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Diffusion Tensor Imaging Analysis of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Debate exists over the extent to which dysfunctions arising from mild traumatic brain injury (mTBI) are distinct from posttraumatic stress disorder (PTSD).

METHODS: This study investigated 1) the white matter integrity of participants with either mTBI or PTSD, and 2) the relationship between white matter integrity and postconcussive syndrome. The sample comprised 110 civilians (mTBI group = 40; PTSD group = 32; age- and sex-matched trauma-exposed control subjects = 38) recruited from community advertising. Indicators of white matter abnormalities were fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. PTSD symptoms were indexed by the Clinician-Administered PTSD Scale, and postconcussive symptoms were assessed using the Somatic and Psychological Health Report measure.

RESULTS: Fractional anisotropy was reduced in mTBI participants in the corpus callosum, tracts of the brainstem, projection fibers, association fibers, and limbic fibers compared with both PTSD and trauma-exposed control subjects. This decrease in fractional anisotropy was observed in the context of concurrent changes in radial diffusivity, axial diffusivity, and mean diffusivity. Postconcussive symptoms were largely explained by PTSD severity rather than by changes in brain white matter. mTBI appears to be characterized by distinct reductions in white matter integrity, and this cannot be attributed to PTSD.

CONCLUSIONS: PTSD symptoms appear to be more strongly associated with postconcussive syndrome than with white matter compromise. These findings extend epidemiological evidence of the relative associations of PTSD and mTBI with postconcussive syndrome.

Keywords: Concussion, Diffusion tensor imaging, Mild traumatic brain injury, Postconcussive syndrome, Posttraumatic stress disorder, White matter integrity

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Mild traumatic brain injury (mTBI) is increasingly recognized as a major public health issue (1). The World Health Organization defines mTBI after head injury as confusion or disorientation, loss of consciousness for 30 minutes or less, posttraumatic amnesia for <24 hours, and a Glasgow Coma Scale score of at least 13 (2). Approximately 1.7 million people in the United States alone are diagnosed with TBI, with 75% of all injuries classified as mild (3). While these are most commonly observed after motor vehicle accidents owing to the acceleration-deceleration forces, they may also occur following assaults, falls, and industrial accidents. In the context of combat, much recent attention has also focused on the effects of blast injuries (4). mTBI can result in ongoing functional problems, including emotional, cognitive, and behavioral disturbances (5), which are collectively referred to as postconcussive symptoms (PCS).

One of the controversies in recent years has been articulation of the causes of the constellation of symptoms that is frequently termed PCS. Although traditionally PCS have been regarded as the unique constellation of symptoms that arise from the neurological insult arising from mTBI, accumulative evidence suggests that these symptoms may be attributed to psychological stress associated with the mTBI (6). mTBIs that occur in the context of war, motor vehicle accidents, or assaults typically involve a perceived threat to one's safety, and therefore represent a psychologically traumatic experience, which can lead to severe stress reactions including posttraumatic stress disorder (PTSD). Numerous studies have noted that the impairments observed following mTBI can be accounted for by symptoms of PTSD (7–10), and they are equally likely in people with and without mTBI (11,12). Alternatively, other studies indicate that mTBI is associated with PCS beyond the association with PTSD (13). Compounding this debate is the observation that PTSD symptoms overlap somewhat with symptoms of PCS, including hyperarousal, sleep disturbance, irritability, and concentration deficits (14).

One potential way to investigate the neural basis of the deficits associated with mTBI is by evaluating the relative associations of mTBI and PTSD with brain white matter integrity. Diffusion tensor imaging (DTI), a technique that measures the movement of water molecules within the living tissue, can

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index the anatomical integrity of neural structures. Fractional anisotropy (FA) and mean diffusivity (MD) are two global diffusivity measures, in which the former is used as an estimate of the degree of preferred direction and the latter describes average diffusion (15). Numerous studies have used DTI to study the neural underpinnings of PTSD and mTBI. One recent systematic review of 37 DTI studies conducted on mTBI populations noted the disparate findings regarding sites of white matter compromise in mTBI patients (16); however, this review did note that 24 of 37 studies reported that the corpus callosum was affected. This accords with a prior meta-analysis that included earlier studies that also concluded that the corpus callosum (particularly the splenium) was most affected in mTBI (17). Numerous studies have also focused on the relationship between PCS and white matter compromise in mTBI patients (18,19). For example, PCS has been associated with microstructural compromise in the uncinate fasciculus, inferior fronto-occipital fasciculus, internal capsule, and corpus callosum, as well as in the parietal and frontal subcortical white matter (20). Cognitive deficits associated with mTBI have been associated with diffuse axonal injury in the anterior corona radiata, uncinate fasciculus, inferior longitudinal fasciculus, cingulum bundle, and genu of the corpus callosum (21). Further, improvement in PCS severity is associated with reductions in white matter abnormality (22). These findings are mixed, however, with evidence of no association between white matter integrity and PCS (23). Summarizing these studies, one meta-analysis found that memory and/or attention deficits after mTBI were associated with impaired white matter integrity in the corpus callosum, fornix, internal capsule, arcuate, and uncinate fasciculi (24).

There is also evidence of diffuse microstructural changes in people with PTSD, with numerous studies noting deficiencies in the cingulum, uncinate fasciculus, and corpus callosum (25–36), although other studies have found no white matter abnormalities (37–39). In terms of the association of PTSD with white matter microstructure in mTBI, a longitudinal study found that patients who developed PTSD 6 months following an mTBI event exhibited abnormal white matter characteristics relative to those who did not and healthy control subjects during both subacute and chronic stages following mTBI. Patients who did not develop PTSD were distinct relative to control subjects only during the acute phase, yet demonstrated recovery in white matter after 20 days (40). Another study documented that after controlling for PTSD symptoms, white matter abnormalities in mTBI patients were associated with physical, but not emotional or cognitive, PCS (13). In summary, there is a body of evidence attesting to the association of mTBI with compromised white matter integrity in the corpus callosum; however, the extent to which mTBI is related to other tracts appears mixed. There is considerably less evidence of PTSD affecting white matter integrity, although it needs to be noted that this research is less developed.

The present study extended on previous research in a number of ways. First, it profiled white matter integrity in three distinct groups: 1) mTBI, 2) PTSD, and 3) trauma-exposed control subjects. This design allowed determination of the differential associations of PTSD and mTBI with white matter integrity. Second, by measuring PTSD symptoms and PCS, the study also permitted examination of the differential associations of PTSD symptoms and microstructural integrity to PCS. On the basis of evidence that mTBI can result in compromised white matter integrity, we hypothesized that mTBI patients would have poorer white matter integrity relative to PTSD and control participants, particularly in the cingulum, uncinate fasciculus, and corpus callosum. Further, we predicted that postconcussive symptoms would be associated with observed white matter deficits more so than posttraumatic stress symptoms.

METHODS AND MATERIALS

Participants

This study was approved by the Sydney West Area Health Service; all participants provided informed consent before participation. The sample comprised 110 participants, of whom 40 (27 men, 13 women) had a history of mTBI, 32 (18 men, 14 women) were diagnosed with current PTSD, and 38 (20 men, 18 women) were healthy control subjects who had never been diagnosed with a psychiatric disorder and never suffered a traumatic brain injury. Participants were interviewed regarding exposure to a traumatic event; all participants had been exposed to a psychologically traumatic event (as defined by the DSM-IV Criterion A stressor), including motor vehicle accidents, assaults, or traumatic falls. mTBI was defined on the basis of participants' self-reported head injury, loss of consciousness of $<$30 minutes, and posttraumatic amnesia of $<$24 hours. PTSD was defined as no history of head injury, exposure to a psychologically traumatic event, and meeting the DSM-IV criterion for PTSD. Trauma-exposed control subjects reported exposure to a traumatic event, had no history of head injury, and did not satisfy either the re-experiencing or avoidance clusters of the PTSD criteria, or the criteria for any other Axis I disorder. Participants' demographic information is presented in Table 1.

Measures

PTSD, as defined by the DSM-IV, was measured by the Clinician-Administered PTSD Scale-IV (CAPS) (41). The CAPS is a structured clinical interview that possesses good sensitivity (0.84) and specificity (0.95) relative to the Structured Clinical Interview for DSM PTSD diagnosis, and also possesses sound test-retest reliability (0.90). In addition to the CAPS, the presence of trauma history was assessed in all participants.

Postconcussive syndrome was assessed by adapting eight items on the 34-item Somatic and Psychological Health Report measure (42). This measure indexes a range of somatic symptoms, and we selected those that address core PCS, such as headaches, dizziness, concentration deficits, memory problems, fatigue, and irritability. These selected items had strong internal consistency in the current sample (Cronbach's α = .87).

The Mini-International Neuropsychiatric Interview (version 5.5) (43) was used to assess Axis I psychiatric disorders. The Mini-International Neuropsychiatric Interview is a short, structured diagnostic interview based on the DSM-IV and the ICD-10 classification of mental illness. We administered the Mini-International Neuropsychiatric Interview to determine

Table 1. Participant Characteristics

	mTBI Participants		PTSD Participants		Trauma-Exposed Control Subjects	
	Mean	SD	Mean	SD	Mean	SD
Age, Years	43.4	10.2	41.3	11.9	37.7	11.8
CAPS Score	6.6	1.3	70.7	3.6	6.1	1.6
PCS[a]	13.8	0.7	12.2	1.2	6.8	0.9
Time Since Index Trauma, Months[b]	125.6	121.4	155.1	179.6	151.3	111.1

CAPS, Clinician-Administered PTSD Scale; mTBI, mild traumatic brain injury; PCS, postconcussive symptoms; PTSD, posttraumatic stress disorder.

[a]Measured by the Somatic and Psychological Health Report augmented by specific postconcussive symptoms.

[b]Time since brain injury for mTBI participants and psychological trauma for other participants.

presence of major depressive episode, panic disorder, agoraphobia, social phobia, PTSD, obsessive compulsive disorder, generalized anxiety disorder, alcohol abuse and dependence, and marijuana abuse and dependence.

Image Acquisition

All magnetic resonance imaging was performed on a 3.0T GE Signa HDx scanner (GE Healthcare, Milwaukee, WI) using an eight-channel head coil. A spin-echo DTI–echo-planar imaging sequence was used to acquire diffusion-weighted images. Seventy contiguous, axial, 2.5-mm-thick slices (providing whole-brain coverage) were acquired in 42 gradient directions with a b-value of 1250 s/mm^2. The imaging parameters were as follows: repetition time = 17,000 ms; echo time = 95 ms; fat saturation = ON; number of excitations = 1; frequency direction = right/left; in-plane resolution = 1.72 mm $\times$ 1.72 mm; 128 $\times$ 128 matrix. Four baseline (b = 0) images were acquired at the start of the sequence and were used in the DTI fit.

Image Processing

All images were preprocessed, including skull stripping, eddy current correction, and head movement correction using FDT (FMRIB's Diffusion Toolbox), available as part of the FSL software. A binary brain mask was created using the baseline non–diffusion-weighted image, and diffusion tensor models were fitted for each brain voxel. FA, MD, and first, second, and third eigenvalue images were generated for each participant.

Using tract-based spatial statistics (TBSS), all participant FA images were registered to the standard FMRIB58_FA template and transformed to Montreal Neurological Institute 152 1 mm^3 standard space using nonlinear registrations (44). After all images were transformed, an average FA image was generated and then thinned to create a white matter skeleton comprising centers of white matter tracts that were common to all participants. The FA skeleton was set at a threshold level of FA $\geq$0.2, such that only major white matter pathways would be included. Next, every participant's FA was projected onto the mean FA skeleton where each skeleton voxel was assigned a maximum value observed perpendicular to the tract (45).

Voxelwise between-group comparisons were conducted on the skeletonized data using "randomise" permutations testing available through the FSL software. Permutations testing was set at 5000 permutations using the threshold-free cluster enhancement option. To correct for multiple comparisons, cluster-level correction was set at $p < .05$. To label clusters with significant FA differences, John Hopkins University International Consortium for Brain Mapping 81 white matter labels atlas was used. To extract values for each tract, a binary mask was generated for each label cluster and the average FA was estimated for each participant for each label cluster.

To further characterize significant FA differences, radial diffusivity (RD), axial diffusivity (AD), and MD diffusion parameters were also examined. The non-FA maps were projected onto the skeleton using the same parameters as for the FA images. The cluster binary mask in each label was used to extract values for AD (represented by λ_1), RD (represented by the average value of λ_2 and λ_3), and MD.

Data Analyses

Using TBSS, we first evaluated FA differences between the mTBI group relative to PTSD and for each of these groups relative to trauma-exposed control subjects. For the latter comparisons relative to control subjects, in addition to the whole-brain analysis we also performed voxelwise analysis of FA restricted to a single mask of the clusters, which were significantly different between the mTBI and PTSD groups. This was done to specifically evaluate if the white matter differences identified between these groups were also altered relative to control subjects. To accommodate the multiple comparisons between the three groups, a Bonferroni adjustment was made such that an alpha of .016 was used to determine significance. Next, to evaluate the relative associations of mTBI versus PTSD severity on white matter FA, we compared participants with mTBI and those without (i.e., PTSD and trauma-exposed control subjects), controlling for CAPS using whole-brain TBSS. Last, to evaluate the relative associations of white matter integrity changes and PTSD symptoms on PCS in the mTBI group, we performed regression analyses using FA values extracted from significant clusters that were observed in the mTBI versus PTSD comparison. Comparable analyses were conducted using RD, MD, and AD values. SPSS, version 25 (IBM Corp., Armonk, NY) was used in stepwise regression analyses in which FA was entered as the first predictor, followed by the overall CAPS score to predict postconcussive syndrome.

RESULTS

Participant Characteristics

One-way analyses of variance indicated that there were no differences between groups in terms of age ($F_{2,107}$ = 2.25,

p = .11), time since injury ($F_{2,108}$ = 213.9, p = .000), or sex (see Table 1). A one-way analysis of variance indicated that PTSD participants had higher CAPS scores than either the mTBI or control participants ($F_{2,108}$ = 213.9, p = .000). Importantly, there was no difference between the PTSD and mTBI participants in terms of PCS; however, both groups had more PCS than control subjects ($F_{2,108}$ = 213.9, p = .000).

White Matter Integrity Profiles for the mTBI, PTSD, and Trauma-Exposed Control Groups

Significant white matter differences were observed between mTBI and PTSD participants. FA was significantly lower in mTBI participants compared with PTSD participants in 44 white matter regions identified with the John Hopkins University atlas (Table 2). These regions included the corpus callosum; association fibers, namely the bilateral sagittal stratum, and bilateral external capsule; projection fibers such as the bilateral corona radiata (anterior, posterior, and superior portions); bilateral thalamic radiation; internal capsule (bilateral retrolenticular part and right posterior limb); limbic fibers such as the bilateral cingulum, bilateral fornix, and bilateral uncinate fasciculus; and structures of the brainstem such as the bilateral cerebral peduncle, bilateral superior cerebellar peduncle, middle cerebellar peduncle, bilateral inferior cerebral peduncle, and bilateral medial lemniscus. Figure 1 shows selected slices depicting significant clusters superimposed over the white matter skeleton.

For a number of these tracts, MD was found to be increased for the mTBI group relative to the PTSD group. Additionally, majority of the 44 regions showed significantly increased RD in mTBI participants compared with PTSD participants. There were also significant differences in AD: mTBI participants had a significant increase in AD in the splenium of the corpus callosum and bilateral posterior corona radiata, while a decrease in AD was found in the middle cerebellar peduncle, right anterior corona radiata, right posterior limb of internal capsule, right cingulum (cingulate gyrus portion), left fornix, right uncinated fasciculus, and fornix body. For the significant clusters from the mTBI versus PTSD contrast, the mTBI group also had significantly lower FA in majority of the white matter tracts as compared with trauma-exposed control subjects.

Decreased FA was observed in a number of regions including the genu, body, and splenium of the corpus callosum; bilateral cerebral peduncle; middle cerebral peduncle; bilateral corticospinal tract; right anterior corona radiata; left superior corona radiata; bilateral posterior corona radiata; right posterior limb of internal capsule; bilateral internal capsule; bilateral thalamic radiation; bilateral sagittal stratum; bilateral superior longitudinal fasciculus; left cingulum (cingulate gyrus portion); bilateral fornix; and fornix body (see Table 3).

However, the PTSD cohort was not significantly different in FA for any of these tracts relative to trauma-exposed control subjects. To further explore any other differences, a whole-brain analysis was performed to compare the PTSD and control groups and no other significant between group differences were observed.

The RD, MD, and AD values were also examined relative to control subjects in both the PTSD and mTBI groups. The mTBI group showed increased MD and AD compared with the control group in a number of tracts. RD was found to be reduced in the mTBI group compared with control subjects. Similarly, the PTSD group showed increased MD and AD compared with control subjects. RD values showed both significant increase and decrease in the PTSD group relative to control subjects. A summary of these findings is presented in the Supplement (Supplemental Tables S1–S9).

Associations of mTBI Versus PTSD Severity on White Matter FA

To further evaluate the relative associations of mTBI and PTSD severity on white matter, especially considering that there was a difference in CAPS between the mTBI and PTSD groups, we compared FA for participants with and without mTBI after controlling for total CAPS score. After controlling for PTSD severity, mTBI was associated with reduced FA in a number of white matter tracts, including the right cerebral peduncle, genu, body and splenium of corpus callosum, bilateral internal capsule, right posterior limb of internal capsule, and body fornix. These tracts also showed significant decrease in FA in the mTBI and PTSD comparison, thus suggesting that PTSD severity does not contribute to white matter alterations in these neural structures.

Although the mTBI and PTSD groups did not significantly differ in their PCS scores, we evaluated the associations of postconcussive symptomatology by measuring the impact of mTBI on FA while controlling for total PCS score. The majority of the tracts from the PTSD versus mTBI analysis remained significant, thus indicating that PCS are not uniquely associated with white matter alterations (see Supplemental Table S10).

Relative Associations of White Matter Integrity Changes and PTSD Severity With Postconcussive Syndrome in mTBI

Stepwise regression analyses were conducted to identify the relative associations of FA changes and CAPS severity to PCS in those tracts that showed significant difference between the mTBI and PTSD groups. CAPS severity was shown to be the only significant predictor of PCS in mTBI. That is, after controlling for CAPS, changes in FA did not significantly contribute to PCS (see Table 4).

DISCUSSION

This study observed decreased FA and increased MD across a range of white matter fiber bundles in mTBI participants relative to PTSD participants. These changes in global anisotropy measures could be attributed to predominantly increased RD for the mTBI group. Similarly, the mTBI group showed reduced FA compared with the control group. Interestingly, the white matter alterations that characterized mTBI were independent of PTSD severity. These findings suggest that at least for a number of tracts in the mTBI group, PTSD has little association with the microstructural white matter alterations, which is consistent with the FA finding that there were no detectable white matter differences between the PTSD and control participants. This pattern accords with prior studies indicating that deficits in white matter integrity observed in mTBI are independent of PTSD (13), and also with evidence that PTSD is not

Table 2. Summary of Mean Fractional Anisotropy Values for Significant Tracts for the mTBI Versus PTSD Tract-Based Spatial Statistics Comparisons

	PTSD Participants		mTBI Participants			
White Matter Cluster	Mean	SD	Mean	SD	Difference, %	*p* Value
Tracts in the Brainstem						
Left cerebral peduncle	0.75	0.03	0.72	0.03	3.00[a]	.001
Right cerebral peduncle	0.75	0.02	0.73	0.03	3.40[a]	.000
Middle cerebellar peduncle	0.56	0.02	0.43	0.02	23.20[a]	.000
Left superior cerebellar peduncle	0.73	0.02	0.71	0.03	3.00[a]	.001
Right superior cerebellar peduncle	0.70	0.02	0.68	0.03	2.80[a]	.003
Left medial lemniscus	0.68	0.03	0.66	0.04	3.40[a]	.008
Right medial lemniscus	0.68	0.02	0.66	0.04	2.90[a]	.025
Right inferior cerebral peduncle	0.65	0.03	0.62	0.04	3.50[a]	.007
Left inferior cerebral peduncle	0.63	0.03	0.61	0.04	3.70[a]	.007
Left corticospinal tract	0.66	0.03	0.62	0.05	5.80[a]	.000
Right corticospinal tract	0.64	0.03	0.59	0.04	7.60[a]	.011
Pontine crossing tract	0.55	0.04	0.52	0.05	4.80[a]	.012
Corpus Callosum						
Genu	0.72	0.04	0.70	0.05	3.30[a]	.027
Body	0.70	0.03	0.67	0.04	3.40[a]	.017
Splenium	0.82	0.03	0.79	0.04	3.00[a]	.003
Projection Fibers						
Left anterior corona radiata	0.59	0.04	0.56	0.05	5.20[a]	.007
Right anterior corona radiata	0.49	0.07	0.51	0.06	1.99[a]	.058
Left superior corona radiata	0.56	0.03	0.54	0.04	4.40[a]	.009
Right superior corona radiata	0.54	0.04	0.53	0.04	1.70[a]	.022
Left posterior corona radiata	0.52	0.03	0.50	0.04	5.10[a]	.001
Right posterior corona radiata	0.54	0.04	0.51	0.04	5.30[a]	.002
Right posterior limb of internal capsule	0.73	0.02	0.50	0.04	31.70[a]	.000
Right retrolenticular part of internal capsule	0.62	0.03	0.59	0.04	4.90[a]	.001
Left retrolenticular part of internal capsule	0.62	0.03	0.59	0.03	4.00[a]	.002
Left posterior thalamic radiation	0.65	0.03	0.63	0.04	3.50[a]	.007
Right posterior thalamic radiation	0.65	0.04	0.63	0.04	4.40[a]	.003
Association Fibers						
Left sagittal stratum	0.60	0.04	0.57	0.04	4.90[a]	.003
Right sagittal stratum	0.60	0.04	0.57	0.04	5.10[a]	.002
Left external capsule	0.53	0.03	0.50	0.03	4.90[a]	.000
Right external capsule	0.50	0.03	0.47	0.03	5.40[a]	.000
Left anterior limb of internal capsule	0.71	0.03	0.69	0.04	2.40[a]	.076
Right posterior limb of internal capsule	0.73	0.02	0.71	0.03	2.40[a]	.011
Left posterior limb of internal capsule	0.73	0.02	0.72	0.03	2.30[a]	.014
Left superior longitudinal fasciculus	0.53	0.03	0.51	0.03	4.30[a]	.002
Right superior longitudinal fasciculus	0.56	0.04	0.53	0.05	5.50[a]	.003
Limbic Fibers						
Left cingulum (cingulate gyrus)	0.63	0.03	0.59	0.05	5.20[a]	.003
Right cingulum (cingulate gyrus)	0.60	0.04	0.57	0.04	5.10[a]	.002
Left cingulum (hippocampus)	0.56	0.05	0.51	0.05	8.50[a]	.000
Right cingulum (hippocampus)	0.58	0.05	0.55	0.06	6.00[a]	.007
Right fornix/stria terminalis	0.58	0.04	0.56	0.04	4.90[a]	.004
Left fornix/stria terminalis	0.57	0.04	0.54	0.04	5.40[a]	.004
fornix body column	0.39	0.07	0.37	0.05	6.50	.065
Right uncinate fasciculus	0.62	0.04	0.60	0.05	3.60[a]	.049
Left uncinate fasciculus	0.59	0.03	0.56	0.06	4.50[a]	.023

Tracts that survived the threshold-free cluster correction of $p < .05$ are listed.
mTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.
[a]Significant difference ($p < .05$).

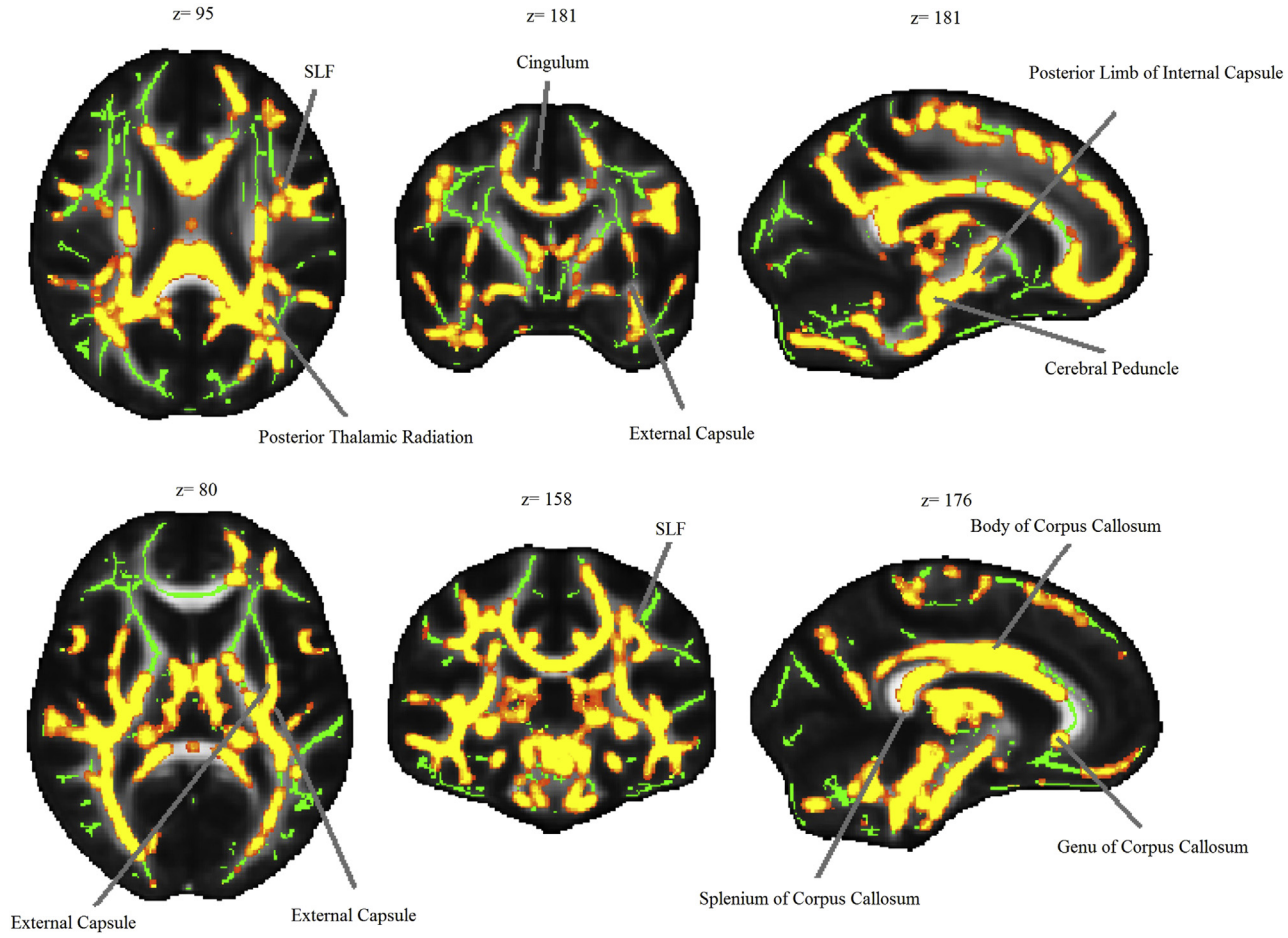

Figure 1. Significant white matter clusters for mild traumatic brain injury vs. posttraumatic stress disorder comparison overlaid on mean fractional anisotropy image. SLF, superior longitudinal fasciculus.

associated with white matter abnormalities (37,38). We do note, however, that the PTSD group showed increased MD and AD compared with control subjects, which accords with many studies suggesting white matter abnormalities in PTSD (29).

The mTBI group showed decreased FA compared with the PTSD group in the body and splenium of the corpus callosum. This interhemispheric fiber bundle is involved in transfer and integration of information between the hemispheres and has been previously implicated in mTBI. One review of DTI studies suggests that this structure is the most frequently affected region in mTBI (46). Several studies have also suggested changes within this structure in PTSD (27). In the present study, however, we did not observe significant FA changes within the corpus callosum in PTSD compared with trauma-exposed healthy control subjects. This discrepancy could be attributed to the predominant use in the previous studies of nontraumatized healthy control subjects, thus confounding the potential interpretations of results. It is possible that white matter alterations in the corpus callosum are better explained by a history of mTBI, with PTSD having no detectable contribution.

The finding of altered white matter architecture in the cingulum is consistent with several prior mTBI studies (47,48). The cingulum is a limbic fiber bundle that has been previously implicated in emotional processing and memory owing to its connections with the frontal cortex, amygdalae, and hippocampus (49). The observed changes could potentially explain the emotional disturbances, such as irritability, depression, and anxiety, frequently reported in mTBI. Our findings of reduced FA within the bilateral cingulum in mTBI, together with lack of change in PTSD compared with trauma-exposed control subjects, suggest that emotional problems incurred in mTBI may be related to microstructural cingulum compromise; this possibility remains speculative at this point and deserves closer attention in future studies.

There was reduced FA in the mTBI relative to PTSD patients in the right uncinate fasciculus. Although several studies have implicated this fiber bundle in anxiety (50), only one study to date has found reduction in FA in a traumatized population (51). This study, however, investigated the role of trauma in children, and hence its results are not directly comparable to the present findings. In contrast, there is considerable

Table 3. Summary of Mean Fractional Anisotropy Values for Significant Tracts for the mTBI Versus Trauma-Exposed Control Subjects Tract-Based Spatial Statistics Comparison

	Trauma-Exposed Control Subjects		mTBI Participants			
White Matter Cluster	Mean	SD	Mean	SD	Difference, %	*p* Value
Tracts in the Brainstem						
Left cerebral peduncle	0.75	0.03	0.72	0.03	3.83[a]	.000
Right cerebral peduncle	0.76	0.02	0.73	0.03	3.30[a]	.000
Middle cerebellar peduncle	0.67	0.06	0.61	0.06	9.13[a]	.000
Right corticospinal tract	0.74	0.05	0.72	0.05	3.24[a]	.028
Left corticospinal tract	0.71	0.04	0.68	0.04	3.76[a]	.004
Corpus Callosum						
Genu	0.72	0.04	0.69	0.06	3.85[a]	.022
Body	0.70	0.04	0.67	0.05	3.59[a]	.011
Splenium	0.82	0.03	0.80	0.04	3.13[a]	.003
Projection Fibers						
Left superior corona radiata	0.54	0.05	0.51	0.06	5.91[a]	.013
Right superior corona radiata	0.55	0.05	0.52	0.06	5.37[a]	.024
Left posterior corona radiata	0.51	0.03	0.49	0.04	4.03[a]	.011
Right posterior corona radiata	0.51	0.03	0.49	0.04	4.19[a]	.010
Right posterior limb of internal capsule	0.67	0.03	0.65	0.04	2.79[a]	.012
Right retrolenticular part of internal capsule	0.61	0.03	0.58	0.04	4.09[a]	.006
Left retrolenticular part of internal capsule	0.52	0.05	0.5	0.05	4.13	.062
Left posterior thalamic radiation	0.64	0.04	0.62	0.04	3.44[a]	.012
Right posterior thalamic radiation	0.65	0.04	0.62	0.04	4.64[a]	.002
Association Fibers						
Right sagittal stratum	0.60	0.04	0.57	0.04	4.99[a]	.001
Left superior longitudinal fasciculus	0.55	0.05	0.52	0.05	5.01[a]	.022
Right superior longitudinal fasciculus	0.55	0.04	0.53	0.05	4.95[a]	.007
Right external capsule	0.51	0.03	0.49	0.03	2.31[a]	.002
Limbic Fibers						
Left cingulum (cingulate gyrus)	0.58	0.04	0.55	0.06	5.72[a]	.010
Right fornix/stria terminalis	0.59	0.04	0.56	0.04	5.38[a]	.001
Left fornix/stria terminalis	0.57	0.04	0.54	0.05	4.49[a]	.002
Fornix body column	0.41	0.06	0.37	0.05	10.79[a]	.001

Tracts that survived the threshold-free cluster correction of $p < .05$ are listed.
mTBI, mild traumatic brain injury.
[a]Significant difference ($p < .05$).

evidence of alterations in this bundle in mTBI patients (52,53). In this sense, the results of the current study are consistent with past research.

Changes within a number of brainstem fiber bundles were also observed in mTBI. This finding accords with evidence of brainstem association fibers being affected in military personnel affected by blast injuries (54). Specifically, we observed decrease in FA in the middle cerebellar peduncle and bilateral superior cerebellar peduncle. As the sequelae of mTBI can involve somatic as well as affective and cognitive impairments, changes in these brainstem tracts could potentially be implicated in these physiological complaints. Although the cerebellum has traditionally been implicated in motor responses, some studies suggest that it may also be contributing to higher-order cognitive processes, such as memory (55), and this may also reflect cognitive complaints often reported by mTBI patients.

We also observed white matter alterations within a number of projection fiber bundles, including the corona radiata and internal capsule in the mTBI group. These tracts contain extensive fibers that connect frontoparietal cortical areas to the thalamus, subcortical nuclei, and spinal cord (56). Owing to their anatomical positioning, these tracts are involved in performing perceptual, motor, and higher-order cognitive functions. Decreased FA within these structures has been previously observed in both mTBI and PTSD. For example, it has been noted that PTSD symptom severity in mTBI patients is associated with decreased FA in the left retrolenticular part of the internal capsule (57). Further, PTSD has been associated with reduced FA in the right anterior corona radiata in combat veterans (58). On the other hand, another study showed that patients with remitted PTSD exhibit decreased FA in the left posterior corona radiata, whereas no change was observed in the persistent PTSD group (59). Similarly, in the present study

Table 4. Summary of Stepwise Regression Parameters Predicting Postconcussive Symptoms

White Matter Cluster	*B*	SE *B*	β	*p*
Tracts in the Brainstem				
Right cerebral peduncle	0.095	0.044	.394	.039[a]
Left cerebral peduncle	0.092	0.044	.383	.046[a]
Middle cerebellar peduncle	0.098	0.042	.407	.028[a]
Left corticospinal tract	0.088	0.044	.367	.054
Right corticospinal tract	0.092	0.043	.384	.042[a]
Corpus Callosum				
Genu	0.069	0.047	.289	.152
Body	0.088	0.044	.366	.059
Splenium	0.090	0.044	.376	.052
Projection Fibers				
Right anterior corona radiata	0.118	0.041	.490	.008[a]
Left superior corona radiata	0.099	0.046	.411	.043[a]
Right superior corona radiata	0.115	0.041	.480	.009[a]
Left posterior corona radiata	0.098	0.044	.402	.036[a]
Right posterior corona radiata	0.096	0.043	.400	.035[a]
Right posterior limb of internal capsule	0.087	0.044	.364	.056
Right retrolenticular part of internal capsule	0.089	0.043	.370	.049[a]
Left retrolenticular part of internal capsule	0.090	0.043	.377	.047[a]
Left posterior thalamic radiation	0.094	0.043	.393	.038[a]
Right posterior thalamic radiation	0.093	0.043	.387	.040[a]
Association Fibers				
Left sagittal stratum	0.097	0.043	.406	.031[a]
Right sagittal stratum	0.093	0.042	.388	.036[a]
Left external capsule	0.088	0.043	.368	.052
Right external capsule	0.091	0.042	.380	.041[a]
Left superior longitudinal fasciculus	0.091	0.046	.379	.060
Right superior longitudinal fasciculus	0.089	0.044	.373	.051
Limbic Fibers				
Left cingulum (cingulate gyrus)	0.088	0.044	.365	.055
Right fornix/stria terminalis	0.095	0.044	.395	.039[a]
Left fornix/stria terminalis	0.082	0.043	.340	.071
Fornix body	0.089	0.044	.371	.052

[a]Significant difference ($p < .05$).

we did not observe FA changes in the PTSD group. This discrepancy could be attributed to the control group used as well as trauma type.

A number of association fibers demonstrated decreased FA in the mTBI group compared with the PTSD and control groups. Of particular interest was the decrease in FA in the bilateral superior longitudinal fasciculus compared with PTSD group. In contrast, one earlier study found no difference in mTBI participants with and without PTSD (60). This discrepancy could be attributed to this prior sample's not including any non-mTBI participants, and hence may have had a distinct neural profile relative to the non-mTBI participants reported in the current study.

We note several procedural limitations. First, mTBI was assessed retrospectively and hence we were not able to directly validate the extent of the relevant indices of mTBI, such as the Glasgow Coma Scale score or duration of loss of consciousness. Relatedly, we could not assess the extent to which these relevant mTBI factors were related to the white matter findings. Second, we note that whereas TBSS allows the study of whole-brain white matter without the necessity of definitive prior hypotheses, whole-brain analysis is limited in terms of its ability to describe the exact architecture of the observed changes (61). However, the focus on region-of-interest analysis is limited by selection of specific tracts that could potentially result in omission of significant changes in fibers that were not preselected for the analysis. Third, we intentionally recruited mTBI participants without PTSD to maintain the distinction between these conditions; however, one limitation in this design is that it precludes the role of PTSD in mTBI. Fourth, the lack of a non–trauma-exposed healthy control condition does not allow us to disentangle the effects that may be attributed to trauma exposure. This could be addressed in future studies by including mTBI participants following sports injuries or other mTBIs in which the injury is not associated with psychological trauma.

In summary, the current findings extend current knowledge by indicating that mTBI is associated with global white matter changes that are distinct from changes that may accompany PTSD. This conclusion accords with the balance of available evidence that compromised white matter integrity is commonly observed in the aftermath of mTBI, and that there is relatively little evidence that this pattern is evident in the context of PTSD. The current finding that PCS are associated more with PTSD severity than compromised white matter integrity is intriguing because it suggests that the symptoms commonly described as PCS may be a result of numerous factors and not limited to microstructural damage (62). Commentators have noted in recent years that PCS often present as medically unexplained symptoms and can be influenced by numerous psychological and contextual factors (63). We recognize that these are complex issues, and future studies should examine the relationships of white matter integrity and clinical manifestations of mTBI in relation to single versus multiple brain injuries and blast versus impact injuries, and importantly, map the course of white matter integrity alterations over time after mTBI. Although this study points to distinct microstructural alterations in mTBI relative to PTSD, the overlap between these conditions highlights that PTSD reactions should be considered in future attempts to delineate the specific associations of mTBI on neural integrity.

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