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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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ABSTRACT

The effects on the human brain of mild traumatic brain injury (mTBI), which is defined as a brief alteration (AOC) or loss of consciousness (LOC), are incompletely understood. Major psychiatric illnesses such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) are common after mTBI. Prior research suggests that individuals who develop MDD after blast-related mTBI versus those who do not show significant white matter disruption and higher rates of LOC, suggesting that LOC might be uniquely associated with brain changes that increase the risk of developing mental illness after neurotrauma. Therefore, the objective of this study was to examine the effects of LOC, MDD, and PTSD on white matter integrity in individuals who reported experiencing mTBI during combat in Operations Enduring and Iraqi Freedom. We hypothesized that LOC would be associated with significant disruption of white matter, above and beyond putative effects of MDD and PTSD. To test this hypothesis, 46 individuals who experienced blast-related mTBI underwent a detailed clinical assessment and diffusion tensor imaging. As hypothesized, LOC versus AOC individuals displayed significantly lower fractional anisotropy (FA) in 14 regions, which included the superior longitudinal fasciculus and corpus callosum. No regions of significant FA difference were identified between individuals with and without PTSD, or between individuals with and without MDD. These preliminary results show that LOC is associated with detectable alterations in brain microstructure and may suggest a brain basis for psychiatric symptoms and mental illness after mTBI.

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 (Warden, 2006). 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 (Warden, 2006; Finkel, 2006) resulting in a brief (i.e., maximum of 20 min) 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 (Schneiderman et al., 2008; Terrio et al., 2009). Although neurotrauma that results in LOC >20 min (i.e., moderate/severe TBI) often produces brain damage that is detectable with clinical neuroimaging techniques (Povlishock and Katz, 2005), 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) (Warden, 2006; Koponen, et al., 2002; Hoge et al., 2008). Prior research has shown that 30% of a brigade of warriors exposed to OIF combat subsequently experienced MDD and/or PTSD (Hoge et al., 2008). 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 (Mollica et al., 2009). 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 (Matthews et al., 2011). 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

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matter tracts such as the superior longitudinal fasciculus (SLF), (Matthews et al., 2011). 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.

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 (Matthews et al., 2011; Matthews et al., 2011), 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 1, subjects: (a) provided written informed consent; (b) completed a semi-structured interview based on the DSM-IV (First et al., 1997); (c) completed the Combat Exposure Scale (CES) (Blake et al., 1995), the Beck Depression Inventory-2 (BDI-2) (Beck et al., 1996), the Patient Health Questionnaire-15 (PHQ-15) (Kroenke et al., 2010) and the Clinician Administered PTSD Scale (CAPS) (Keane et al., 1989) to quantify the severity of combat exposure, depressive, somatic and PTSD symptoms; and (d) completed the Defense and Veterans Brain Injury Center TBI Screening Tool, i.e., the Brief Traumatic Brain Injury Screen (BTBIS) (Schwab et al., 2006), 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 min, the source of injury (e.g. blast versus blunt) and the duration of any physical or mental sequelae (e.g., nausea, disorientation). During session 2 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 min related to blast exposure, which is consistent with blast-related concussion (Borg et al., 2004; Carroll et al., 2004; Holm et al., 2005; Peloso et al., 2004). 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 min (i.e., moderate/severe TBI), alcohol/substance dependence or abuse within 30 days of scanning, 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 3 T General Electric Excite scanner with an eight-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). High angular resolution diffusion images (HARDI) (Frank, 2001) 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 (Jones et al., 1999), 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 echo time and reduction of eddy current artifacts (Reese et al., 2003). The following sequence parameters were applied; echo time/repetition time=93.1/13,900 ms, field of view=240 mm, matrix=128 × 128, 43 contiguous slices, 3 mm slice thickness, b-value=1500 s/mm^2, one average. Two field maps were collected for unwarping to correct for signal loss and geometric distortion due to B0 field inhomogeneities (Jezzard and Balaban, 1995; Andersson and Skare, 2002).

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) (Johansen-Berg et al. 2004). 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) (Smith et al., 2006). 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 (Smith et al., 2004; Smith et al., 2006; Johansen-Berg et al., 2007).

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 (Friston et al., 2005) does not assume independence of data. Based on prior studies (Bava et al., 2010) 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 level of $p<0.01$.

3. Results

3.1. Clinical findings

All subjects reported a history of concussion (i.e., LOC or AOC for a maximum of 20 min) 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