Evaluation of Cortical Thickness after Traumatic Brain Injury in Military Veterans

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Abstract

Military service members frequently sustain traumatic brain injuries (TBI) while on active duty, a majority of which are related to explosive blasts and are mild in severity. Studies evaluating the cortical gray matter in persons with injuries of this nature remain scarce. The purpose of this study was to assess cortical thickness in a sample of military veterans with chronic blast-related TBI. Thirty-eight veterans with mild TBI and 17 veterans with moderate TBI were compared with 58 demographically matched healthy civilians. All veterans with TBI sustained injuries related to a blast and were between 5 and 120 months post-injury (M = 62.08). Measures of post-traumatic stress disorder (PTSD) and depression were administered, along with a battery of neuropsychological tests to assess cognition. The Freesurfer software package was used to calculate cortical thickness of the participants. Results demonstrated significant clusters of cortical thinning in the right hemispheric insula and inferior portions of the temporal and frontal lobe in both mild and moderate TBI participants. The TBI sample from this study demonstrated a high incidence of comorbid PTSD and depression symptoms, which is consistent with the previous literature. Cortical thickness values correlated with measures of PTSD, depression, and post-concussive symptoms. This study provides evidence of cortical thinning in the context of chronic blast-related mild and moderate TBI in military veterans who have comorbid psychiatric symptoms. Our findings provide important insight into the natural progression of long-term cortical change in this population and may have implications for future clinical evaluation and treatment.

Key words: cortical thickness; magnetic resonance imaging; military veterans; traumatic brain injury

Introduction

Military service members engaged in modern conflicts frequently sustain traumatic brain injury (TBI) while on active duty. Recent studies have estimated that more than 20% of military veterans from Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) return from combat exhibiting symptoms consistent with TBI, the majority of which are mild in severity. The diagnosis and management of mild TBI in the military population has been a particularly unique challenge to clinicians, because a significant portion of these injuries occur in the context of explosive blasts, as opposed to the traditional contact-induced TBI seen in the civilian population. Regardless of etiology, diagnosis of mild TBI is currently restricted to self-reported and observed symptoms.

Blast-related TBI may occur from a combination of several injury mechanisms. The detonation of an explosive device causes the rapid expansion of a solid or liquid into the gas phase forming a pressure wave. This wave then interacts with air- or fluid-filled body organs, such as the brain, inducing a sudden increase in intracranial pressure and resulting in penetration of brain tissue, disruption of axonal pathways, and damage to capillaries. These blast-induced effects are referred to as primary injury. The blast wave may also propel objects toward a person causing secondary injury or it may force the person into other solid objects (i.e., tertiary injury). While secondary and tertiary injury are also consistent with contact-induced TBI, primary injury is generally unique to blast events and may have independent consequences on brain tissue structure and function.

Mild TBI is thought to result from damage to both cortical tissue and white matter tracts through a combination of direct tissue compression, hemorrhage, and axonal injury. Conventional neuroimaging using CT or MRI is typically normal after blast-related mild TBI, likely because of the microscopic nature of the injury. Despite the lack of positive findings, more than 50% of veterans meet...
neural networks in both cortical and subcortical areas. These changes are thought to result from disruptions in the integrity of neural networks evaluating cortical gray matter, especially after blast-related injury.

Surface based morphometry (SBM) is a well-established method of evaluating the thickness of cortical gray matter from magnetic resonance images. SBM has detected cortical thinning in pediatric patients and patients with severe TBI, although examinations of mild TBI and blast-related TBI remain underrepresented in brain morphometric research. A previous examination of cortical thickness after blast-related TBI in the military reported thinning in the left superior temporal and superior frontal gyri. This study did not assess changes in cortical thickness beyond the acute phase of injury and was limited by sample size. Cortical thickness measurements in persons with post-acute TBI would allow for further elucidation of the potential neuropathology associated with TBI and to evaluate long-term cortical changes related to blast injury.

A high incidence of comorbid post-traumatic stress disorder (PTSD) has also been documented in military personnel with blast-related injuries. A study by Hoge and colleagues found that 9.1% of veterans returning from OEF/OIF met criteria for PTSD. This incidence rose to 43.9% in those veterans who experienced mild TBI with loss of consciousness (LOC), suggesting that physical injury increases vulnerability to psychological stress. Further, PTSD severity in the military population has been found to inversely correlate with cortical thickness independent of TBI. This study also found evidence for an additive effect of comorbid mild TBI and PTSD associated with additional areas of cortical thinning.

Blast-related TBI has been linked to a variety of cognitive and behavioral difficulties, although the severity of these impairments in relation to cortical changes remains unclear. Cognitive functions such as learning, memory, attention, and executive function have all been shown to relate with blast-related TBI. Performance on neuropsychological measures in these domains has also been linked to differences in neural activity in veterans with mild TBI as measured by magnetoencephalography (MEG). These changes are thought to result from disruptions in the integrity of neural networks in both cortical and subcortical areas.

Thus far, cortical thinning has been shown to correlate with performance on measures of verbal memory and visuomotor speed, which are common cognitive domains affected in persons with TBI. However, no studies, have investigated these factors in relation to each other in a sample of veterans with blast-related injuries.

The present study sought to enhance our understanding of the effects that TBI has on cortical gray matter by investigating changes in cortical thickness during the chronic phase of blast-related TBI. We further assessed the relationship between severity of injury and cortical thickness by comparing mild and moderate blast-related TBI groups. We expected TBI participants to exhibit decreased cortical thickness (i.e., cortical thinning) compared with demographically matched healthy controls. Further, it was expected that a “dose-dependent” relationship would exist between injury severity and the degree of cortical thinning (moderate TBI cortical thinning>mild TBI cortical thinning).

We also investigated the relationship between cortical thinning and scores on neuropsychological tests, as well as measures of PTSD and depression symptoms. Based on previous literature, it was expected that cortical thinning would be related to poorer performance on neuropsychological tests, as well as severity of psychiatric symptom reporting.

Methods

Participants

Seventy-one military veterans with TBI were recruited from primarily urban areas across the United States as part of a larger ongoing study. Participants were excluded from the study if they were: (1) nonfluent English speakers, (2) an undocumented alien, incarcerated, or active duty military, (3) under age 18, (4) intellectually disabled, or (5) if they had a pre-existing condition that would preclude standard administration of study procedures, such as deafness or blindness. All veterans had sustained a TBI at a minimum of 5 months before enrollment in the study.

All participants signed an informed consent document and were enrolled in the study for 2 days. On day 1, a research assistant administered a semistructured diagnostic interview to collect demographic, medical, psychiatric, and injury history information. In addition, participants were evaluated for current level of disability using the Disability Rating Scale (DRS) and the Community Integration Questionnaire (CIQ), which were also administered by a research assistant. Neuroimaging studies, including structural MRI, were conducted on the second day of study participation.

The Defense and Veterans Affairs Affairs consensus definition of TBI was used to classify injury severity based on participant injury characteristics (duration of LOC, duration post-traumatic amnesia, duration of confusion, initial imaging findings, and initial Glasgow Coma Scale scores, when available). The injury severity data collected during interview with the participants was verified via review of medical records when possible. Based on these criteria, all military veterans had sustained a nonpenetrating mild or moderate blast-related TBI. Research has suggested a high comorbidity of psychiatric and neurological disorders in patients with TBI; therefore, these disorders were screened for but not used as exclusion criteria.

Sixty-two healthy persons were also recruited from the St. Louis metropolitan area to create a demographically matched healthy control group for comparison. Additional exclusion criteria for the healthy control group included history of psychiatric or neurological illness, substance use disorder, and other cognitive or developmental disorders.

Neuropsychological evaluation

The following neuropsychological tests were administered as part of a larger battery and included in analyses: the Digit Span subtest from Wechsler Adult Intelligence Scale Third Edition (WAIS-III DS), Trail Making Test Part A (TMT A), Trail Making Test Part B (TMT B), the California Verbal Learning Test Second Edition (CVLT-II) Total Recall and Long Delay Free Recall trial scores, and Condition 1 from the Verbal Fluency subtest from the Delis Kaplan Executive Functioning System (DKEFS VFI). The Neurobehavioral Symptoms Inventory (NSI) was administered to assess for post-concussive symptoms.

In addition, the Patient Health Questionnaire-9 (PHQ-9) was used to assess for comorbid depression, and the PTSD Checklist Civilian version (PCL-C) was given to assess symptoms of PTSD. A trained research assistant administered all tests, and raters were blind to the participants’ grouping at the time of testing. Analysis of variance (ANOVA) statistical analyses were also performed to identify differences between healthy controls and the TBI groups on neuropsychological measures.

MRI data acquisition and cortical thickness assessment

T1-weighted MRI data with 1-mm isotropic resolution was acquired on all subjects using a Philips Achieva 3-Telsa MRI scanner with an 8-channel birdcage headcoil. T1 images were acquired using a turbo field echo scan with an 8 degree flip angle and sense
parallel acquisition of factor 2. Semiautomated cortical segmentation was performed using FreeSurfer v5.0.0 software (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA; http://surfer.nmr.mgh.harvard.edu) as described by Dale and associates.18

Tissue classification into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) was calculated using signal intensity differences and known previous spatial statistics.42,43 Pial and WM surfaces were constructed using a meshing algorithm of classified voxels.20,44 At each node, the cortical thickness was estimated from the calculated minimal distance between the pial and WM surface meshes.19 Automated registration of major cortical landmarks and spatial warping was performed to optimize curvature similarities of the cortical alignment with the surface atlas.45 Once aligned and warped to the atlas space, the surfaces were labeled according to known anatomical regions.46

Two independent researchers visually checked the pial and WM surfaces created for each subject. Any errors in tissue classification that occurred during the automated processing were manually edited and rerun through the FreeSurfer processing pipeline. In addition, the MRIs were scored for image quality. Low image quality scores were more likely to have poor reconstructions, and seven subjects (two healthy controls, four mild TBI, one moderate TBI) were removed for this reason. Two subjects (1 mild TBI and 1 moderate TBI) were removed because of uncorrectable cortical reconstructions, and two healthy controls were removed because of mild ventricular dilatation on radiological review. A total of nine military veteran subjects were also excluded because their primary mechanism of injury was not blast-related (e.g., assault, motor vehicle accident). Fifty-five military veterans with TBI (54 male, 1 female) and 58 healthy controls (54 male, 4 female) made up the final study sample.

Cortical thickness statistics

Cortical thickness maps were convolved with a two-dimensional 15-mm Gaussian surface smoother. The data were imported into the QDec general linear modeling interface included with FreeSurfer and analyzed using a different offset different slope model. To address familywise error, the Monte Carlo null-Z method was used to correct for multiple comparisons.47 A one-sided null-Z correction at p < 0.05 was used to test the hypothesis of cortical thinning in the TBI groups.

Correlation between neuropsychological measures and significant cortical thickness cluster

To investigate the relationship between neuropsychological measures and cortical thickness values, the mild and moderate TBI groups were combined, and statistical analyses were performed in comparison with the healthy control group. The resulting familywise error corrected cluster was traced and generated into a subject label in QDec. The average cortical thickness was fit for each subject using the FreeSurfer command, minis.anatomical.fit, isolated to the p < 0.05 cluster region of interest (ROI). The average cortical thickness over the ROI was parsed out of each file using python and compiled into a text file, which was imported into SPSS to calculate Pearson correlations with neuropsychological test scores, as well as measures of depression and PTSD.

Results

Demographic and clinical characteristics

Of the participants with TBI, 38 had sustained mild TBI and 17 sustained moderate TBI. No significant differences were observed between the groups for mean age, education, or frequency of sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy controls (n = 58)</th>
<th>Mild TBI (n = 38)</th>
<th>Moderate TBI (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 54</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Female 4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian 27</td>
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</tr>
<tr>
<td></td>
<td>African American 24</td>
<td>1</td>
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<td></td>
<td>Hispanic 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asian/Pacific Islander 4</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>Other 2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Duration LOC</td>
<td>&gt;24 h</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30 min to 24 h</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0–30 min</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Unknown/unavailable -16</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duration of PTA</td>
<td>&gt;24 h</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>0–24 h</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unknown/unavailable -3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Initial CT scan</td>
<td>Positive</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Negative -9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unknown/unavailable -28</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>DRS Score</td>
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<td>5</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>2</td>
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<tr>
<td></td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Demographic and Clinical Characteristics for the Healthy Control, Mild Traumatic Brain Injury, and Moderate Traumatic Brain Injury Groups

TBI, traumatic brain injury; LOC, loss of consciousness; PTA, post-traumatic amnesia; CT, computed tomography; DRS, disability rating scale.

1Pearson χ² = 32.41, p < 0.001; 2Pearson χ² = 15.31; p < 0.01; 3Pearson χ² = 12.29; p < 0.01; 4Pearson χ² = 14.24; p < 0.01

Entries are numbers of participants, unless otherwise specified.

(Table 1). The mild TBI group was found to range from age 23 to 52 years (range 29), moderate from 25 to 62 years (range 37), and civilian control from 18 to 54 (range 36). All veterans with TBI sustained injuries related to a blast and were between 5 and 120 months post-injury (M = 62.08). The moderate TBI group showed greater incidence and duration of LOC (χ² = 15.31, p < 0.01) and post-traumatic amnesia (χ² = 12.29, p < 0.01) compared with the mild TBI group.

The findings from initial neuroimaging (CT scan) were largely unavailable or unknown. Patients with more moderate TBI had known abnormalities on the initial CT scan compared with participants with mild TBI. The mild and moderate TBI groups did not show differences in the frequency of scores on the DRS nor were there statistically significant differences between groups on the CIQ. Both groups scored lower on the CIQ compared with the control group, indicating that both TBI groups had a relatively similar level of current disability. See Tables 1 and 2 for descriptive statistics and further results from these analyses.
Table 2. Means and Standard Deviations for Demographic and Neuropsychological Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls</th>
<th>Mild TBI</th>
<th>Moderate TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td>30.53</td>
<td>8.70</td>
<td>58</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.74</td>
<td>2.43</td>
<td>58</td>
</tr>
<tr>
<td>Months Post-Injury</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NSI(^1)</td>
<td>5.14</td>
<td>8.05</td>
<td>58</td>
</tr>
<tr>
<td>CIQ(^2)</td>
<td>21.23</td>
<td>6.29</td>
<td>58</td>
</tr>
<tr>
<td>PCL-C(^3)</td>
<td>23.16</td>
<td>6.34</td>
<td>57</td>
</tr>
<tr>
<td>PHQ-9(^4)</td>
<td>1.80</td>
<td>2.03</td>
<td>57</td>
</tr>
<tr>
<td>WAIS-III Digit Span(^5)</td>
<td>18.47</td>
<td>3.78</td>
<td>58</td>
</tr>
<tr>
<td>TMT A</td>
<td>27.67</td>
<td>10.42</td>
<td>58</td>
</tr>
<tr>
<td>TMT B</td>
<td>67.16</td>
<td>37.10</td>
<td>58</td>
</tr>
<tr>
<td>CVLT-II 1–5 Total</td>
<td>46.95</td>
<td>7.54</td>
<td>58</td>
</tr>
<tr>
<td>DKEFS VF1(^6)</td>
<td>43.50</td>
<td>11.04</td>
<td>58</td>
</tr>
</tbody>
</table>

TBI, Traumatic Brain Injury; M, mean; SD, standard deviation; NSI, Neurobehavioral Symptom Inventory; CIQ, Community Integration Questionnaire; PCL-C, Post-Traumatic Stress Disorder Checklist Civilian version; PHQ-9, Patient Health Questionnaire-9; WAIS-III, Wechsler Adult Intelligence Scale Third Edition; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; CVLT-II, California Verbal Learning Test Second Edition; LDFR, Long Delay Free Recall; DKEFS, Delis Kaplan Executive Functioning System; VF1, Verbal Fluency Condition 1.

\(^1\)Analysis of variance (ANOVA) \(F_{(2,109)} = 127.22, p < 0.001\); \(^2\)ANOVA \(F_{(2,110)} = 8.23, p < 0.001\); \(^3\)ANOVA \(F_{(2,108)} = 84.58, p < 0.001\); \(^4\)ANOVA \(F_{(2,107)} = 66.07, p < 0.001\); \(^5\)ANOVA \(F_{(2,109)} = 784.58, p < 0.001\); \(^6\)ANOVA \(F_{(2,109)} = 6.29, p < 0.01\).

\(^a\)Means with different superscripts are statistically significantly different, \(p < 0.05\).

Cortical thickness group analyses

Several clusters of cortical thinning were found when comparing the healthy controls with TBI participants. The output statistical maps are displayed in Figure 1. After null-Z familywise error rate correction, only one cluster encompassing the right inferior temporal, right insula, and right inferior frontal areas remained statistically significant \((t[93]) = 4.15, p = 0.00008\); cluster size = 7844 mm\(^2\).

No areas in the left hemisphere exhibited significant cortical thinning. The resulting clusters can be seen in Figure 2A. Null-Z corrected statistical comparison between controls and moderate TBI highlighted a cluster of cortical thinning in the inferior temporal area \((t[72]) = 4.53; p = 0.00011\); cluster size = 5393 mm\(^3\); see Figure 2B. The combined grouping of mild and moderate TBI compared with healthy controls resulted in a larger cluster over the inferior frontal, temporal, and insula regions \((t[109]) = 3.84; p = 0.0002, cluster size = 120678 mm\(^3\)); see Figure 2C. Within this cluster, mild and moderate TBI participants were compared but were not statistically different at the significance level of \(p < 0.01\) \((t[54]) = 0.37; p = 0.72\). The average cortical thickness in the region of significance for each subject group is graphically represented in Figure 3.

Neuropsychological analyses

Results from ANOVA with Tukey honest significant difference (HSD) post hoc analyses involving the neuropsychological measures are provided in Table 2. Generally, results showed that the control group scored higher than the mild and moderate TBI groups on WAIS-III digit span and on VF1 from the DKEFS. Scores were not significantly different between groups on other included measures of cognitive functioning. The moderate TBI group reported a greater number of post-concussive symptoms compared with the mild TBI group as measured using the NSI total score. Both TBI groups reported a greater number of post-concussive symptoms compared with the control group (moderate TBI scored higher compared with mild TBI). With regard to symptoms of depression and PTSD, ANOVA with Tukey HSD post hoc analyses showed that the moderate TBI group reported the highest number of clinically significant symptoms. The mild TBI group also showed higher symptom reporting compared with the control group.

We also calculated two-tailed Pearson correlational coefficients between neuropsychological tests scores, scores on measures of depression and PTSD, and average cortical thickness cluster scores. Results showed statistically significant correlations between...
cortical thickness cluster scores and the NSI total scores \((r = 0.330, p < 0.001)\), DKEFS VF1 \((r = 0.212, p < 0.05)\), PHQ-9 total scores \((r = -0.251, p < 0.01)\), and PCL-C total scores \((r = -0.249, p < 0.01)\). Correlations between cortical thickness clusters and other neuropsychological measures were nonsignificant.

After applying Bonferroni correction to the significant correlations to control for familywise error (significant threshold of \(p < 0.005\), only the NSI total score correlated significantly with the cortical thickness cluster values. These results suggest that cortical thickness values had limited low magnitude inverse correlation with post-concussive syndrome symptoms and other aspects of emotional and behavioral functioning, as well as a possible direct relationship with a cognitive measure. The exact implications of these findings are unclear, however, because of their statistical nonsignificance when using the most conservative interpretive criterion.

Discussion

In the current study, healthy civilian controls were compared with military veterans with mild or moderate blast-related TBI using the SBM method. To our knowledge, this is the first such study to examine cortical thickness in a sample of veterans with chronic blast-related TBI. As expected, we found statistically significant cortical thinning in multiple areas, including the right inferior temporal, right insular, and right inferior frontal gyrus, associated with blast-related mild TBI. The moderate TBI groups showed similar localized findings in the right inferior temporal lobe, but to a smaller spatial extent. Our findings showed no differences in cortical thickness between mild and moderate TBI groups; thus, we were unable to detect a linear dose-response relationship as originally hypothesized.

Our results showed areas of significant cortical thinning that were lateralized and localized in nature. Based on the literature to date, it has been suggested that primary blast injury results in traumatic axonal injury and punctate microvascular disruptions.66–68 Because primary blast injury may also be accompanied by secondary and tertiary contact-based injury, however, it is possible that variations in injury mechanism are responsible for the lateralization and localization that was observed. There have been several articles in contact-based TBI that show injury in the orbitofrontal and anterior temporal lobe associated with the brain colliding with the sphenoid ridge and the free-edge of the tentorium cerebelli.9,45,46 As mentioned, despite a lack of positive findings on traditional neuroimaging studies, more than 50% of veterans meet the criteria for post-concussive disorder at long-term follow up.15 In the present study, TBI participants reported a greater number of post-concussive symptoms based on NSI total scores, which is consistent with the previous TBI literature.49,50 Further, the area of significant cortical thinning in the TBI population positively correlated with NSI scores, suggesting that post-concussive symptoms are related to right frontotemporal dysfunction. The NSI scale is not specific to TBI, however, because persons with affective disorders (i.e., PTSD) have been found to endorse higher symptom severity compared with persons with TBI alone.

Based on previous studies showing that cortical thinning is associated with several cognitive functions, we also examined relationships between cortical thickness values and neuropsychological measures.51,52 Our findings showed a low magnitude correlation between average cortical thickness values and a measure of verbal fluency skills (DKEFS Verbal Fluency Condition 1); however, this finding was not statistically significant after Bonferroni correction. Other cognitive variables that were examined did not correlate significantly with cortical thickness in our sample.

These findings suggest that there are limited relationships between cortical thickness and cognitive functioning in this sample of veterans with chronic TBI. A possible explanation for this is that neuropsychological tests often assess cognitive functions requiring complex cortical and subcortical networks that may be disrupted differentially by a heterogeneous injury such as TBI. If present, cortical alterations that correspond to the neurocognitive measures used may have been too subtle to detect through the current SBM technique.
The TBI groups demonstrated a high incidence of PTSD and depression symptoms, which is consistent with the previous literature.2,5,3 The moderate TBI group had significantly higher scores on PCL-C and PHQ-9 compared with the mild TBI participants, suggesting a higher level of psychological stress. We also saw low magnitude correlations between cortical thickness and scores on measures of depression and PTSD symptoms; however, these correlations also were nonsignificant after Bonferroni correction.

Although blast exposure is considered to be the main contributor to initial injury, PTSD and depression may play a role in long-term cortical changes. Other studies have also suggested that PTSD affects cortical thickness independently of blast exposure.27,54 This is particularly pertinent in clinical evaluation and treatment of combat veterans, because PTSD has been shown to occur at a rate of more than four times as often in those with blast-related TBI compared with non-TBI veterans.2

It is clear that the impact of blast-related TBI versus comorbid psychiatric symptoms on cortical thickness represents an area for subsequent research and that the affected brain regions identified in this study may offer insights into this complex relationship. For example, the right inferior frontal, inferior temporal, and insular lobe have been shown to have strong connections to subcortical structures involved in PTSD, such as the amygdala and hippocampus, and thus may partially explain the relationship between TBI and PTSD in affecting cortical thickness.35

It is important to add that this study extends the investigation of Tate and coworkers,26 which analyzed mild blast-related TBI participants who were an average of 1 month post-injury. The results from Tate and associates26 showed left hemispheric regions of thinning in the superior temporal lobe and superior frontal lobe, which is clearly different from our findings of inferior temporal, right insular, and right inferior frontal gyrus thinning.

There are multiple reasons why variable results may have been obtained between our study and that of Tate and colleagues.26 These differences include: mean time since injury (1 month vs. 5 years), the number of subjects analyzed (22 vs. 113), and the designation of healthy controls (non-TBI veterans vs. healthy civilians). Our study also extended the work performed by Tate and coworkers,26 since they did not examine correlations between cortical thickness and measures of neuropsychological and psychological functioning.

Limitations

There are several limitations of this study that merit discussion. The SBM method only looks at cortical thickness and does not assess subcortical structures, some of which are expected to be associated with PTSD and TBI (e.g., amygdala and hippocampus).55 Another limitation is that blast-induced TBI is likely to be a heterogeneous injury and may not fully be elucidated by aggregated group difference studies. The participants recruited in this study included healthy controls and persons with blast-related TBI, but we did not assess military personnel having experienced combat without incurring a TBI. We cannot assess the effect of military training and combat on cortical thickness and how it affects the resulting regions of statistical significance. Further, we did not assess for duration or number of deployments in the military veteran group.

It also has recently been shown that early life interpersonal trauma positively correlated with both PTSD and cortical thinning in combat veterans.56 Early life trauma was not assessed in the present study, and therefore it is unclear how early life trauma contributes to our findings. In addition, our assessment of post-concussive, PTSD, and depression symptoms was limited because we relied on retrospective self-report questionnaires, as opposed to evaluation and diagnosis by a clinician or using a structured interview format. Future research endeavors likely should use more thorough methods for evaluating PTSD and depression and their impact on cortical thickness in the context of brain injury.

Conclusion

This study provides evidence of cortical thinning after chronic blast-related mild or moderate TBI in military veterans and provides important insight into the natural progression of long-term cortical change after blast-related injury. We also found relationships between cortical thinning and aspects of cognitive and psychiatric functioning, including PTSD symptoms. Because of the high incidence of PTSD and depression symptoms in our sample, we cannot exclusively attribute cortical thinning to blast-related TBI. This sample, however, is highly representative of veterans with blast-related injury, who often have comorbid psychiatric issues.

Our findings provided added insight into the potential factors affecting their symptom presentation, which has implications for diagnosis and treatment of this patient group. Future studies should be pursued to further examine the isolated effects of blast-induced TBI and PTSD on cortical thinning in comparison with healthy controls.

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Author Disclosure Statement

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