferior and superior longitudinal fasiculus and inferior fronto-occipital fasciculus (R)	0.31	0.16	0.02	0.37	0.20	0.42*
Cingulate gyrus (L); body of the corpus callosum	0.22	−0.17	−0.15	0.63**	0.36	0.60**
Anterior limb of the internal capsule (L)	0.04	−0.17	−0.24	0.09	−0.13	0.27
Body of corpus callosum	0.12	−0.14	−0.21	.45*	0.04	0.24
Inferior fronto-occipital fasciculus; inferior longitudinal fasciculus (R); body of the corpus callosum	0.15	−0.14	−0.24	0.32	−0.04	0.39
Superior longitudinal fasciculus (R)	0.01	−0.16	−0.17	0.47*	0.40*	0.27
Superior longitudinal fasciculus (L)	0.04	−0.08	−0.29	0.51**	0.46*	0.41
Anterior corona radiata (R)	0.02	−0.17	−0.33	0.30	0.31	0.36

BDI-2= Beck Depression Inventory-2, CAPS= Clinician Administered PTSD Scale, PHQ-15= Patient Health Questionairre-15.

Note: To minimize the likelihood of identifying spurious correlations, relationships were considered significant at p≤.01**, and trend level relationships (p<.05*) are also reported.