Volumetric and shape analyses of subcortical structures in United States service members with mild traumatic brain injury

David F. Tate[1,2], **Benjamin S. C. Wade**[3], **Carmen S. Velez**[1], **Ann Marie Drennon**[4], **Jacob Bolzenius**[1], **Boris A. Gutman**[3], **Paul M. Thompson**[3], **Jeffrey D. Lewis**[5], **Elisabeth A. Wilde**[2,6], **Erin D. Bigler**[7], **Martha E. Shenton**[8,9], **John L. Ritter**[10], and **Gerald E. York**[11]

[1]Missouri Institute of Mental Health, University of Missouri, St. Louis, 4633 World Parkway Circle, Berkeley, MO 63134-3115, USA

[2]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, USA

[3]Imaging Genetics Center, University of Southern California, Marina del Rey, CA, USA

[4]Defense and Veterans Brain Injury Centers, San Antonio Military Medical Center, San Antonio, TX, USA

[5]Department of Neurology, Uniformed Services University of the Health Sciences School of Medicine, Bethesda, MD, USA

[6]Michael E. DeBakey VA Medical Center, Houston, TX, USA

[7]Departments of Psychology and Neuroscience, Brigham Young University, Provo, UT, USA

[8]Psychiatry Neuroimaging Laboratory, Department of Psychiatry and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[9]Brockton Division, VA Boston Healthcare System, Brockton, MA, USA

[10]Department of Radiology, Brooke Army Medical Center, San Antonio, TX, USA

[11]Alaska Radiology Associates, TBI Imaging and Research, Anchorage, AK, USA

Abstract

Mild traumatic brain injury (mTBI) is a significant health concern. The majority who sustain mTBI recover, although ~20 % continue to experience symptoms that can interfere with quality of life. Accordingly, there is a critical need to improve diagnosis, prognostic accuracy, and monitoring (recovery trajectory over time) of mTBI. Volumetric magnetic resonance imaging (MRI) has been successfully utilized to examine TBI. One promising improvement over standard

volumetric approaches is to analyze high-dimensional shape characteristics of brain structures. In this study, subcortical shape and volume in 76 Service Members with mTBI was compared to 59 Service Members with orthopedic injury (OI) and 17 with post-traumatic stress disorder (PTSD) only. FreeSurfer was used to quantify structures from T1-weighted 3 T MRI data. Radial distance (RD) and Jacobian determinant (JD) were defined vertex-wise on parametric mesh-representations of subcortical structures. Linear regression was used to model associations between morphometry (volume and shape), TBI status, and time since injury (TSI) correcting for age, sex, intracranial volume, and level of education. Volumetric data was not significantly different between the groups. JD was significantly increased in the accumbens and caudate and significantly reduced in the thalamus of mTBI participants. Additional significant associations were noted between RD of the amygdala and TSI. Positive trendlevel associations between TSI and the amygdala and accumbens were observed, while a negative association was observed for third ventricle. Our findings may aid in the initial diagnosis of mTBI, provide biological targets for functional examination, and elucidate regions that may continue remodeling after injury.

Introduction

Traumatic brain injury (TBI) affects many individuals and is a major health concern among U.S. Service Members and Veterans. Utilizing clinical and medical information from the Defense Medical Surveillance System (DMSS) and Theater Medical Data Store (TMDS), estimates indicate that more than 330,000 service members have sustained a TBI since 2000 (https://dvbic.dcoe.mil/sites/default/files/DoD-TBI-Worldwide-Totals%202000-2015Q1-May15-2015.pdf). TBI occurs both during deployment related operations and in garrison, with the majority of TBI diagnoses (~80 %) occurring in the mild range of severity according to the VA/DoD criteria (i.e., loss of consciousness < 30 min, post-traumatic amnesia <24 h, or alteration of consciousness <24 h, no abnormal day-of-injury imaging findings [22]). A diagnosis of a mild TBI (mTBI) suggests that most Service Members and Veterans will experience full cognitive and functional recovery [29, 69]. However, there are a number of individuals (~20 %) who continue to experience residual symptoms that could impact unit readiness, return to duty, safety of troop operations, and troop retention [13, 27, 67]. Thus, there is significant interest in improving diagnosis, prognostic accuracy, monitoring recovery or decline, and assessing treatment effects, especially for those experiencing persistent symptoms.

One of the primary clinical and research tools employed in examining the effects of TBI on brain structure has been medical imaging, especially quantitative or volumetric magnetic resonance imaging (MRI; [5, 6, 17, 61, 72]). Across the range of TBI severity, these studies have demonstrated a number of consistent findings including global atrophy (i.e., ventricle-to-brain ratio; [5, 65]), white and gray matter atrophy [6, 47, 64], regional vulnerability (temporal and frontal poles [4]) specific subcortical nuclei atrophy (i.e., thalamus, [43]), and

cortical thinning [38, 66, 73]). Recent advances in automated volumetric analysis (i.e., FreeSurfer) not only dramatically hasten the work, but typically improve reliability and consistency in measurements, making it possible to examine multiple regions of interest (ROI) concurrently. For example, a FreeSurfer analysis of a mixed sample of TBI severity pediatric patients demonstrated volumetric changes across a range of structures, highlighting the diffuse nature of TBI [7]. Volumetric and cortical thickness measures have been especially useful when employed in research paradigms that assess the influence of various clinical factors and/or treatments on the evolution of TBI pathology [42, 66, 73]. In this manner, studies have implicated a number of clinical and functional measures that appear to be related to volumetric changes including neuropsychological measures of executive function, attention, memory, and processing speed [15, 40] and clinical features of injury including Glasgow Coma Scale (GCS) scores [19], loss of consciousness (LOC), and post-traumatic amnesia (PTA) [8, 60].

One method for detecting subtle volumetric changes is shape analysis. This method uses geometric modeling of the three-dimensional surfaces from volumetric data to examine the expansions and contractions along the entire surface of an ROI. Utilizing these methods, a number of studies have demonstrated different and specific spatial patterns that suggest localized changes in the complex cytoarchitecture of subcortical nuclei. For example, shape analyses of subcortical nuclei in moderate and severe TBI show reductions in localized areas of the hippocampus (head and tail), thalamus, and basal ganglia [40, 51], demonstrating vulnerability of specific regions within these complex subcortical nuclei. Furthermore, the significant shape findings were found to be functionally relevant in these samples and were associated with white matter changes as measured by other diffusion MRI sequences, including diffusion weighted imaging (DWI). However, these studies were in moderate and/or severe TBI participants, and to the authors' knowledge there have been no published studies of shape analyses exclusively in mTBI.

Importantly, mTBI or concussion, poses several challenges to clinicians and researchers alike when looking for objective evidence of injury. Volumetric/morphometric changes in certain ROIs have been demonstrated in small cohorts of mTBI patients [34, 41, 44], but these findings are often equivocal or inconsistent across studies. There are a number of possible methodological (i.e., group analyses, sensitivity of gross volumetric measurements, different analysis tools) and even clinical (i.e., subtleness of the injury, unique spatial distributions of injury) reasons for the lack of reproducible findings. However, the increased sensitivity of shape analyses for detecting subtle differences in surfaces of subcortical structures as applied to other neurological disorders [35, 46, 70] may extend or improve the detection of differences between groups in volumetric studies of mTBI. Ultimately, these analyses may potentially prove more useful in detecting injury, predicting outcomes, evaluating long term structural change and plasticity, and/or evaluating therapeutic effects of interventions.

In this study, the volumetric measures from FreeSurfer output and shape information of subcortical ROIs in a cohort of U.S. Military Service Members with symptomatic mTBI were examined. The volumetric and shape measurements from the mTBI cohort were compared to the measurements from a cohort of orthopedically injured (OI) and PTSD only

(no TBI history) U.S. Military Service Member controls. We hypothesized that the shape analyses would be more sensitive to injury compared to gross volumetric analyses and that shape would be associated with both demographic and/or clinical features in the mTBI participants.

Methods

Participants

Participants included 153 (134 male, 18 female) U.S. Service Members recruited at a large military treatment facility (MTF). The study consisted of three demographically comparable groups including symptomatic mTBI, orthopedic injury (OI) only control, and PTSD only control participants. Basic demographic data for each of the groups is found in Table 1.

TBI participants

MTBI participants were 76 (71 male, 5 female) Service Members recruited consecutively from referrals to a large MTF TBI clinic. Each was diagnosed as having sustained mTBI using the Veteran Affairs (VA)/Department of Defense (DoD) Clinical Practice Guidelines (i.e., loss of consciousness (LOC) <30 min, alteration of consciousness (AOC) <24 h, post-traumatic amnesia (PTA) <24 h, and no day of injury imaging abnormalities [22]). Furthermore, participants with mTBI were required to have persistent cognitive symptoms as measured by the Neurobehavioral Symptom Inventory (NBSI or NSI; positive responses to the four cognitive questions at the moderate level). Additional inclusion criteria included an age range between 18 and 55 years, having sustained head injury during deployment (OEF/OIF/OND) activities, having sustained head injury three to 24 months prior to recruitment, and be able to speak, read, and write in English.

Orthopedic injured only participants

Orthopedic injured (OI) only groups have been a standard control group in many TBI studies as they are considered to share many of the same injury-related experiences including hospitalizations, pain and/or other medication use, and injury-related stress [46, 59]. For these reasons, we recruited an orthopedic injured (OI) only control that consisted of 59 (47 male, 12 female) Service Members identified through the Orthopedic Clinic at the same MTF. Potential participants were excluded if they had any self-reported or objective evidence of a previous closed head injury (regardless of severity), and/or a current PTSD diagnosis (DSM-IV criteria) as identified by the standardized Clinician-Administered PTSD Scale (CAPS) structured interview. In addition, OI only control participants were required to be within a similar age range to mTBI participants, deployed within the past 3–24 months, and able to speak, read, and write in English.

PTSD only participants

Given that post-traumatic stress disorder (PTSD) has a significant brain imaging signal [53, 68] and is a significant comorbid condition observed in Service Members with mTBI [29–32], a small cohort of Service Members with PTSD without TBI (N = 17; 16 male, 1 female) were recruited from the Behavioral Health Clinic, Warrior in Transition Battalion, and/or Orthopedic Clinic at the same large regional MTF. In addition, each participant in this group

was required to meet the categorical criterion for PTSD diagnosis using the CAPS (DSM-IV criteria). PTSD only participants were selected using similar inclusion/exclusion criteria including age range, deployment history (within the past 3–36 months), and English proficiency. Furthermore, PTSD symptoms were required to be combat related, and participants were excluded if symptoms were primarily related to any other stressors or events. It should be noted that the deployment history inclusion criterion had to be extended by 12 months in this particular medical setting as PTSD-associated symptoms requiring intensive treatment were often being identified and treated after longer post-deployment intervals. For this reason, fewer potential Service Members with a diagnosis of PTSD were seen in this active duty MTF medical setting.

In addition, participants (regardless of experimental group) were excluded if they had any MRI contraindications (i.e., claustrophobia, shrapnel, and pregnancy), neurologic comorbidities (i.e., seizures, psychosis, and bipolar disorder), history of moderate/severe TBI, spinal cord injuries, were on scheduled narcotic pain medications, or were unable to use their dominant hand.

Recruitment procedures

Potential participants were identified by clinic personnel and were then interviewed by study staff who after explanation of the research (including aims, risks, and benefits) obtained written informed consent. Each participant then underwent medical record review to further determine eligibility. Those participants meeting basic inclusion/exclusion criteria underwent an additional screening interview by a trained TBI medical professional to further rule in/out closed head injury and/or concussion during military service using a semi-structured interview. Participants meeting basic inclusion/exclusion criteria were then scheduled for additional study procedures. This research was approved and monitored by the local hospital IRB (protocol #3743378) and Human Research Protection Office (HRPO) at the US Army Medical Department Medical Research and Materiel Command (USAMRMC) (protocol #A-17660).

Demographic and clinical variables

Basic demographic information was collected from each participant. Variables included age, sex, education, rank, branch of military service, number of deployments, and years in service. Service Members with prior psychiatric (i.e., major depressive disorder, anxiety disorders, posttraumatic stress disorder (PTSD)) or learning disability [i.e., attention deficit hyperactivity disorder (ADHD)] diagnoses were not excluded, but these diagnoses were documented for each participant. Each participant's subjective reporting was then verified independently via a medical chart review and a binary (0 = no diagnosis, 1 = at least one diagnosis) variable was created for analysis purposes. For the mTBI group, clinical variables including time since injury (TSI, day of assessment—day of injury), duration of LOC, duration of AOC, PTA duration, mechanism of injury (blast vs. non-blast), and number of self-reported prior head injuries and blast exposures were captured. Descriptive statistics for these variables are seen in Table 1.

Imaging acquisition

Each participant underwent multimodal MRI utilizing the same 3 Tesla Siemens Verio Syngo scanner running version MR B17. Sequences administered included a T1- weighted MPRAGE, T2-weighted, fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), diffusion tensor imaging (DTI), blood oxygenation level dependent (BOLD) resting state and task-related functional imaging, and chemical shift imaging (CSI) spectroscopy. For this report, only the volumetric T1- weighted sequence (1 mm^3 isotropic voxels) acquired utilizing a 32-channel head coil was examined (sequence parameters: field of view (FOV) = 256 mm, repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, flip angle = 9°, and a slice thickness = 1 mm). Scan time was approximately 9:50.

Imaging post-processing volumetric procedures

After each T1-weighted sequence data were visually inspected for artifacts that might affect processing (i.e., motion, complete anatomy coverage, inhomogeneity) and examined for consistent scan acquisition (same scan parameters), the raw DICOM data were submitted to the FreeSurfer 5.3 (MGH Martinos Center, Boston, MA) processing pipeline. All the data were batch-processed using one of two identical MacPro dual processor (2×3.06 GHz 6-core Intel Xeon) machines running the same Mac OS X software (Version 10.8). Though these procedures are described in detail elsewhere [18] the following processes were employed for each imaging data set.

The data were first processed using the *recon-all* command to produce fully segmented and labeled images (*aseg.mgz*). Upon completion, the *aseg.mgz* files were visually inspected for any obvious abnormal results (i.e., skull stripping errors). For the purposes of this study, we examined a number of volumes statistically by plotting the distribution of the measures to reveal possible volumetric outliers. Statistical outliers were then re-inspected visually, manual edits were conducted if needed, and the volumes were recalculated for each of the ROIs. Finally, the volumetric data for each structure of interest were extracted from the *aseg.stats* file. For this study, the volumes of the following ROIs were examined: lateral ventricles, third ventricle, fourth ventricle, brain stem, thalamus, caudate, pallidum, nucleus accumbens, hippocampus, amygdala, cerebellum white/gray matter, and anterior and posterior corpus callosum volumes.

Imaging post-processing shape procedures

Following segmentation and manual inspection of the ROIs with FreeSurfer, two shape descriptors were defined on the surfaces of seven bilateral (14 total) subcortical structures: thalamus, putamen, pallidum, amygdala, accumbens, caudate and hippocampus. A parametric representation of each surface was obtained using the Medial Demons method detailed in [23, 25]. In brief, each surface was conformally mapped to a spherical template. These spherical maps were rigidly rotated to a probabilistic atlas. Next, the spherical demons [24] algorithm was used to nonlinearly warp the spherical maps on the basis of curvature. Two surface-based functions were defined at this stage; first, the global orientation function which defines the direction of the surface; and second, the local thickness of the surface with respect to a skeletonized medial core. Finally, the spherical demons algorithm was

implemented a second time using both the newly defined medial core in conjunction with surface-based curvature to match each surface to the atlas. Each surface was composed of a number of vertices that scaled roughly with the structure's average volume and also offered a sufficient resolution of the surface to describe variation in its local topology. Two shape features were defined at each surface vertex: (1) the radial distance (RD), a proxy for thickness (the distance from each surface point to the core 2D line skeleton), and (2) the log of the Jacobian determinant (JD) which indicates local surface area dilation or contraction. Because changes in surface area can be driven by underlying changes in either concavity or convexity of the surface we report the underlying RD along with regions of significant change in JD to discern the direction of this change. Across all 14 subcortical surfaces there were a total of 27,120 vertices. Supplemental Table 1 outlines the number of vertices constituting each surface. Figure 1 illustrates the subcortical surfaces to which shape analyses were applied.

The value of these shape descriptors lies in their ability to reveal local regions of variation within a structure's surface. This is valuable complementary information in addition to the standard simple volumetric descriptions of a structure which are only able to report gross overall variation in a single direction (i.e., increased or decreased volume). The addition of localized descriptions of topology allows investigators to report subtler changes in the morphometry of a surface whose signal may have been lost when averaged across the whole ROI, thereby revealing patches of significant variation. This also allows investigators to report regions of equal but opposite variation within a single surface which would have otherwise been canceled out had they been reduced to a single, scalar value.

While numerous shape descriptors have been developed, we have chosen to use the RD and the JD due to their relatively intuitive interpretations. RD measures how thick the structure is at a given point defined on its surface while the JD is a measure of regional surface area deformation following registration. RD, JD and volume, therefore, all provide insight into different aspects of the structure's topology. They are all, of course, moderately correlated with one another since they are descriptions of the same structure, but their combined use remains valuable.

Statistical procedures

All statistical procedures were coded and run using R-project version 3.2.0. The following basic statistical regression model was utilized for both the volumetric and shape analyses:

$$Y = \beta_0 + \beta_1(\text{Main Effect}) + \beta_2(\text{Age}) + \beta_3(\text{Sex}) + \beta_4(\text{TICV}) + \beta_5(\text{Education}) + \varepsilon,$$

where Main Effect is one of group (TBI, ortho or PTSD status; modeled dichotomously), TSI (modeled continuously), MOI (modeled dichotomously), premorbid mental health diagnosis, and/or attention disorder/learning disability. Premorbid mental health diagnosis was modeled dichotomously with a positive status for any participant having prior history of any of major depressive disorder, anxiety disorders, and post-traumatic stress disorder. Similarly, participants having either a prior history of ADHD or a learning disability were collapsed into a single group. These groups were collapsed due to the small numbers of

participants having individual cases of sub-diagnoses which would have been poorly estimated individually. Associations with TSI and method of injury (MOI) were assessed only within the TBI cohort as these variables were not tracked or of primary interest in the orthopedic or PTSD only cohorts. For shape analyses, the outcome Y is simply the vertex-specific RD or JD value, while for volumetric analyses, Y is the global volumetric measure. For each model we report the t value derived from the Student's t test assessing the significance of the slope derived from the regression of the outcome, Y, on the main effect after correcting for the other covariates. Given the significant number of variables (see Supplementary Table 1), the analyses were corrected for multiple comparisons using a false discovery rate (FDR) correction. Main effect variables were selected based on interest in both exploring group differences and/or common variables identified as important in other research/clinical studies. The first main effect examined was group, which included mTBI, OI only controls, and/or PTSD only controls. For each model the following variables of interest were examined for main effects on the volume of interest or shape vertices: group (TBI, OI only, PTSD only); time since injury (TSI) for the mTBI patients only, mechanism of injury (MOI) for mTBI patients only (binary variable: blast vs other); and premorbid mental health diagnosis (binary variable: depression, anxiety, PTSD vs. no diagnosis), and premorbid attention disorder/learning disability (binary variable: attn/LD vs. no diagnosis). Several covariates were utilized regardless of model examined. These were selected based on the previous literature and are common covariates observed in many imaging studies. Covariates included age, sex, total intracranial volume (TICV), and education. All covariates were modeled as fixed effects due to their continuous nature, and in the case of education, due to the small number of categories which would limit the estimation variance across the categories.

Results

Demographic Variables

As noted in Table 1, there were a number of significant demographic differences between the groups. Namely, the OI only controls were older (5 years on average) and more educated (more post high school degrees) while the mTBI included more women. Other demographic variables are provided as a characterization of the sample in Table 1.

Mild traumatic brain injury versus orthopedic injury

The surface areas (JD measure) of the bilateral anterior medial accumbens and left anterior medial caudate were significantly expanded in the mTBI group, relative to OI controls (Fig. 2a, b). Additionally, the surface area of the left posterolateral thalamus was significantly reduced in the mTBI group (Fig. 2c). No significant RD or volumetric measures were identified in association with the mTBI and OI contrast (see Supplemental Tables 2 and 3 for volumetric statistics). However, with the exceptions of bilateral pallidum, brainstem, and fourth ventricle, subcortical regions in mTBI participants tended to be larger, although not to a significant degree (Fig. 3).

Time since injury

TSI was significantly positively associated with RD of the right anterior amygdala (Fig. 4) indicating increased thickness of this region in participants further removed from their injury. Among the vertices that were significant in this association, 75 % of the RD values were significantly associated with TICV (mean $T = 3.08$); none were significantly associated with age, sex or education. Volumetric associations with TSI failed to survive FDR correction. However, trend-level associations were observed with the right amygdala ($p = 0.18$, $T = 3.06$, $df = 65$; $\beta_{TSI} = 136.10$; 8 % increase per year) and left accumbens area ($p = 0.18$; $T = 3.14$; $df = 65$; $\beta_{TSI} = 78.79$; 18 % increase per year) with these measures being larger in subjects further removed from their injury. The third ventricle space ($p = 0.14$; $T = -3.52$; $df = 65$; $\beta_{TSI} = -179.51$; 20 % decrease per year) tended to be reduced in size over time (Supplemental Table 3 and Fig. 1). No other structures' shape or volume was significantly associated with TSI prior to or following FDR correction.

Given the possibility of nonlinear effects of age and to further elucidate the relationship between age and TSI, post hoc analyses were conducted to examine the potential interaction of these variables. Age was dichotomized into younger (below the average age of mTBI participants; 33 years old) and older (>33 years old) and the results demonstrated an interaction effect (Fig. 4b–d) where younger mTBI participants had a robust increase in thickness measures (RD) in the right amygdala with increased TSI while the older participants had a flat or slightly negative slope in thickness with increasing TSI. In addition, there appeared to be an interaction between the age and TSI JD values in the right amygdala and right putamen, where older participants show additional dilation of the surfaces with increasing TSI and the younger participants have less dilation of the surfaces with increasing TSI.

Method of injury

No significant shape or volumetric differences were observed between participants with mTBI resulting from a blast versus those who did not experience blast injuries, after controlling for multiple comparisons. Associations of mechanism of injury with subcortical morphometry before multiple comparison corrections are shown in Fig. 5 and the effect sizes are calculated in Supplementary Table 4.

Prior clinical history

No significant shape or volumetric differences were observed (1) between mTBI and PTSD participants; (2) between PTSD and OI participants; (3) between participants with and without a prior history of ADHD or learning disability; (4) between participants with and without a prior history of psychiatric disturbances. Null results not shown.

Discussion

Using state-of-the-art surface-based shape descriptors and volumetric analyses, we investigated whether a distinct profile of subcortical brain abnormalities could be identified in cognitively symptomatic US military Service Members 3–24 months post mTBI. We compared Service Members with mTBI to both those with strictly orthopedic injuries and

those with PTSD only. We further investigated whether the morphometry of these structures expressed a relationship with TSI, MOI, and several other clinical variables of interest. The main findings of our study include increased surface area (i.e., dilation) of bilateral accumbens and left caudate and reduced surface area (i.e., atrophy) of left thalamus in Service Members with mTBI, relative to OI only controls. Additionally, we observed a time-dependent increase in the thickness (RD measure) of the right amygdala with participants further removed from their injuries having thicker amygdalae. Though the volumetric (i.e., FreeSurfer volumes) group comparisons did not reveal any significant differences between the groups, the TSI RD amygdala finding was partially corroborated by trend-level increases in the volume of the right amygdala with respect to TSI (see Figure Supplementary Fig. 1A and 1B). Additional post hoc analyses of this finding also revealed a more complex relationship between TSI and age of injury (Fig. 4) such that older participants may have an attenuated recovery trajectory in the amygdala and putamen. However, additional studies (prospective studies) will be needed to further corroborate and elucidate these findings.

Diffuse and regional cerebral atrophy has been noted in a number of TBI studies, especially when including participants with more severe injuries. Abnormal findings (i.e., primarily atrophy) have been reported in number of gray matter ROIs, including the basal ganglia, thalamus, cingulate gyrus, and mammillary bodies [1, 7, 45]. However, volumetric research focused on mTBI is limited, and results are often equivocal or with varied ROI differences. This occludes ROIs that are consistently affected in mTBI patient samples, if any. Nevertheless, studies of mTBI patients (especially those with persistent symptoms) remain important as elucidation of a consistent pattern of injury in this unique clinical population may lend important insights into why a number of mTBI patients develop chronic functional and clinical symptoms.

Similar to the findings in this study, thalamic lesions and volume abnormalities appear to be a consistent finding across TBI studies [20] regardless of the methods used to quantify the differences in thalamic size (i.e., manual, automated, and voxel based methods). In one of the only studies to use shape analyses, global atrophic surface changes were seen in bilateral thalami in a sample of 21 moderate to severe TBI patients [40]. This is in contrast with our findings in this mTBI sample, of more localized (i.e., pulvinar) left thalamus changes. Regardless, functional deficits are common in patients with thalamic lesions or abnormalities and likely implicate the sensory integrative roles and cortical interconnectedness that the thalamus plays in cognitive function. Given that this study used a sample of mTBI patients that presented with cognitive complaints, it is possible that the abnormal thalamic findings observed could represent a common anatomic finding in patients with persistent symptoms. The pulvinar has known projections to association cortex in the posterior parietal area of the brain and is implicated in a number of cognitive symptoms, including executive dysfunction, visual spatial attention or salience, and working memory [26, 36, 40, 62]. However, any association with cognitive performance remains speculative in this sample as additional research would be required to determine the specific relationship between observed thalamic abnormalities and cognitive function.

This study is one of the first to implicate abnormalities in the nucleus accumbens in mTBI patients. This may be related to the fact that historically the nucleus accumbens was a

difficult ROI to measure, primarily because of its border continuity with the caudate. However, using more automated methods like FreeSurfer to segment and label the nucleus accumbens has led to improvements in accuracy and consistency of measurement. The anatomical organization of the nucleus accumbens is heterogenous and it receives projections from a number of different areas of the brain (including the thalamus and amygdala). Given these heterogeneous projections to and from the nucleus accumbens, its functional importance is complicated though it has been implicated in a number of TBI relevant outcomes, including depression, addiction, emotional regulation, inattention, and learning [3, 9, 10]. Thus, any abnormal findings in this ROI are intriguing. Beyond these shape changes, TBI studies have demonstrated abnormal white matter integrity of the fiber tracts that project to and/or are adjacent to the nucleus accumbens and may be related to abnormalities in shape or volume [48]. Shear/strain forces in TBI, even at the mild range, often result in axonal damage to deep white matter structures which in turn may produce a Wallerian type degeneration that could alter structure [37]. This hypothesis certainly could be the focus of future investigations (i.e., longitudinal studies) in this patient population by examining the adjacent white matter tracts in combination with volume and/or shape over time. This would not only improve our understanding of the relationship between these measures, but could lend additional insights into the exact pathology that underlie these findings.

Basal forebrain abnormalities might also have clinical implications for recovery and rehabilitation efforts in mTBI. In a recent animal model of TBI, injury to the basal forebrain (a major cholinergic center of the brain) moderated the effects of intensive rehabilitation efforts by limiting functional recovery and attenuating the histopathological improvements observed in intact cholinergic system animals [71]. This model of rehabilitation focused on motor lesions and recovery of motor functionality in these animals, so broader implications for functional recovery beyond motor function remain speculative. Thus, this finding will require further investigation in future studies to fully understand the extent of the nucleus accumbens' vulnerability and any functional implications abnormalities might have in recovery or rehabilitation efforts in this patient population.

It is possible that the differences in shape observed in nucleus accumbens, amygdala and posterior thalamus in the mTBI group versus the OI group are interrelated. These three structures are known to be interconnected [33, 57, 63], and involved with processing visual information for emotional [50] and reward salience [11, 74]. Nucleus accumbens and amygdala are both involved with fear conditioning [52], and nucleus accumbens volume has been correlated with trait anxiety [39]. A sample of individuals without diagnosis of PTSD, but exposed to a prolonged traumatic event (coal mine flood disaster) had smaller gray matter volumes of the right pulvinar versus a control population [12]. Anxiety, lack of motivation and mood symptoms are common complaints in patients who have sustained mTBI, but until more prospective studies are conducted, it is unclear if persistent symptoms are related directly to injury or the exposure to the traumatic event [30]. Prospective studies with premorbid assessments in the military population are lacking and should be encouraged.

In cross-sectional imaging studies of mTBI, TSI is an important clinical factor to consider [16, 54]. A number of studies in both human and animal models demonstrate TSI as one of the more consistent correlates of cognitive and imaging findings [2, 28, 55, 56]. Namely, with increasing TSI, most TBI (especially mTBI) patients demonstrate improved function [49] and fewer imaging abnormalities. In contrast to functional/cognitive outcomes, imaging studies reveal more persistent differences over time, though the temporal evolution and progression of these imaging abnormalities is not well characterized currently and may be moderated by other factors such as age of injury. Importantly, however, a number of structural, functional, and metabolic differences can remain evident for 6 months to more than a year post-injury [14, 21] and these findings require additional investigation in a prospective longitudinal manner. In this study, the shape analysis demonstrated amygdala surface dilation with increasing TSI. There was also a notable, though statistically nonsignificant, trend in the volumetric data suggesting that the amygdala was larger in mTBI patients further from injury. However, as noted, age of injury appears to moderate this finding with the younger participants demonstrating increased thickness and less surface dilation with increasing TSI (Fig. 4). Again, as this study is cross-sectional and because of the known segmentation variability noted in the amygdala, it is difficult to say that these findings are related to any reparative and/or compensatory pathological changes post-injury. However, given the known functional association that the amygdala has with emotional regulation and tone, further investigation is warranted especially in US Service Members and Veterans with mTBI, where PTSD is a common comorbidity [29, 31].

Visual inspection of the shape analyses before adjustment for multiple comparisons also revealed interesting findings that may inform future hypothesis in larger datasets. For example, in the group comparisons illustration (Fig. 2), the contrast between anterior (i.e., dilation) and posterior (i.e., reduction) regions of the brain may indicate a gradient of injury and reparative pathological changes that require further examination in a prospective manner. These findings may also be useful and informative when examining other MRI sequences and post-processing methods in combination with shape analyses. Examination of the MOI illustration prior to FDR correction (Fig. 5) reveals a pattern of difference occurring on the medial surfaces of several subcortical nuclei bordering the lateral ventricles with the blast induced mTBI participants having reductions in thickness. Recent evidence in blast studies suggest that structures adjacent to the ventricles may be at particular risk due to the fluid dynamics associated with the primary blast wave [58]. Again, these hypotheses remain speculative, but shape analyses may prove to be a useful tool in examining ROIs in this unique population.

Traditionally, TBI studies regardless of severity have incorporated volumetric methods in attempts to improve diagnosis, determine the extent of injury severity, and to inform clinical and functional prognosis. The results of this study demonstrate the additional, more nuanced information that shape descriptors provided that were especially useful in discriminating the mTBI patients from the controls groups. However, there are a number of limitations that should be considered when interpreting the data. For example, despite attempts to equate the groups on major demographic variables, there are a number of variables including age, sex, and education that are different between the groups. To deal with these issues, several statistical procedures were undertaken (namely including these variables as covariates) to

account for demographic differences, though we recognize that this remains an issue. In addition, mTBI patients in this study only included cognitively symptomatic participants and as such the results may not generalize to the other military or veteran samples that might include all mTBI participants. Inclusion of an asymptomatic mTBI sample might have also proved to be another important "control" group when looking for consistent patterns of shape or volume differences. The sample size of the PTSD only group is also underpowered for this type of analysis. Any signal associated with PTSD may have not been visible with such a small sample size. It should be noted that the PTSD only group was challenging to recruit for several reasons, including the fact that many individuals who were deployed to active combat zones and who were having clinically significant PTSD symptoms were often exposed to a blast and/or had sustained a mTBI. The difficulty in recruitment may also reflect the prioritization of medical disorders in this specific treatment setting which results in potential participants presenting for PTSD assessment and treatment further from the deployment setting. However, this group of patients should remain a focus of investigation as many of the mTBI patients included in this sample manifest PTSD symptom. Finally, it is impossible to say for certain what these changes mean clinically or pathologically. Use of additional MRI sequences and post-processing methods to confirm and to extend these findings might be a good first step in trying to understand what is happening at the histopathology level. Despite these limitations, the significant shape findings remain intriguing and warrant consideration.

Though this study is one of the larger mTBI studies (i.e., sample size) to date, it is clear that additional analyses and/or studies are needed to further elucidate important clinical and functional relationships associated with mTBI in US Combat Soldiers and Veterans. Future studies using shape analyses should include measures of neuropsychological function or conducted in longitudinal settings as these opportunities would expand our understanding of this potentially useful tool, and provide additional measures that could be used in developing and/or evaluating treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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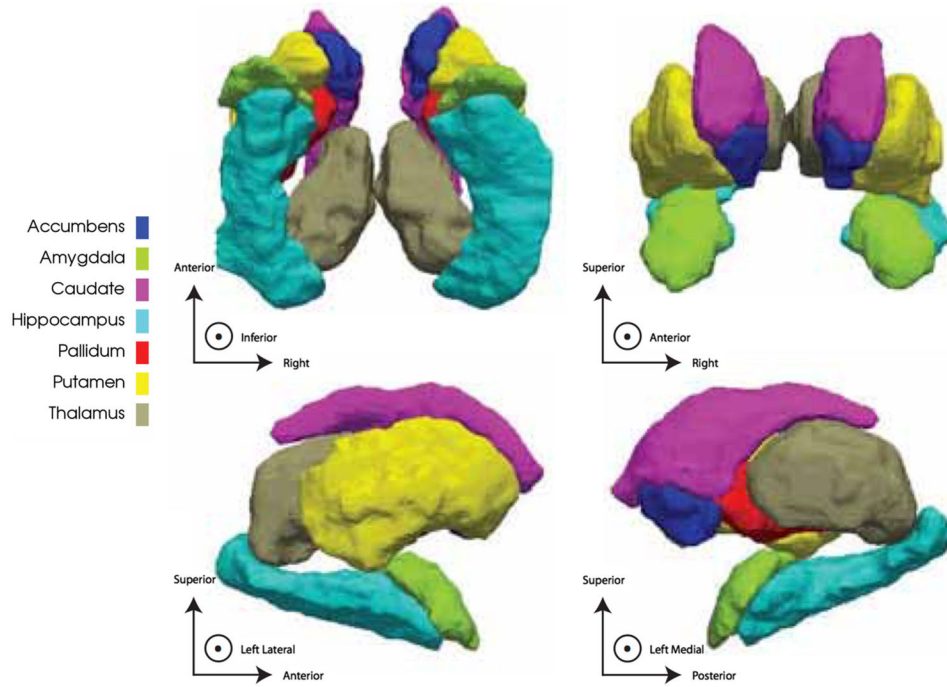
Fig. 1.
Illustration of subcortical surfaces reported in this study. Note that all images are in radiological convention throughout this manuscript, that is, the right hemisphere appears on the *left side* of the *image*
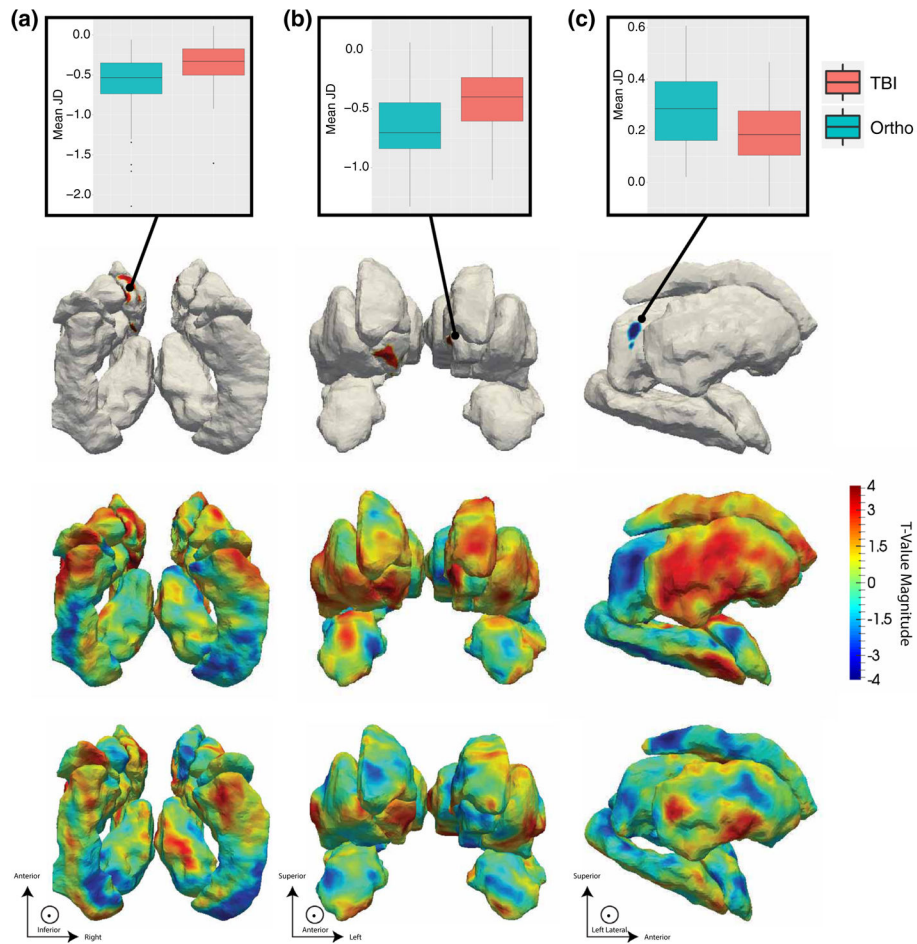
Fig. 2.

t-Value maps of the regression of the Jacobian determinant (JD) on the ortho-TBI contrast from **a** inferior, **b** anterior and **c** left perspectives. Note that all images are in radiological orientation, i.e. left–right flipped. The *top row* plots the average JD within regions differing significantly between TBI and Orthopedic groups. The *second row* illustrates FDR-thresholded *t* value maps in which only highlighted regions are significant. The *third row* maps Jacobian *t* values across the entire set of surfaces. The *bottom row* compliments this by mapping the associated *t* values for the local thickness (RD) measure to determine whether changes in local surface area result from concavity or convexity. Here, the directions of the JD and RD associations agree within regions of significance indicating that regions in *red* result from dilation while regions in *blue* are suggestive of atrophy. All coefficient *t* values had 125 degrees of freedom
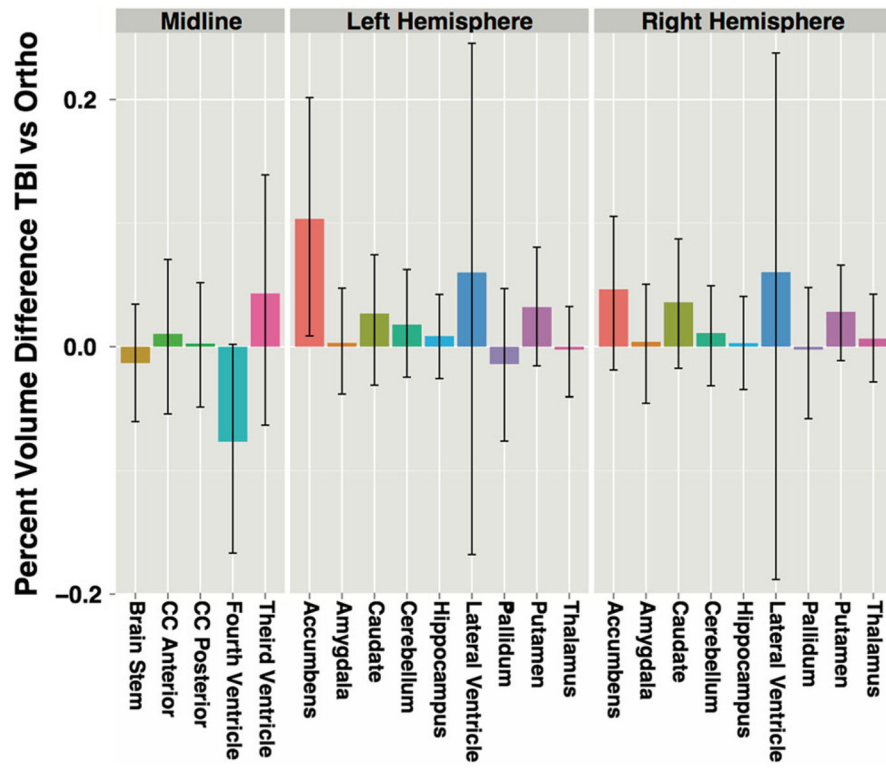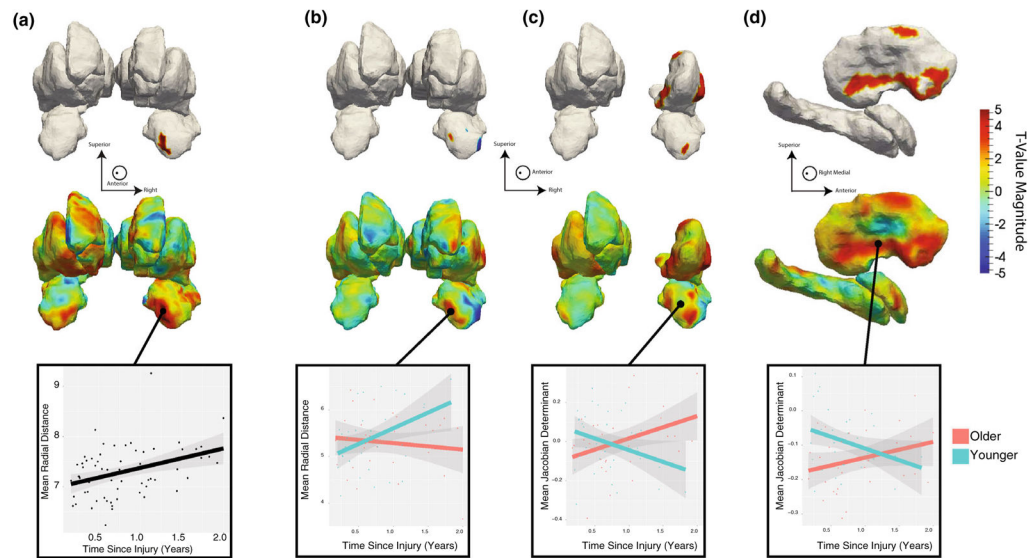
Fig. 3.
Percent volume change in TBI participants relative to orthopedic controls by region and hemisphere with bootstrapped 95 % confidence intervals

Fig. 4.

t Value maps of **a** the regression of thickness features (RD) on TSI shown from an anterior perspective showing a significant increase in the thickness of the right anterior amygdala with extended TSI. The *top row* of maps is FDR-thresholded with the remaining highlighted regions being those that are significantly associated. The *second row* of maps is unthresholded showing the global distribution of associations. Wherever significant associations are present we plot the least squares fit of the association for the vertices surviving FDR correction. All coefficient *t* values in **a** had 60 degrees of freedom. **b**–**d** Plot associations between the thickness (**b**) or surface area (JD measure) with the interaction of TSI and age. **b** Reveals a significant differential association between the thickness of the right amygdala between older and younger participants with the younger cohort having a more rapid expansion of this region than older participants. Identify regions of the **c** anterior right amygdala and **d** right pallidum with significantly differing trajectories of surface area changes. In both cases, the older participants exhibit gains in surface area at extended TSI while younger participants show significant reductions in the surface area of these regions. Associations in **b**–**d** had 59 degrees of freedom. Note that these figures are in radiological orientation, left–right flipped

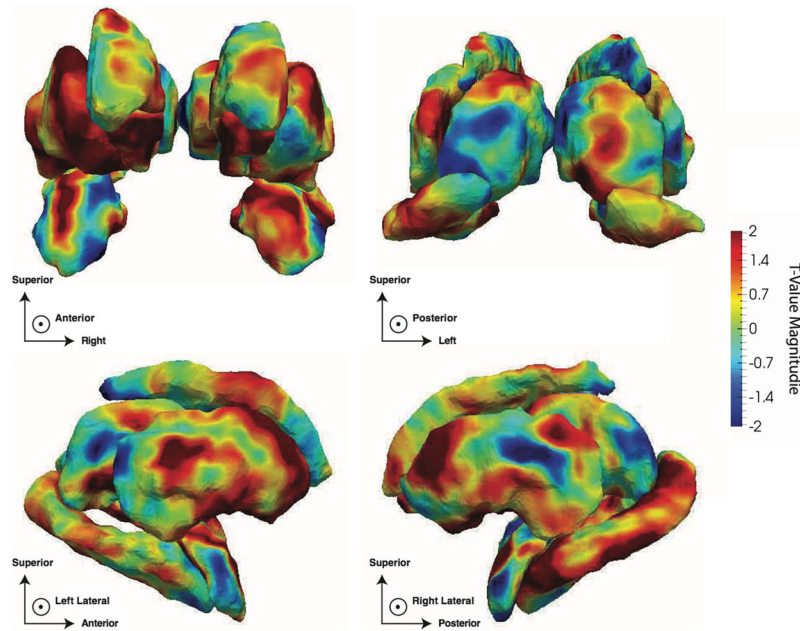**Fig. 5.**
Association of surface area (JD) with method of injury (MOI). Positive associations of surface area and MOI are shown in warmer colors and are seen to be more spatially concentrated in anterior lateral regions of the subcortical structures. While these effects are slightly below statistical significance, the trend of spatial distribution is suggestive of the nature of a blast injury

Table 1

Demographic variables for each group

	mTBI group	PTSD only group	OI only group	Total group	Significance
N	76	17	59	152	N/A
Age	32.85 years (9.25)	37.47 years (6.55)	36.95 years (6.75)	34.92 years (8.33)	$F = 11.96$
					$p < 0.001$
					(mTBI group different)
Sex (% female)	6.4 %	5.9 %	18.9 %	11.2 %	$\chi^2 = 6.33$
					$p < 0.04$
					(OI group different)
Race	73.7 % W	58.8 % W	65.5 % W	66.9 % W	$\chi^2 = 35.54$
	10.5 % AA	17.6 % AA	31.0 % AA	19.4 % AA	$p < 0.001$
	15.8 % other	23.6 % other	3.5 % other	13.7 % other	OI has more AA and less other
Education	60.5 %	HS 41.2 % HS	22.4 % HS	43.8 % HS	$\chi^2 = 39.09$
	32.6 % C	47.1 % C	53.4 % C	40.9 % C	$p < 0.01$
	6.9 % PG	11.7 % PG	24.2 % PG	15.3 % PG	(OI group different)
Branch of Service	93.4 % USA	94.1 % USA	72.4 % USA	84.4 % USA	$\chi^2 = 19.66$
	2.6 % USAF	5.9 % USAF	20.7 % USAF	10.7 % USAF	$p = 0.003$
	4 % other	0 % other	6.9 % other	4.9 % other	(OI group has more USAF)
Years in Service	10.81 years (7.97)	14.29 years (6.38)	15.64 years (6.51)	13.03 years (7.59)	$F = 14.27$
					$p < 0.001$
					(mTBI group different)
Number of deployment	36.8 % 1X	47.4 % 1X	31.6 % 1X	36.9 % 1X	$\chi^2 = 14.69$
	11.8 %	2X 26.3% 2X	36.8% 2X	34.4 % 2X	$p < 0.14$
	9.2 % 3X	15.8 % 3X	26.3 % 3X	20.6 % 3X	
	21.1 % 4X	5.3 % 4X	5.3 % 4X	6.3 % 4X	
	2.6 % 5X	5.3 % 6X		1.3 % 5X	
				0.6 % 6X	
Prior psychiatric diagnosis	21.8 %	5.9 %	22.9 %	19.4 %	$\chi^2 = 3.08$
					$p = 0.54$
Prior learning disability	5.3 %	0 %	1.7 %	3.1 %	$\chi^2 = 2.99$

	mTBI group	PTSD only group	OI only group	Total group	Significance
					p = 0.24
Time since injury	308.6 days (176.6)	N/A	N/A	N/A	N/A
	(Median 270 days)				
LOC	42.1 %	N/A	N/A	N/A	N/A
AOC	69.7%	N/A	N/A	N/A	N/A
PTA	7.9 %	N/A	N/A	N/A	N/A
Prior head injury (subjective reporting)	31.6 % no prior	None reported/denied	None reported/denied	N/A	N/A
	19.7 % 1 prior				
	9.2 % 2 prior				
	13.2 % 3 prior				
	3.9 % 4 prior				
	19.8 % > 5 prior				
	2.6 % no data				
Method of injury	57.9 % blast	N/A	N/A	N/A	N/A
	42.1 % other				

The *p* value for the group comparison are also shown

W white, *AA* African American, *O* other race, *HS* high school, *C* College (Associates and/or Bachelor's Degree), *PG* post graduate degree, *USA* United States Army, *USAF* United States Air Force