Original Article

White Matter Changes in Posttraumatic Stress Disorder Following Mild Traumatic Brain Injury: A Prospective Longitudinal Diffusion Tensor Imaging Study

Li Li[1,2], Gang Sun[2], Kai Liu[2], Min Li[2], Bo Li[2], Shao-Wen Qian[2], Li-Li Yu[3]

[1]Institute of Postgraduates, The Second Military Medical University, Shanghai 200032, China
[2]Department of Medical Imaging, Jinan Military General Hospital, Jinan, Shandong 250031, China
[3]Department of Statistics, Jinan Military General Hospital, Jinan, Shandong 250031, China

Abstract

Background: The ability to predict posttraumatic stress disorder (PTSD) is a critical issue in the management of patients with mild traumatic brain injury (mTBI), as early medical and rehabilitative interventions may reduce the risks of long-term cognitive changes. The aim of the present study was to investigate how diffusion tensor imaging (DTI) metrics changed in the transition from acute to chronic phases in patients with mTBI and whether the alteration relates to the development of PTSD.

Methods: Forty-three patients with mTBI and 22 healthy volunteers were investigated. The patients were divided into two groups: successful recovery (SR, $n = 22$) and poor recovery (PR, $n = 21$), based on neurocognitive evaluation at 1 or 6 months after injury. All patients underwent magnetic resonance imaging investigation at acute (within 3 days), subacute (10–20 days), and chronic (1–6 months) phases after injury. Group differences of fractional anisotropy (FA) and mean diffusivity (MD) were analyzed using tract-based spatial statistics (TBSS). The accuracy of DTI metrics for classifying PTSD was estimated using Bayesian discrimination analysis.

Results: TBSS showed white matter (WM) abnormalities in various brain regions. In the acute phase, FA values were higher for PR and SR patients than controls (all $P < 0.05$). In subacute phase, PR patients have higher mean MD than SR and controls (all $P < 0.05$). In the chronic phase, lower FA and higher MD were observed in PR compared with both SR and control groups (all $P < 0.05$). PR and SR groups could be discriminated with a sensitivity of 73%, specificity of 78%, and accuracy of 75.56%, in terms of MD value in subacute phase.

Conclusions: Patients with mTBI have multiple abnormalities in various WM regions. DTI metrics change over time and provide a potential indicator at subacute stage for PTSD following mTBI.

Key words: Diffusion Tensor Imaging; Mild Traumatic Brain Injury; Posttraumatic Stress Disorder; Tract-based Spatial Statistics

Introduction

Posttraumatic stress disorder (PTSD) may results in serious social and professional consequences because it is often poorly recognized, leading to a lack of early medical, and rehabilitative interventions.[1,2] A number of studies have demonstrated the presence of PTSD following mild traumatic brain injury (mTBI).[3-5] The frequency of PTSD, followed by mTBI, varies between 17% and 33%.[6,7] However, the biggest challenge is that many individuals with mTBI do not develop PTSD. The ability to predict PTSD is a critical issue in the management of patients with mTBI, as early medical and rehabilitative interventions may reduce the risks of long-term cognitive changes.[8]

A widely accepted hypothesis for PTSD may be due to microstructural white matter (WM) damage as a result of straining, stretching, deforming, or even shearing forces.[9,10] Diffusion tensor imaging (DTI) can investigate WM integrity, which provides quantitative markers of WM lesions and an extensive description of water

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Address for correspondence: Prof. Gang Sun, Department of Medical Imaging, Jinan Military General Hospital, Jinan, Shandong 250031, China
E-Mail: cjr.sungang@vip.163.com

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diffusion. A commonly applied DTI metric is fractional anisotropy (FA), which represents the degree of alignment of cellular structures within fiber tracts and their structural integrity. However, previous DTI studies that focused on mTBI/PTSD remain controversial,[11,12] which is probably due to the variety of methods and their evolution with time. In a recent longitudinal DTI study,[13] Croall *et al*. found a link between cognitive dysfunction and WM injury after mild–moderate injury; however, this work did not consider PTSD diagnosis. Further investigations of DTI metric changes and microstructural WM damage of patients with mTBI/PTSD are needed.

In this study, we investigated how diffusion abnormalities changed in the transition from the acute to chronic injury phases by using the tract-based spatial statistics (TBSS) method in patients with mTBI and whether differences in FA or mean diffusivity (MD) values related to the development of PTSD. We tested the hypothesis that DTI metrics change over time in patients with mTBI, and FA or MD values may provide a potential indicator at one of the stages for PTSD following mTBI.

Methods

Subjects

This study was prospective, multicenter, open, and longitudinal. Participants were recruited in the Emergency Departments of three hospitals, Jinan Military General Hospital, Shandong Jiaotong Hospital, and the No. 4 Hospital of Jinan. A total of 65 consecutive patients with mTBI were initially recruited; this was defined according to the mTBI committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine. The definition includes loss of consciousness of <20 min, posttraumatic amnesia of fewer than 24 h, and an initial Glasgow Coma Scale (GCS) of 13–15. Any patient with acute abnormal findings on magnetic resonance imaging (MRI) (such as parenchymal hematoma, subarachnoid hemorrhage, or subdural hematoma) was excluded. Twenty-two right-handed healthy subjects (men/women, 8/14; age, 36.1 ± 7.11 years) with no known history or MRI evidence of central nervous system disease were also recruited in the study for reference values. The participants were excluded if they had a history of head injury or neurological or psychiatric disease, or had contraindications to MRI. The protocol was approved by the Ethics Committee of Jinan Military General Hospital. Written informed consents were obtained from all the participants.

Procedure

Patients with mTBI underwent MRI investigation and clinical assessments at the acute (within 3 days), subacute (10–20 days), and chronic (1–6 months) phases after injury. Healthy volunteers had only one MRI investigation and clinical assessment session. All participants were evaluated with the same standardized neuropsychological tests. The clinical PTSD evaluations were performed at 1 or 6 months after injury; since the course of the illness varies (some people may recover within 3 months, while others have symptoms that last much longer). The evaluation included the psychometric measures for PTSD diagnosis, which is based on Diagnostic and Statistical Manual of Mental Disorders-V criteria, and symptom severity using the clinician-administered PTSD scale (CAPS).[14] The clinical assessments were in the Chinese language versions. After each clinical interview, each participant received an MRI scan of the whole-brain. Longitudinal studies that repeatedly assessed cognitive performance in controlled intervals divided the patients into two groups with successful or poor recovery (PR) patterns over time. Patients without PTSD were considered as having a successful recovery (SR), while patients with PTSD were considered as having a PR.

Magnetic resonance imaging data acquisition

Imaging was performed with the same 3.0T MRI scanner (Discovery MR750; GE HealthCare, Milwaukee, WI, USA) in Jinan Military General Hospital, equipped with a standard head coil. The MRI protocol applied in this study was as follows: (1) the conventional MRI – including localizer sequence, T1-weighted imaging (time of repetition [TR]/time of echo [TE] = 1750/17 ms), T2-weighted imaging (TR/TE = 4850/94 ms), and fluid-attenuated inversion recovery imaging (TR/TE = 8400/17 ms) was acquired using a 5.0-mm section thickness, a 256 × 256 matrix, and a 240-mm field of view (FOV). The conventional MRI data were acquired to exclude subjects with brain abnormalities such as an obvious hemorrhage or encephalomalacia. (2) An axial 50-direction DTI was performed with a spin-echo single shot echo-planar pulse sequence (TR = 4600 ms, TE = minimum, matrix = 256 × 256, FOV = 240 × 240 mm^2, number of excitations = 1, slice thickness = 4.0 mm, slice gap = 0). The diffusion-sensitizing gradients were applied with b value of 1000 and 0 s/mm^2.

Magnetic resonance imaging processing

This study used TBSS to perform the voxel-wise analysis. This is a fully automated whole-brain analysis technique that involves voxel-wise statistics on diffusion metrics but simultaneously minimizes the effects of misalignment by using the conventional voxel-based analysis method.[15,16] Before image processing, all images were confirmed uncontaminated with major head motion. TBSS analysis was performed by using FMRIB Software Library software (FSL version 4.1.9, http://www.fmrib.ox.ac.uk/fsl). First, DTI data were corrected for head movement and eddy currents by using FMRIB's Diffusion Toolbox in FSL. Then, each subject's FA images were first aligned to a 1 × 1 × 1 mm^3 Montreal Neurological Institute (MNI) 152 space. Next, the generated mean FA image was thinned to create a mean FA skeleton. FA data for each subject were then projected onto this mean skeleton, and the resulting data were embedded from the voxel-wise statistics. Following these steps, differences of MD and FA values between groups (SR vs. control groups, PR vs. control groups, and SR vs. PR groups) were assessed, respectively.

Statistical analysis

Clinical data

Clinical statistical results in the present study were expressed as the mean ± standard deviation (SD). Because of the small sample size and because some of the outcome variables had a nonnormal distribution, Wilcoxon rank sum and Kruskal–Wallis tests were used to compare the continuous variables of different groups. Categorical data were analyzed using Fisher's exact test. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 16.0; SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was used to identify statistical significance unless otherwise noted.

Image data

For FSL-TBSS, a nonparametric test of DTI data was carried out in voxel-level. The group differences were tested using permutation-based statistical analysis with 5000 permutations. The threshold for the mean FA skeleton was set to 0.2 to differentiate gray and WM. The results were corrected using the threshold-free cluster enhancement correction method with a family-wise error for multiple comparisons.[17] The value of $P < 0.05$ was considered statistically significant after corrected.

Predictive accuracy of diffusion tensor imaging data

First, *fslmaths* command in FSL was used to create a region of interest masks (group results between SR and PR in different phases), which will be applied to each mTBI patient's DTI data, then mean DTI values from these masked areas were extracted using *fslquery* command. These values were put into an Excel spreadsheet and ultimately into SPSS for analysis. A Bayesian discrimination analysis was used to investigate the predictive accuracy of DTI metrics for classifying patients into SR and PR groups in different phases. For acquiring optimal posterior probabilities, a bootstrap cross-validation method was used, which randomly chose three subjects from each group to be in a test set and then computed the posterior probabilities that the six test subjects were classified into each category (SR vs. PR groups) with the remainder as a training set. The simulation was repeated 1000 times to increase the accuracy of the overall classification. The sensitivity and the specificity of the classification for the two groups were calculated by setting the posterior probability thresholds as $P = 0.5$. The sensitivity of the classification was defined as the ratio between numbers of correctly classified PR patients and the total number of PR patients; the specificity was defined as the ratio between the correctly classified SR patients and the total number of SR patients.

Results

Demographic and clinical features

Of the 65 patients, 17 were excluded, as they met the exclusion criteria (three for subarachnoid hemorrhage, five for a subdural hematoma, two for head trauma history, and seven for withdrawal from study), and five because of poor image quality. A total of 43 right-handed mTBI patients (men/women, 21/22; age, 30.6 ± 8.6 years) were finally included in the study. Head injury was caused by traffic crash in 31 patients, by aggression-related blows to the head in eight patients, and by fall in four patients. Fifteen and six patients who met the criteria for the diagnosis of PTSD, as assessed using CAPS at 1 and 6 months after injury, respectively, were designated to the PR group. Twenty-two patients, who did not develop PTSD within 6 months after injury, were designated the SR group. The demographic and clinical characteristics of each group are summarized in Table 1. There were no significant differences in age, gender composition, or years of education between the SR and PR groups and healthy controls; there were no significant differences in GCS, loss of consciousness, duration of posttraumatic amnesia, and types of accidents between the SR and PR group. As expected, the PR patients had higher scores on the CAPS than the SR patients.

Tract-based spatial statistics results

The present study demonstrated that diffusion changes varied with time in mTBI patients. Compared with healthy controls, PR group showed increased FA in the acute phase, increased MD in the subacute phase, and decreased FA and increased MD in the chronic phase. Compared with healthy controls, SR group only showed increased FA in the acute phase. In comparison to the SR group, PR group showed increased MD in subacute phase, and decreased FA and increased MD in the chronic phase in several WM regions. The most discriminant regions include corpus callosum (CC), inferior fronto-occipital fasciculus (IFF), uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), anterior thalamic radiation (ATR), and corticospinal tract (CT).

In acute phase

The present study showed that FA value was significantly higher (all $P < 0.05$) for PR and SR patients than for healthy control subjects [Table 2]. For each mTBI patient and control, the mean of the FA values in each of the most discriminant regions across the three groups (PR, SR, and controls) was plotted in Figure 1. There was no difference between PR and SR patients in terms of FA values. MD data on the WM skeleton yielded no significant results for the three groups.

In subacute phase

Results of TBSS analysis showed a significant MD increase for PR patients, compared to SR and control groups [Figure 2]. There was no difference in MD between SR patients and controls (all $P > 0.05$) [Table 3]. Interestingly, TBSS analysis showed no discriminant regions for the three groups in terms of FA values.

In chronic phase

Brain diffusion changes were presented in Figures 3 and 4. Compared to SR patients and controls, MD value was significantly higher and FA value was significantly

Table 1: Characteristics of the PR, SR patients, and controls

Characteristics	PR (n = 21)	SR (n = 22)	Controls (n = 22)	χ^2	Z	P*
Age (years), mean ± SD	35.8 ± 7.58	36.7 ± 7.09	36.1 ± 7.11	–	0.40	0.69
Sex (male/female)	9/12	12/10	8/14	0.04	–	0.84
Educations (years), mean ± SD	12.71 ± 2.77	13.27 ± 2.89	13.59 ± 2.34	–	0.66	0.51
CAPS (1 month postinjury), mean ± SD	34.23 ± 3.13	13.81 ± 3.05	–	–	21.65	<0.001
CAPS (6 months postinjury), mean ± SD	32.86 ± 12.12	17.63 ± 9.84	–	–	4.51	<0.001
GCS median score	13	14	–	–	0.88	0.38
Duration of LoC (min), mean ± SD	5.67 ± 5.80	3.72 ± 4.05	–	–	1.27	0.20
Duration of PTA (h), mean ± SD	3.82 ± 6.75	2.96 ± 7.34	–	–	0.40	0.69
Types of accidents, *n*			–	0.77	–	0.68
Traffic accidents	14	17	–			
Blows to the head	5	3	–			
Falls	2	2	–			

*PR versus SR group. –: Not applicable; PR: Poor recovery; SR: Successful recovery; SD: Standard deviation; CAPS: Clinician-administered PTSD scale; PTSD: Posttraumatic stress disorder; GCS: Glasgow Coma Scale; LoC: Loss of consciousness; PTA: Posttraumatic amnesia.

Table 2: Anatomic location of significant FA increase in mTBI patients in acute phase when comparing PR and SR patients with control

Brain regions	Hemisphere	MNI coordinates (mm)			Voxel	t	P
		X	Y	Z			
PR compared with controls							
SLF	Left	−44	−4	24	217	3.532	0.017
Splenium of corpus callosum		11	−38	9	1530	2.971	0.005
Genu of corpus callosum		−19	41	23	76	3.394	0.025
IFF	Right	13	46	−17	66	3.398	0.025
IFF	Left	−34	36	−1	344	3.508	0.012
ATR	Left	−19	46	13	87	3.217	0.025
Corticospinal tract	Right	14	−23	−3	65	3.219	0.025
Uncinate fasciculus	Left	−19	48	0	65	3.218	0.025
SR compared with controls							
SLF	Left	−29	−51	34	194	2.102	0.046
Splenium of corpus callosum	Left	−14	−41	24	9182	2.913	0.008
Inferior longitudinal fasciculus	Left	−19	−59	38	37	2.108	0.046
ATR	Left	−27	−40	28	170	2.861	0.036

FA: Fractional anisotropy; mTBI: Mild traumatic brain injury; PR: Poor recovery; SR: Successful recovery; MNI: Montreal Neurological Institute; IFF: Inferior fronto-occipital fasciculus; SLF: Superior longitudinal fasciculus; ATR: Anterior thalamic radiation.

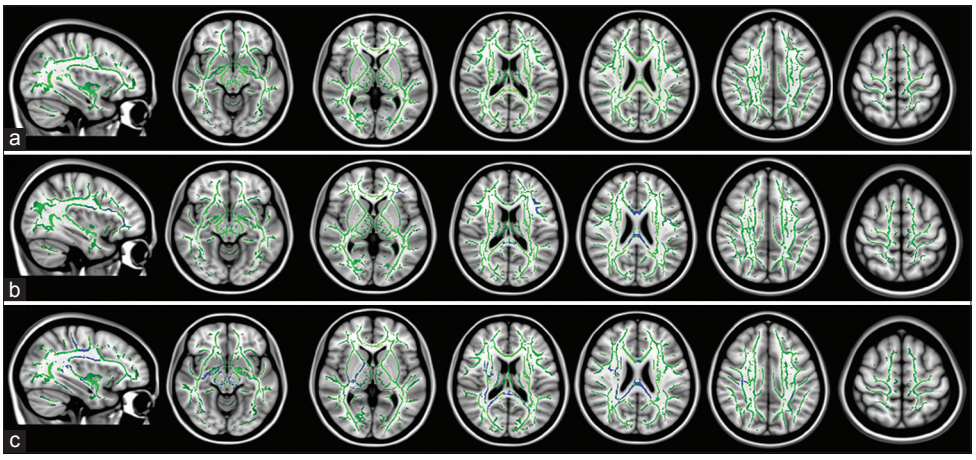

Figure 1: TBSS analysis results in acute phase overlaid on sagittal and axial views of the FA template. PR patients versus SR patients (a); PR patients versus controls (b); and SR patients versus controls (c). There was a significant difference between every two groups. The blue areas were to show the increased FA value areas. Clusters were significant at $P < 0.05$, corrected for multiple comparisons. The skeleton is shown in green. TBSS: Tract-based spatial statistics; FA: Fractional anisotropy; PR: Poor recovery; SR: Successful recovery.

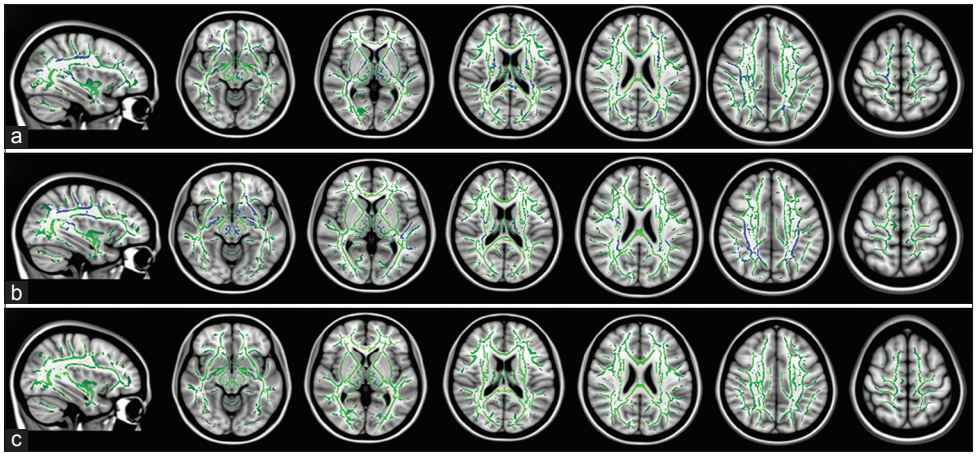

Figure 2: TBSS analysis results in subacute phase overlaid on sagittal and axial views of the MD template. PR patients versus SR patients (a); PR patients versus controls (b); and SR patients versus controls (c). There was a significant difference between every two groups. The blue areas were to show the increased MD value areas. Clusters were significant at $P < 0.05$, corrected for multiple comparisons. The skeleton is shown in green. TBSS: Tract-based spatial statistics; MD: Mean diffusivity; PR: Poor recovery; SR: Successful recovery.

Table 3: Anatomic location of significant MD increase in mTBI patients in subacute phase when comparing PR patients with SR patients and controls

Brain regions	Hemisphere	MNI coordinates (mm)			Voxel	*t*	*P*
		X	Y	Z			
PR compared with SR							
SLF	Right	38	−55	27	97	2.258	0.035
SLF	Left	−22	−36	42	124	2.401	0.023
IFF	Right	28	−69	22	87	2.267	0.039
IFF	Left	−38	−30	4	88	2.269	0.039
ILF	Left	−23	−61	28	103	2.301	0.037
Genu of corpus callosum		−19	45	2	85	2.247	0.039
Splenium of corpus callosum		4	−38	11	93	2.253	0.035
ATR	Right	24	−21	37	90	2.257	0.035
ATR	Left	−5	−32	−23	87	2.246	0.039
CT	Right	21	−19	47	170	2.254	0.036
CT	Left	−13	−10	−10	745	2.971	0.005
UF	Left	−20	22	−11	109	2.300	0.037
PR compared with controls							
SLF	Right	33	−51	32	2892	2.905	0.007
SLF	Left	−31	−46	34	828	2.909	0.007
IFF	Right	28	−41	21	635	2.904	0.007
IFF	Left	−26	42	4	91	2.249	0.038
ILF	Right	27	−10	−10	151	2.405	0.027
Genu of corpus callosum		−24	44	8	89	2.250	0.038
Splenium of corpus callosum		1	−36	11	117	2.401	0.029
ATR	Right	5	−29	−19	1635	2.921	0.007
ATR	Left	−19	−59	35	283	2.919	0.007
CT	Left	−14	−2	4	203	2.910	0.007
Cingulum (hippocampus)	Left	−25	−53	4	86	2.391	0.030
Corticospinal tract	Right	18	−40	−36	87	2.399	0.034
UF	Right	29	45	0	85	2.397	0.034

FA: Fractional anisotropy; mTBI: Mild traumatic brain injury; PR: Poor recovery; SR: Successful recovery; MNI: Montreal Neurological Institute; IFF: Inferior fronto-occipital fasciculus; UF: Uncinate fasciculus; Superior longitudinal fasciculus; ILF: Inferior longitudinal fasciculus; ATR: Anterior thalamic radiation; CT: Corticospinal tract.

lower in PR patients (all $P < 0.05$) from these indices in the most discriminant regions [Tables 4 and 5]. There was no difference in FA/MD between SR patients and controls.

Predictive accuracy

In subacute phase, TBSS analysis showed that the most discriminant mean of the MD values between SR patients

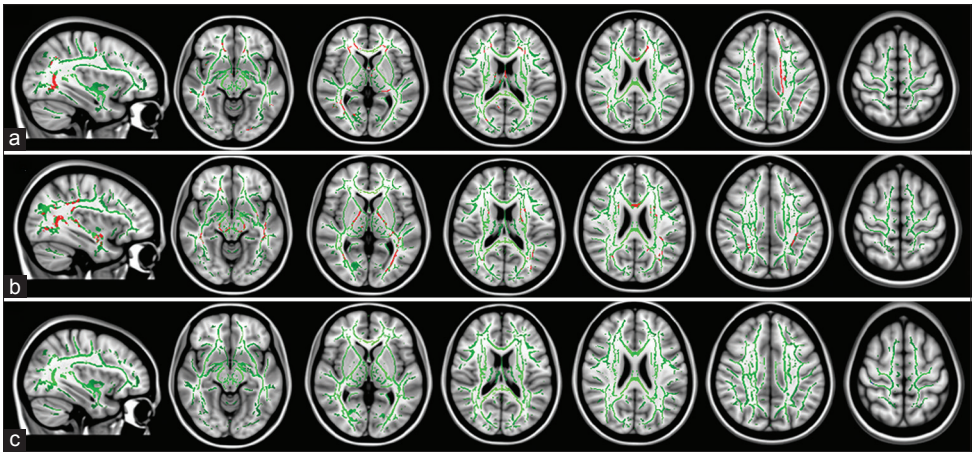

Figure 3: TBSS analysis results in chronic phase overlaid on sagittal and axial views of the FA template. PR patients versus SR patients (a); PR patients versus controls (b); and SR patients versus controls (c). There was a significant difference between every two groups. The red areas were to show the decreased FA value areas. Clusters were significant at $P < 0.05$, corrected for multiple comparisons. The skeleton is shown in green. TBSS: Tract-based spatial statistics; FA: Fractional anisotropy; PR: Poor recovery; SR: Successful recovery.

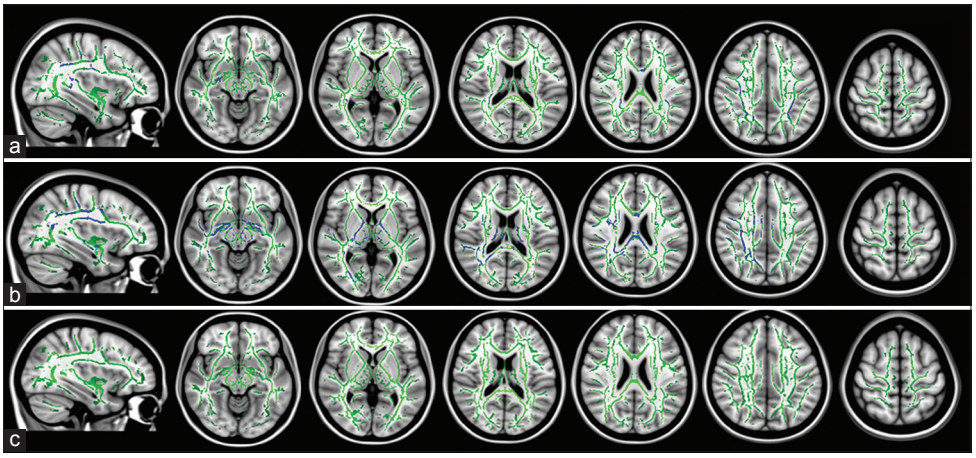

Figure 4: TBSS analysis results in chronic phase overlaid on sagittal and axial views of the MD template. PR patients versus SR patients (a); PR patients versus controls (b); and SR patients versus controls (c). There was a significant difference between every two groups. The blue areas were to show the decreased MD value areas. Clusters were significant at $P < 0.05$, corrected for multiple comparisons. The skeleton is shown in green. TBSS: Tract-based spatial statistics; MD: Mean diffusivity; PR: Poor recovery; SR: Successful recovery.

and PR patients in the 12 regions (genu of CC, splenium of CC, bilateral SLF, bilateral IFF, bilateral ATR, bilateral CT, left ILF, and left UF). The mean of the MD values was significantly higher for PR patients than for SR and control groups (all $P < 0.05$). A Bayesian discriminant analysis that calculated the posterior probability using bootstrap cross-validation was used to test the predictive classification accuracy. The application of the MD values in subacute phase allowed discrimination between PR and SR groups with a sensitivity of 73% and a specificity of 78%, resulting in an accuracy of 75.56%, using the threshold as $P = 0.50$. Applying the same analysis method, FA values did not show discriminative significance.

Discussion

The present results suggest that microstructural changes of WM during the development of mTBI/PTSD, as measured by TBSS analysis. Compared with healthy controls, acutely elevated FA and chronically reduced FA/increased MD in multiple WM regions were found in mTBI/PTSD patients, which is consistent with a previous DTI study.[13] It is often reported that there is reduced FA following mTBI, reflecting disrupted integrity of WM fiber bundles with accompanying freer water dispersion, due to cellular and axonal damage.[18] Increased FA in acute injury may result from vasogenic and/or cytotoxic edema and localized inflammatory responses, which may follow a more prolonged course in human TBI than in the animal models of TBI, peaking between 24 and 48 h postinjury and persisting for days postinjury.[19,20] However, there was no FA or MD difference between the PR and SR patients in the acute phase.

In the subacute phase, patients of the PR group had multiple WM regions with an increased MD, compared with SR patients and controls, which are supported by previous studies for patients with PTSD, who demonstrated MD increase in subacute phase, following mTBI.[21,22] The result

Table 4: Anatomic location of significant FA decrease in mTBI patients in chronic phase when comparing PR patients with SR patients and controls

Brain regions	Hemisphere	MNI coordinates (mm)			Voxel	*t*	*P*
		X	Y	Z			
PR compared with SR							
SLF	Right	38	−7	47	87	3.504	0.016
Superior corona radiate	Right	19	3	39	99	3.527	0.014
Superior corona radiate	Left	−17	−8	37	748	3.521	0.014
IFF	Right	23	38	4	787	3.519	0.014
IFF	Left	−23	33	8	560	3.520	0.014
ILF	Right	35	−58	0	323	3.497	0.016
ILF	Left	−21	−87	−3	94	3.384	0.036
Inferior cerebellar peduncle	Right	12	−42	−38	92	3.381	0.036
Genu of corpus callosum		11	−5	13	190	3.371	0.022
Splenium of corpus callosum	Right	23	−84	8	93	3.410	0.036
ATR	Right	2	−19	−31	85	3.502	0.038
ATR	Left	−9	−8	14	175	3.511	0.032
CT	Right	9	−61	−32	207	3.542	0.016
Cingulum (cingulate gyrus)	Right	10	−54	15	87	3.397	0.037
PR compared with controls							
SLF	Right	32	−48	30	89	3.104	0.035
SLF	Left	−35	−39	22	412	3.270	0.027
Superior cerebellar peduncle	Left	−5	−30	−21	86	3.015	0.035
Splenium of corpus callosum	Left	−16	−53	21	87	3.019	0.035
IFF	Right	29	−64	24	85	3.101	0.035
IFF	Left	−22	−76	14	87	3.106	0.035
ILF	Left	−40	−10	−22	268	3.284	0.026
Genu of corpus callosum		17	37	−8	89	3.108	0.035
Splenium of corpus callosum		32	−64	0	645	3.296	0.025
ATR	Right	9	−20	2	88	3.102	0.035
ATR	Left	−34	−59	9	1934	3.301	0.013
Anterior corona radiata	Left	−26	17	27	86	3.012	0.035
CT	Left	−19	−16	−7	1052	3.306	0.013
Corticospinal tract	Right	8	−25	−9	973	3.302	0.015

FA: Fractional anisotropy; mTBI: Mild traumatic brain injury; PR: Poor recovery; SR: Successful recovery; MNI: Montreal Neurological Institute; IFF: Inferior fronto-occipital fasciculus; SLF: Superior longitudinal fasciculus; ILF: Inferior longitudinal fasciculus; ATR: Anterior thalamic radiation; CT: Corticospinal tract.

may suggest cerebral edema occurs in relatively serious mTBI patients in this phase. Without timely intervention, it may become one of the pathogeneses of PTSD. However, no FA value difference was found between the three groups in the subacute phase, which may be an apparent normalization. One possible explanation may be the combination effect of cytotoxic edema and axonal injury. In addition, it has also been established that most patients with low-level head injury recover fully over time,[23] which may indicate that delayed axonal recovery or axonal regrowth in some extent is possible, as reviewed by Povlishock and Katz.[24]

Furthermore, decreased FA and increased MD mainly in CC, ILFs, and SLF were found in PR group, compared with SR patients and controls in the chronic phase. The observed decrease in FA values may reflect the barriers to axoplasmic transport, the local accumulation of apoptosis in organelles, and secondary Wallerian degeneration in the WM, while the increased MD values may be the result of vasogenic edema. Recent evidence suggests that TBI may induce long-term neurodegenerative processes, such as concealed progressive axonal pathology.[25] Thus, the current findings may suggest axonal degeneration as well as misalignment of fibers in the chronic stage of the disease. It might be the final pathological changes in brain WM of mTBI/PTSD patients. In a recent resting-state fMRI study,[26] functional discrepancy of local coherence between cortical and subcortical regions was identified in PTSD patients. The chronic changes of the microstructural integrity of WM in the present study may be strongly related to behavioral and emotional disorders in PTSD patients.[27]

Predicting the patients who are more prone to suffering with protracted adverse cognitive changes is important,[28] as early pharmacological intervention has been shown to reduce the risks of PSTD.[29] In previous studies, FA value tends to be more sensitive than other DTI indexes for assessing the microstructural integrity and cognitive function after traumatic axonal injury.[30] However, no significant FA difference was found in PTSD patients

Table 5: Anatomic location of significant MD increase in mTBI patients in chronic phase when comparing PR patients with SR patients and controls

Brain regions	Hemisphere	MNI coordinates (mm)			Voxel	*t*	*P*
		X	Y	Z			
PR compared with SR							
SLF	Right	31	−51	34	4108	2.608	0.015
SLF	Left	−36	−39	23	3364	2.594	0.015
IFF	Right	17	10	5	88	3.214	0.038
IFF	Left	−20	36	−6	91	3.207	0.039
ATR	Left	−5	−30	−20	487	3.016	0.025
Corticospinal tract	Left	−3	−23	−13	93	3.284	0.035
UF	Left	−22	17	−10	85	3.281	0.035
PR compared with controls							
SLF	Right	43	17	17	85	3.249	0.037
SLF	Left	−60	−49	34	93	3.216	0.037
IFF	Right	26	16	−11	88	3.232	0.037
Inferior longitudinal fasciculus	Right	38	−73	27	92	3.214	0.038
Genu of corpus callosum		18	40	28	87	3.215	0.038
Splenium of corpus callosum		23	−93	6	85	3.274	0.038
ATR	Right	28	45	2	87	3.291	0.039
Cingulum (hippocampus)	Left	−19	−42	−2	89	3.294	0.038
UF	Right	28	45	−6	94	3.287	0.038
Uncinate fasciculus	Left	−12	28	49	87	3.272	0.038

FA: Fractional anisotropy; mTBI: Mild traumatic brain injury; PR: Poor recovery; SR: Successful recovery; MNI: Montreal Neurological Institute; IFF: Inferior fronto-occipital fasciculus; UF: Uncinate fasciculus; SLF: Superior longitudinal fasciculus; ATR: Anterior thalamic radiation.

during the acute and subacute phase in the present study, which is important for disease intervention and recovery. Presumably, it is because FA values are influenced by combined factors of axonal and myelin pathology, while the pathology of mTBI is too diversified in nature to cause changes in FA values. The present study demonstrates that there was a trend toward significance for WM MD changes and the mTBI patients with PSTD at the subacute phase after injury, which is in agreement with a previous DTI study.[21] It is likely that only MD, among these affected fiber tracts' abnormalities, in the subacute phase may help to identify mTBI patients with an increased risk of PTSD. It must be emphasized, however, the sensitivity, specificity, and accuracy of classification were relatively modest according to the discriminant analysis result – likely a result of the considerable variability that was present across both SR and PR groups. If there are small changes in FA and MD, it would be expected in a small sample size, such as the present study's subject population of mTBI patients; only MD group differences would be detectable with a small sample size.[31] Furthermore, as injury severity increased, FA emerged and became a more indicative parameter for the structural damage group.[32]

There are several potential limitations in our study. First, the sample size of mTBI patients is relatively small, and our findings require replication in larger samples so that relations between DTI metrics and PTSD can be confirmed. Second, in our study, causes of head injury included traffic crash, aggression-related blows, and falls. There is a need to further research different external causes of mild contribute differentially to the development of PTSD. Third, no histologic correlation of DTI findings was available, although our findings suggest that DTI may provide biological insights into mTBI and may help identify mTBI patients who have an increased risk of PTSD.

The present study revealed a significant alteration in the DTI metrics for a group of patients with mTBI, spanning the acute to chronic phases. These changes were highly correlated with PTSD. MD measurements appear to be a relatively better predictive biomarker in the subacute phase, which may render an ideal mechanism for monitoring potential changes associated with PTSD. This may be beneficial in the management of patients with mTBI since early diagnosis and treatment may reduce the risks of PTSD.

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Conflicts of interest

There are no conflicts of interest.

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