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Brain Volume, Connectivity, and Neuropsychological Performance in Mild Traumatic Brain Injury: The Impact of Post-Traumatic Stress Disorder Symptoms

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Abstract

Post-traumatic stress disorder (PTSD) is commonly associated with mild traumatic brain injury (mTBI). To better understand their relationship, we examined neuroanatomical structures and neuropsychological performance in a sample of individuals with mTBI, with and without PTSD symptoms. Thirty-nine subjects with mTBI were dichotomized into those with ($n = 12$) and without ($n = 27$) significant PTSD symptoms based on scores on the PTSD Checklist. Using a region-of-interest approach, fronto-temporal volumes, fiber bundles obtained by diffusion tensor imaging, and neuropsychological scores were compared between the two groups. After controlling for total intracranial volume and age, subjects with mTBI and PTSD symptoms exhibited volumetric differences in the entorhinal cortex, an area associated with memory networks, relative to mTBI-only patients ($F = 4.28$; $p = 0.046$). Additionally, subjects with PTSD symptoms showed reduced white matter integrity in the right cingulum bundle (axial diffusivity, $F = 6.04$; $p = 0.020$). Accompanying these structural alterations, mTBI and PTSD subjects also showed impaired performance in encoding ($F = 5.98$; $p = 0.019$) and retrieval ($F = 7.32$; $p = 0.010$) phases of list learning and in tests of processing speed (Wechsler Adult Intelligence Scale Processing Speed Index, $F = 12.23$; $p = 0.001$; Trail Making Test A, $F = 5.56$; $p = 0.024$). Increased volume and white matter disruptions in these areas, commonly associated with memory functions, may be related to functional disturbances during cognitively demanding tasks. Differences in brain volume and white matter integrity between mTBI subjects and those with mTBI and co-morbid PTSD symptoms point to neuroanatomical differences that may underlie poorer recovery of mTBI subjects who experience PTSD symptoms. These findings support theoretical models of PTSD and its relationship to learning deficits.

Keywords: DTI; head injury; learning; memory network; white matter integrity

Introduction

Approximately 3 million Americans sustain a traumatic brain injury (TBI) each year,[1] the majority of which are mild TBI (mTBI).[2] Mild TBI is commonly expected to resolve within days, weeks, or months. However, reports have documented that 15–20% of these cases continue to experience symptoms 1 year or more post-injury.[3,4] The prevalence of psychiatric disorders is highest within the first year of injury[5] and has been suggested to worsen the prognosis for recovery.[6]

Due in large part to the military operations in Iraq and Afghanistan, post-traumatic stress disorder (PTSD) is one of the common co-morbidities following a TBI.[2,7] In civilian samples, 17% of individuals sustaining mTBI meet criteria for PTSD 6 months following injury.[8,9] In veterans who served in Operations Enduring Freedom and Iraqi Freedom, PTSD was highest among those who had sustained a TBI,[10] with rates as high as 43.9% in those whose TBI was associated with a loss of consciousness.[11] This high rate of co-occurrence has prompted interest in the effects of PTSD on TBI outcomes. While the co-morbid effects of mTBI/PTSD on functional outcomes are well documented,[7,10] the literature on cognitive functioning, brain volume and structural connectivity in mTBI/PTSD is still emerging.

Cognition

Research on TBI has shown impairment occurring in attention and executive functioning, likely owing to damage in frontal regions of the brain.[12] A body of literature has found faulty learning in PTSD symptom development and maintenance, making neuropsychological evaluation of memory functions essential in studying co-morbid TBI and PTSD.[13] Some theories suggest that

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learning impairments occur in the encoding phase, while others purport encoding deficits in the form of improper extinction learning. Although evidence supporting learning theories is mixed, impairments in encoding in PTSD are a robust finding in studies using various behavioral paradigms,[14] as well as neuropsychological assessments.[15]

The interaction and/or relative contributions of mTBI and PTSD to cognitive functioning are less clearly understood. Initial studies of mTBI/PTSD have suggested impairments in aspects of executive functioning, including verbal fluency, response inhibition, and attention.[16–18] Recent studies looking more broadly at cognitive functioning differences between mTBI groups with or without PTSD failed to find differences between groups.[19,20] While these studies do not provide a consensus on the cognitive profile of patients with co-morbid mTBI/PTSD, it is clear that subjects with mTBI and co-morbid PTSD do not improve at the same rate as those with mTBI alone.[10]

Neuroimaging

Early efforts to understand brain structure and function in patients with mTBI/PTSD relied on findings gathered from imaging studies in mTBI-only and PTSD-only to pinpoint overlapping regions of pathology.[21] In TBI, fronto-temporal areas are reported to be most vulnerable to impact.[22,23] Changes in the structure of temporal and mesiotemporal areas (e.g., amygdala) are of particular relevance to the co-morbid presentation of mTBI/PTSD. Alterations in the integrity of white matter tracts have been identified in those with co-morbid mTBI/PTSD, with these patients showing reduced fractional anisotropy (FA) of the cingulum, compared with healthy controls.[24] Studies to date have generally only compared mTBI/PTSD patients with healthy control groups. This methodological design makes it difficult to determine whether differences in brain structure are the sequelae of TBI or PTSD, or reflect cumulative pathology of both.

To better understand the relationship between mTBI and PTSD symptoms, this study examined only individuals who had sustained mTBI. The PTSD literature regarding faulty extinction learning and poorer cognitive outcomes for TBI patients with co-morbid psychopathology led to the use of not only neuropsychological measures, but imaging techniques to analyze brain volume regions of interest (ROIs), as well. Diffusion tensor imaging (DTI) is helpful to examine neural circuits that may be disrupted without detectable volume loss in relevant structures. We hypothesized that mTBI subjects endorsing high PTSD symptoms would show volume changes in brain regions associated with memory and attention for emotionally relevant information, as well as differences in DTI measures of memory circuits, compared with subjects with mTBI alone. Lastly, we hypothesized that subjects with co-morbid mTBI and PTSD would show greater deficits on neuropsychological tests of executive functioning and learning and memory. To our knowledge, this is the first study using multiple neuroimaging techniques and neuropsychological testing to compare mTBI and co-morbid mTBI/PTSD symptoms. As neuroimaging investigations have not previously been conducted to examine mTBI subjects with and without PTSD symptoms, the analyses in the present study were exploratory in nature.

Methods

Recruitment

Participants were obtained from a natural history study following a cohort of subjects with non-penetrating TBI. Recruitment was carried out from 2011–2015 via the National Institutes of Health Patient Recruitment and Public Liaison Office, the Center for Neuroscience and Regenerative Medicine Recruitment Core, and advertisements displayed in the community. Participants were eligible for the natural history study if they were: 1) 18 years of age or older; 2) diagnosed with a non-penetrating TBI; 3) able to provide informed; and 4) enrolled within the first year from injury. Participants were excluded if they had a contraindication to magnetic resonance imaging (MRI) scanning, were unable to read or speak sufficient English to complete the clinical phenotyping assessments, or had medical or psychological instability where they could not reasonably complete the study requirements. Participants were evaluated at 30 days, 90 days, 180 days, and 1 year post-injury and annually thereafter for up to 5 years. A cross-sectional enrollment option was offered to participants who were more than 1 year out from their injury or were unable to commit to longitudinal visits. Similar inclusion and exclusion criteria applied to cross-sectional participants, except that the evaluation had to be conducted within 5 years post-injury. All subjects were seen by our study physician who performed a history and physical and reviewed medical records when available from the subject.

Participants

Subjects included in this study were classified as having sustained a mild TBI using the Department of Veterans Affairs and the Department of Defense TBI severity rating scale[25] or a complicated mTBI if they met criteria for mTBI but had positive (MRI findings. All subjects passed effort tests to ensure score validity. Subjects were dichotomized into two groups based on their highest score on the PTSD Checklist (PCL). A cut-off score of 26 or lower qualified subjects for the mTBI group. Subjects endorsing high PTSD symptoms, as defined by a score of 44 or higher, were grouped into the PTSD positive group (mTBI/PTSD). All subjects in the mTBI/PTSD group, with the exception of three, had also undergone behavioral therapy and/or a course of medication for the treatment of PTSD symptoms. The Beck Depression Inventory II and the Brief Symptom Inventory 18 Anxiety Subscale were used as screening tools to exclude subjects who were symptomatic for co-morbid depression or anxiety. Additionally, the Alcohol Use Disorders Identification Test (AUDIT) was used to screen for alcohol misuse. An AUDIT score of 8 and above identified subjects at risk for alcohol misuse. Of these, two subjects were removed due to history of alcohol dependence. Subjects also were screened for the use of illicit drugs. Subjects with large parenchymal lesions were excluded from this study due to potential for miscalculation of brain volumes in FreeSurfer. Finally, because the mTBI/PTSD group was further out from their injury, the evaluation for the time-point with the highest PCL score was used for the mTBI/PTSD group and the most recent evaluation was used for the mTBI-only group.

Measures

All subjects completed a battery of neuropsychological tests and self-report measures evaluating the following domains: attention and concentration, executive functioning, learning and memory, processing speed, and effort. See Table 1 for a summary of the measures examined in the present study.

In addition to neuropsychological tests, the PCL was used to assess the number and intensity of symptoms characteristic of PTSD. Strong diagnostic sensitivity (0.944) and specificity (0.864) of the PCL has been well documented in relation to the Clinician Administered PTSD Scale (CAPS), with a PCL suggested cut-off score of 44.[26] The Ohio State University TBI Identification instrument was used to collect information regarding subject history of prior TBI.

Image acquisition

Volumetric analysis was performed using T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) scans acquired

Table 1. Neuropsychological Measures

Measure	*Cognitive function*	*Acronym*
California Verbal Learning Test – Second Edition	Learning and memory	CVLT-II
Wechsler Adult Intelligence Scale – Fourth Edition Processing Speed Index and Working Memory Index	Processing speed, working memory	WAIS-IV PSI; WAIS-IV WMI
Trail Making Test A	Processing speed	TMT-A
Trail Making Test B	Executive functioning, processing speed	TMT-B
Booklet Category Test	Executive functioning	BCT
Seashore Rhythm Test	Attention	SSRT
Green's Medical Symptom Validity Test	Effort	MSVT
Wechsler Advanced Clinical Solutions Test of Premorbid Function	Estimated premorbid intelligence quotient	ToPF

on a Siemens Biograph MR 3T scanner. Images were segmented using the longitudinal pipeline within the FreeSurfer software package (version 5.3)[27] with some minor modifications to the preprocessing steps. Briefly, images were corrected for intensity non-uniformity using the N4ITK algorithm,[28] then skull stripped using SPECTRE.[29] The following regions of interest (ROIs) were selected and analyzed: anterior cingulate, middle frontal, lateral orbito-frontal, medial orbito-frontal, entorhinal, middle temporal, and parahippocampal gyri, as well as the amygdala and hippocampus.

Diffusion weighted images were acquired with parameters repetition time=, msec, echo time=98 msec, flip angle=90 degrees, voxel size=2×2×2 mm, matrix size=128×128, and slices=75. The acquisition included 10 images at b=0 sec/mm^2, 10 images with non-collinear directional gradients at b=300 sec/mm^2, and 60 images with non-collinear directional gradients at b=1100 sec/mm^2. Images were processed using the CATNAP software previously described for tensor estimation.[30] Briefly, images were preprocessed for motion and eddy current correction, with adjustments to the gradient table performed based on subject position. Linear tensor estimation was performed followed by computation of FA, axial diffusivity (AD) and radial diffusivity (RD) and segmentation of white matter tracts with the DOTS software. Based on the literature, we selected two *a priori* fiber bundles: cingulum bundle and uncinate fasciculus.

Statistical analysis

All statistical analyses were conducted using SPSS version 22. Independent *t*-tests were performed to compare age, education, premorbid IQ, days since injury, and PCL score between subjects with mTBI and mTBI/PTSD. Due to significant differences in mean age between clinical groups, age was used as a covariate for all subsequent imaging analyses. Analyses of covariance (ANCOVAs) were applied to analyze volumetric and structural connectivity differences between mTBI and mTBI/PTSD subjects. Controlling for intracranial volume and age, we analyzed volumes of frontal and temporal areas, as well as sub-cortical structures (i.e. amygdala and hippocampus). Controlling for age, ANCOVAs also were used to analyze the DTI fibers tracts of interest. Based on findings related to processing speed, we performed *post hoc* ANCOVAs to analyze two more fiber bundles, namely the inferior and superior longitudinal fasciculi. Two subjects from the mTBI/PTSD group and four subjects from the mTBI only group were excluded from DTI analysis due to incomplete DTI scanning. Finally, to analyze neuropsychological variables, ANCOVAs were used to compare performance between groups on Trail Making Test (TMT) A, TMT B, Working Memory Index, Processing Speed Index (PSI), California Verbal Learning Test (CVLT) Free Recall, and CVLT Long Delay Free Recall. ANCOVAs also were applied to other neuropsychological measures (i.e., Booklet Category Test total errors and Seashore Rhythm Test), though these measures were not obtained from every cross-sectional subject. Due to the exploratory nature of the present study, we did not correct for multiple comparisons. Thus, findings should be interpreted with caution as they are meant to inform further research rather than to be generalized across the mTBI population.

Table 2. Demographic, Mild Traumatic Brain Injury, and Post-Traumatic Stress Disorder Characteristics for Clinical Groups

	mTBI	*mTBI/PTSD*	p
n	27	12	–
Male/female	17/10	9/3	–
Mean age (SD)	48.2 (18.1)	34.5 (8.8)	0.003*
Mean education (SD)	15.9 (2.5)	14.4 (1.8)	0.068
Ethnicity			–
Caucasian	20	9	–
Asian	1	0	–
Hispanic	2	1	–
African-American	4	0	–
Mixed race	0	2	–
Mean premorbid IQ (SD)	108.6 (12)	100.9 (15.7)	0.124
Mean days since injury	601.8 (361.5)	810.8 (691.5)	0.340
PCL score	21.1 (3)	54.9 (10.4)	< 0.0001*
Mechanism of injury			–
Falls	17	1	–
Assault	1	1	–
Impact against object	4	3	–
Acceleration/ deceleration	4	2	–
Blast	1	5	–
Multiple head injury ‡	13	6	–
Sedative medication	10	8	–
PTSD therapy	–	6	–
PTSD medication	–	8	–

*$p < 0.05$

‡ History of multiple head injuries was collected using the Ohio State University TBI Identification instrument. All prior head injuries involved at least an alteration in consciousness, in accordance with the Veterans Affairs/Department of Defense TBI severity rating scale. No prior head injury was classified as more severe than mild. Data presented as mean (standard deviation).

mTBI, mild traumatic brain injury; PTSD, post-traumatic stress disorder; SD, standard deviation; PCL, Post-Traumatic Stress Disorder Checklist.

Results

Demographics

A total of 39 subjects were included in this study. Twelve subjects met the criteria for the mTBI/PTSD group and 27 for the mTBI only group. Demographic and clinical outcome between groups are shown in Table 2. A significant difference was found for age between groups; thus, age was used as a covariate in imaging analyses. No significant differences in education, premorbid IQ, and days since injury were shown between groups. In the mTBI/PTSD group, five of the 12 subjects were current or former military with blast as the mechanism of injury. However, only one of 27 in the mTBI group had a military blast exposure as mechanism of injury.

Cortical and subcortical volumes

Volumetric analyses revealed that subjects with mTBI/PTSD had significantly larger volume in the right entorhinal cortex (EC), compared with subjects with mTBI ($F = 4.28$; $p = 0.046$). No significant differences were found for other frontal and temporal cortical structures between groups. Analyses examining subcortical structures between groups were not significant. Table 3 provides a summary of all volume outcomes.

DTI indices

Analysis of FA, RD, and AD between mTBI and mTBI/PTSD subjects revealed significantly reduced AD ($F = 6.04$; $p = 0.020$) in the right cingulum bundle in patients with co-morbid PTSD. No significant differences were found between clinical groups in the uncinate fasciculus. *Post hoc* analyses on the inferior and longitudinal fasciculi also did not reveal differences in white matter integrity. Table 3 provides a summary of DTI fiber tract outcomes.

Neuropsychological performance

There were significant between-group differences in subjects with mTBI/PTSD showing significantly poorer performance on TMT A and B, Wechsler Adult Intelligence Scale-Fourth Edition PSI, CVLT Trials 1–5 and CVLT Long Delay Free Recall, relative to subjects with mTBI-only. There were no differences on other neuropsychological measures that included executive functioning and auditory attention tasks. All neuropsychological outcomes are summarized in Table 4.

Discussion

The present study found neuroanatomical and neuropsychological differences between patients with mTBI with and without co-morbid PTSD symptoms. The location of brain volume changes, white matter alterations, and the neuropsychological testing results suggest an association with learning and memory, particularly encoding and retrieval. In addition, patients with mTBI and PTSD performed significantly worse in several measures of processing speed, compared with those with mTBI alone.

Table 3. Cortical Volume (mm^3) and Diffusion Tensor Imaging Outcomes in Clinical Groups

	Left			*Right*		
ROI	*mTBI*	*mTBI/PTSD*	p	*mTBI*	*mTBI/PTSD*	p
Cortical Volumes						
Anterior cingulate cortex	685.3 (151.2)	710.9 (141.9)	.984	768.3 (155)	749.4 (169.5)	.356
Middle frontal cortex	2411.8 (304.4)	2389.9 (336.1)	.094	2135.5 (347.9)	2257.3 (529.8)	.655
Lateral orbitofrontal cortex	2647 (307.3)	2847.8 (353.9)	.977	2488 (306.1)	2695.1 (308.7)	.575
Medial orbitofrontal cortex	1830.7 (261.5)	1870.6 (348.2)	.159	1895.1 (253.8)	1983.4 (255.8)	.293
Entorhinal cortex	403.3 (76)	432.3 (93.1)	.684	339.2 (62)	406.6 (91)	.046*
Middle temporal cortex	3160.7 (396.3)	3316.5 (577)	.511	3514.4 (430.1)	3649.8 (457.2)	.596
Parahippocampal cortex	729.6 (103)	752.9 (112.9)	.154	707.8 (102.6)	732.7 (115.9)	.627
Subcortical Volumes						
Hippocampus	4231.7 (663.1)	4595.3 (622.4)	.993	4285.6 (574.1)	4683.7 (698.9)	.816
amygdala	1593.2 (273.7)	1776.8 (404.4)	.888	1652.4 (309.9)	1820.3 (308.6)	.985
Diffusion tensor imaging						
Uncinate fasciculus[1]	.1711 (.02128)	.1752 (.02831)	.807	.1570(.02729)	.1453 (.02180)	.184
Uncinate fasciculus[2]	.0010 (.00012)	.0009 (.00010)	.527	.0010 (.00019)	.0009 (.00010)	.661
Uncinate fasciculus[3]	.0012 (.00014)	.0012 (.00008)	.435	.0012 (.00020)	.0011 (.00010)	.789
Cingulum[1]	.1795 (.02310)	.2067 (.05694)	.277	.2588 (.03267)	.2761 (.03105)	.698
Cingulum[2]	.0010 (.00015)	.0009 (.00007)	.942	.000900 (.00013)	.000865 (.00011)	.085
Cingulum[3]	.0012 (.00014)	.0012 (.00006)	.855	.001224 (.00012)	.00122 (.00009)	.020*
Inferior longitudinal fasciculus[1]	.1929 (.02016)	.1991 (.02449)	.719	.1862 (.01997)	.2002 (.01926)	.269
Inferior longitudinal fasciculus[2]	.0009 (.00012)	.0008 (.00005)	.602	.0009 (.00012)	.0008 (.00005)	.594
Inferior longitudinal fasciculus[3]	.0011 (.00012)	.0011 (.00003)	.702	.0011 (.00012)	.0011 (.00004)	.914
Superior longitudinal fasciculus[1]	.2027 (.03115)	.2223 (.02156)	.260	.2179 (.02692)	.2257 (.03133)	.862
Superior longitudinal fasciculus[2]	.0008 (.00012)	.0008 (.00005)	1.00	.0009 (.00013)	.0008 (.00008)	.692
Superior longitudinal fasciculus[3]	.0011 (.00012)	.0011 (.00004)	.332	.0011 (.00012)	.0011 (.00005)	.673

*$p < 0.05$

[1]Fractional anisotropy.

[2]Radial diffusivity.

[3]Axial diffusivity.

Data are controlled for age and intracranial volume (for brain volumes). Cortical volume and diffusion tensor imaging (DTI) data are presented as mean (standard deviation).

ROI, region on interest; mTBI, mild traumatic brain injury; PTSD, post-traumatic stress disorder.

Table 4. Mean T-scores of Neuropsychological Assessments of mTBI Patients With and Without Post-Traumatic Stress Disorder Symptoms

Assessment	*mTBI (n = 27)*	*mTBI/PTSD (n = 12)*	*F*	p
Common Data Elements				
TMT A ‡	50.6 (9.4)	42.3 (11.2)	5.56	.024*
TMT B ‡	53.3 (8.5)	44.1 (7.9)	10.01	.003*
CVLT- Trials 1–5	57.1 (12.6)	47.2 (9.2)	5.98	.019*
CVLT- Long Delay Free Recall	54.8 (13.3)	42.9 (11.2)	7.32	.010*
WAIS-IV WMI ‡	55.3 (8.1)	51 (12.6)	1.65	.207
WAIS-IV PSI ‡	56.8 (8.5)	46.8 (7.4)	12.23	.001*
Other Assessments				
BCT- Total Errors	49 (16.8)	44.6 (8.6)	.597	.447
SSRT	48.2 (12)	40.9 (11.6)	2.28	.144

*$p < 0.05$

Data are presented as mean (standard deviation). Time since injury is used as a covariate in all analyses.

‡ One subject from the mTBI group was excluded from these analyses due to missing data.

BCT: $n = 19$ mTBI, 10 mTBI/PTSD; SSRT: $n = 18$ mTBI, 9 mTBI/PTSD.

mTBI, mild traumatic brain injury; PTSD, post-traumatic stress disorder; F, female; TMT, Trail Making Test; CVLT, California Verbal Learning Test; PSI, Processing Speed Index' BCT, Booklet Category Test; SSRT, Seashore Rhythm Test.

Prior studies suggest the involvement of the EC in learning and memory.[31–33] The EC serves as a gateway between the hippocampus and frontal aspects of the neocortex, playing a central role in memory retrieval.[31] In our sample of mTBI/PTSD subjects, the EC was unexpectedly found to be enlarged, compared with mTBI-only subjects. Together with memory retrieval deficits in mTBI/PTSD subjects, it is possible that an enlarged EC may be contributing to abnormal memory retrieval in situations where retrieval is needed to be focused solely on the task at hand—that is, intrusion of other interfering memories may play a role in impaired memory retrieval in our list-learning task. In terms of PTSD symptomatology, these abnormalities may contribute to overactive retrieval of trauma memories that could result in persistent intrusive thoughts and re-experiencing symptoms. If this were to be true, these individuals also may exhibit higher avoidance symptoms as triggers in the environment may more powerfully contribute to the retrieval of unpleasant trauma memories.

Further support for the hypothesis of an abnormal memory system in patients with PTSD comes from studies showing that a fronto-hippocampal modulatory network actively engages in voluntary encoding interference and retrieval suppression of unpleasant memories.[34] In the healthy brain, the right dorsolateral and ventrolateral prefrontal cortices appear to exercise top-down control over the hippocampus, limiting the encoding of unpleasant memories and inhibiting the retrieval of those unpleasant memories that were encoded. Such mechanisms gradually lead to these memories becoming less accessible over time and are conducive to maintaining a positive emotional state.[35–38] Not only do our mMTBI/PTSD subjects exhibit a neuropsychological profile that is consistent with a deficient memory suppression system; our results also demonstrate white matter integrity abnormalities that align with this hypothesis. Specifically, mTBI/PTSD subjects show reduced structural integrity in the right cingulum bundle relative to mTBI-only patients. This finding supports prior studies that propose this white matter tract as a candidate for facilitating memory suppression processes.[39]

In addition, a study comparing mTBI/PTSD subjects with controls also found decreased FA in the left cingulum in the posterior cingulum/posterior corpus callosum region.[24] The implications of this finding and the relationship to the default mode network are clear and show the potential for effects on executive and memory functioning. If the right lateral prefrontal-hippocampal network is indeed contributing to encoding interference and retrieval suppression of unpleasant memories, and the right cingulum bundle serves to connect these regions, then reduced cingulum integrity may be interfering with the normal communication of this memory suppression network. As a result, mTBI/PTSD patients may be unable to prevent the pathological encoding of trauma memories or suppress these unpleasant memories when they arise in the forefront of conscious awareness, making these individuals more vulnerable to intrusive thoughts. In combination with the enlarged EC, these structural alterations may help to provide neurobiological evidence for the formation and maintenance of PTSD symptoms, particularly those associated with re-experiencing and avoidance.

The cingulum bundle also connects the cingulate gyrus with the EC. As such, compromised integrity of the cingulum may interfere with communication between the anterior cingulate cortex (ACC) and the hippocampus—two areas implicated in PTSD psychopathology. Our findings show that mTBI/PTSD patients exhibit reduced cingulum integrity; this finding lends partial support to prior research findings that show a relationship between cingulum integrity and severity of PTSD symptomatology.[40] Additionally, given that cingulum integrity may be important to communication between the ACC and the hippocampus in extinguishing conditioned fear responses, mTBI patients that exhibit co-morbid PTSD symptoms may have a reduced ability to properly extinguish learned fear responses to trauma memory cues.

Another finding of note is processing speed deficits in patients with mTBI and PTSD, relative to those with only mTBI. While slower processing speed has been associated with PTSD,[15] it is uncertain if these findings are a direct result of the presence of PTSD. In addition, processing speed also has been associated with decreases in white matter integrity in long-range fiber bundles. Should processing speed be impaired, we would have expected to see concomitant abnormalities in long-range white matter tracts, including the inferior and superior longitudinal fasciculi.[41] One possible explanation for the finding of decreased processing speed in the PTSD group may be found in the use of sedative medications, which were used by 58% of subjects in the mTBI/PTSD group, but only 39% of mTBI subjects. These medications may not only impact processing speed, but also higher order executive functions that processing speed supports. Prior work showing that Symbol Search and TMT A performance accounts for 43% of variance in TMT B performance[42] underscores the importance of processing speed in executive functions.

Limitations

This study was exploratory in nature, had a small sample size and used a population with a higher than average level of education, which may limit our ability to generalize these findings to other samples. In addition, in describing the cohort, we relied on the PCL and did not perform a formal Clinician-Administered PTSD Scale interview. Although there is high concordance between the two, there may be some degree of misclassification in our cohort. An additional limitation is inherent to utilizing an ROI analysis in our methodological design. It is possible that other fronto-temporal areas not included in this analysis, as well as parietal and occipital

areas, may have sustained damage. Another question that this study is unable to answer is whether individuals who develop PTSD symptoms become deficient in the encoding and retrieval aspects of memory as a result of the disorder or if individuals with these deficits are predisposed to the development of PTSD symptomatology. Longitudinal studies may be better poised to clarify this relationship. Finally, this study only compares individuals with mTBI and those who have co-morbid mTBI and PTSD. Expanding this comparison to include control subjects is beyond the scope of the present study. As such, our findings are limited to differences between mTBI patients with and without PTSD symptoms and cannot be generalized to the non-brain injured population.

Conclusions

Our findings support the idea of a neuroanatomical mechanism underlying PTSD symptoms. The findings of this study also lend support for the theory of learning and memory problems in the formation of PTSD symptoms. These findings converge well with evidence of successful PTSD treatments (e.g., cognitive processing therapy, eye-movement desensitization reprocessing) that involve exposure as a method to help improve extinction learning. Treatments for PTSD may benefit from emphasizing focus on the encoding and retrieval problems and associated re-experiencing and avoidance symptoms. These symptoms appear to be cognitively and neurobiologically distinct from attention problems associated with mTBI.

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Author Disclosure Statement

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