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Alterations in microstructure and local fiber orientation of the white matter are associated with outcome following mild traumatic brain injury

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Abstract

Mild traumatic brain injury (mTBI) can result in long-lasting consequences. We investigated white matter (WM) alterations at 6-12 months following mTBI using diffusion tensor imaging and assessed if the alterations associate with outcome.

Eighty-five patients with mTBI underwent diffusion-weighted MRI on average eight months post-injury and patients' outcome was assessed at the time of imaging using extended Glasgow outcome scale. Additionally, thirty age-matched patients with extracranial orthopedic injuries were used as control subjects. Voxel-wise analysis of the data was performed using tract-based spatial statistics approach and differences in microstructural metrics between groups were investigated. Furthermore, the susceptibility of the abnormalities to specific fiber orientations was investigated by analyzing the first eigenvector of the diffusion tensor in the voxels with significant differences.

We found significantly lower fractional anisotropy and higher mean and radial diffusivity in patients with mTBI compared to control subjects while no significant differences were observed in axial diffusivity between the groups. The differences were present bilaterally in several WM regions and correlated with outcome. Moreover, multiple clusters were found in the principal fiber orientations of the significant voxels in anisotropy, and similar orientation patterns were found for the diffusivity metrics. These directional clusters correlated with patients' functional outcome.

Our study showed that mTBI is associated with WM changes at the chronic stage and these alterations occur in several WM regions. In addition, several significant clusters of WM alterations in specific fiber orientations were found and these clusters were associated with outcome.

Keywords: Diffusion tensor imaging; mild traumatic brain injury; tract-based spatial statistics; outcome

Abbreviations

- AD = Axial Diffusivity
- CC = Corpus callosum
- DAI = Diffuse Axonal Injury
- DTI = Diffusion Tensor Imaging
- DW-MR = diffusion-weighted magnetic resonance
- FA = Fractional Anisotropy
- FDR = False discovery rate
- FWE = Family-Wise Error
- GCS = Glasgow Coma Scale
- GOSe = Extended Glasgow Outcome Scale
- MD = Mean Diffusivity
- mTBI = Mild Traumatic Brain Injury
- ROI = Region of interest
- RD = Radial Diffusivity
- TBI = Traumatic Brain Injury
- TBSS = Tract-Based Spatial Statistics
- WM = white matter

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability especially among youth ^{1,2}. TBI is defined as any injury to the head by an external force leading to alteration in brain function or structure ³. Almost 80% of TBI cases are classified as mild (mTBI) ⁴ but even mTBI can be a disabling injury with sometimes lifelong consequences ². Conventional brain imaging methods such as CT or structural MRI, such as T1, T2 or fluid attenuated inversion recovery (FLAIR) imaging may be unable to detect subtle changes associated with TBI such as diffuse axonal injury (DAI) ⁵⁻⁹, and may also inadequately localize the injury ^{10,11}. Diffusion weighted (DW-MRI) techniques such as diffusion tensor imaging (DTI) ^{12,13} are more sensitive in detecting subtle white matter (WM) damage following TBI such as DAI. Mechanism of DAI is suggested to be the axonal damage caused by rapid head movements ^{14,15}. Furthermore, biomechanical computational models suggest that the orientation of the WM fibers could be an injury predictor in patients with mTBI ^{16,17}.

DW-MRI methods are promising imaging markers for TBI ^{6,8,18-23}. More specifically, WM damage can be quantified with several DTI measures such as fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD). The anisotropy and diffusivity measures are shown to be capable of characterizing WM microstructural properties quantitatively *in vivo* ²⁴⁻²⁷.

Many studies have reported reduced FA and/or increased diffusivity in acute or sub-acute TBI, including mTBI ²⁸⁻³⁵. Anisotropy changes have been reported to vary based on imaging time post-injury ³⁶ and studies suggest that the reduction of FA evolves over time after TBI ^{19,37,38}. Several studies demonstrated decreased anisotropy and elevated diffusivity also at the chronic phase of mTBI ³⁹⁻⁴². Most of the aforementioned studies looked at a defined number of locations in the brain. However, due to the complexity and individuality of TBI, it is challenging to define precisely where to look for traumatic alterations in the brain ⁴³. It is of note, that a global whole-brain approach, either solely or along with

region of interest (ROI) analyses, has also been used in some studies to investigate WM abnormalities following TBI without taking any specific brain region as a priori into account ⁴⁴⁻⁴⁶.

In this study, we assessed WM alterations following mTBI using DTI. We compared patients with mTBI in 6-12 months post-injury i.e. chronic stage and orthopedically injured (OI) controls. In addition, we investigated directional susceptibility of these alterations to investigate at which orientations diffusivity and anisotropy changes most often occur. Furthermore, we assessed the association of WM changes with patients' outcome.

Materials and methods

Subjects

During the EU-funded international TBICare (Evidence-based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries) project, 85 prospectively recruited patients with mTBI (mean age = 47, range = 66 years, min-max [18-84] years) underwent DW-MRI in Turku, Finland from on average, 8 months after the injury (mean imaging time = 251, range = 356 days, min-max [100-456] days) (Table 1). In addition, 30 control subjects with acute extracranial orthopedic injuries without acute or previous brain disorders (mean age = 50, range = 68 years, min-max [22-90] years) were recruited (Table 1). The Ethical Committee of the Hospital district of South-West Finland approved the study protocol (decision 68/180/2011). All patients or their next of kin were informed about the study in both oral and written form. A written informed consent was obtained according to the World Medical Association's Declaration of Helsinki.

Inclusion criteria were as follows: age ≥ 18 years, clinical diagnosis of mTBI (see below) and indications for acute head CT according to NICE criteria (<http://www.nice.org.uk/guidance/cg176>). Exclusion criteria were: blast-induced or penetrating injury, chronic subdural hematoma, inability to live independently due to pre-existing brain disease, TBI or suspected TBI not needing head CT, more than two weeks from the injury, not speaking native language, and no consent obtained. Extracranial

orthopedic injuries were permitted in the mTBI patient group. The control group consisted of patients with acute orthopedic non-trivial trauma without any signs of acute central nervous system involvement, previous central nervous system disease, or history of previous TBI excluding concussions not related to a current episode of hospitalization. All patients with any signs or suspicions of an injury to the head or neck, patients with multiple trauma or high-energy injuries or patients in need of intensive care were excluded from the control group.

Patients presenting with Glasgow Coma Scale (GCS) scores of 13–15 were considered as having an mTBI. GCS in the scene of accident assessed by paramedics or an emergency physician were retrieved from the ambulance sheets. GCS scores at the emergency department of Turku University Hospital were assessed upon admission. Lowest recorded GCS was used to classify the patients^{47,48}.

Fazekas grading⁴⁹ is a potential indicator of small vessel disease in the brain and it was used in our study to account for WM hyperintensities. All included patients had Glasgow Outcome Scale Extended (GOSE) scores⁵⁰ assessed at the time of MR imaging 6–12 months post-injury [assessed by an experienced neurologist (OT), who was blinded to DTI results]. No dichotomization to different outcome classes was used.

MRI acquisition

MR imaging was performed using a Siemens 3T MRI scanner (Magnetom Verio 3T, Siemens Healthcare, Erlangen, Germany). We acquired axial DW-MRI images by using a spin-echo echo-planar imaging sequence with the FOV of 192×192 mm, TE of 106 ms, TR of 11.7 s, which resulted in images with a $2 \times 2 \times 2$ mm voxel size and 77 axial slices. Diffusion-weighted data were acquired with a b-value of 1000 s/mm^2 in 64 gradient orientations. Additionally, susceptibility-weighted imaging (SWI) and FLAIR images were obtained and were further used to assess WM hyperintensities by an expert neuroradiologist (J.H).

DTI processing

DW-MR images were analyzed using tract-based spatial statistics (TBSS) voxel-wise method in FMRIB Software Library (FSL) ⁵¹. Subject motion and eddy current induced distortions were corrected using ExploreDTI ^{52,53}. Since all subjects in this study were adults, FA images were registered non-linearly to the FMRIB_FA template as recommended by FSL’s user guide. Then, FA, MD, AD and RD were calculated along the WM skeleton. Statistical analysis of the TBSS results was performed using age, gender, and Fazekas as covariates with the *randomise* tool ⁵⁴ in FSL, and 5000 permutations were performed using threshold-free cluster enhancement ⁵⁵. To differentiate between the possible effect of the WM hyperintensities and the trauma-related effects, we repeated the statistical analyses in the patients with mTBI without WM hyperintensities (49 patients with Fazekas grade 0) compared to the orthopedic control subjects (21 orthopedic controls with Fazekas grade 0). All of the analyses were corrected for multiple comparisons using family-wise error rate (FWE). The microstructural properties of the significant clusters detected with TBSS and containing 10 voxels or more were analyzed in more detail using the JHU ICBM DTI-based WM atlas ⁵⁶. Average values of the anisotropy and diffusion metrics were calculated within each cluster and associations between these values and GOS were investigated. In addition to the TBSS analysis, an ROI-based analysis was performed to investigate WM abnormalities in all WM regions defined by the JHU ICBM DTI-based WM atlas.

Directional analyses

The principal fiber orientation of the WM abnormalities was further investigated by analyzing the first eigenvector of the diffusion tensor in the voxels with significant (FWE-corrected p-value < 0.05) changes in anisotropy and diffusivity measures. The eigenvectors were projected to the mean WM skeleton by using TBSS ⁵¹, after which the principal eigenvectors were rotated to account for changes in the imaging orientation between subjects prior to calculating the average orientation of the diffusion

tensor in each of the significant voxels. To visualize the results, the frequency of the significant voxels was then mapped onto a unit spherical surface based on the sample-wise average first eigenvector, thus giving more specific information about the susceptibility of the microstructural abnormalities to specific WM fiber orientations. K-means Clustering method was then used to create clusters based on the directionality. The optimal number of clusters was calculated as $k=4$ using the Silhouettes method⁵⁷. Average anisotropy and diffusivity metrics in all of the direction-dependent clusters were calculated in each patient and the associations of these values and patients' outcome were investigated.

Statistical analyses

The normality of the data was assessed using the Kolmogorov-Smirnov test. Homogeneity of variance was evaluated using Levene's test for continuous variables. Age, time of scan post-injury, and diffusion measures were considered as continuous variables and gender was treated as a nominal variable in all the analyses. Furthermore, Fazekas score and GOSE were considered as ordinal variables.

The difference in gender and Fazekas score between groups was assessed using Chi-square test. The age difference between the two groups was compared using an independent t-test.

Generalized linear model was used to compare anisotropy and diffusivity measures between patients and controls in different brain regions. Statistical analyses were performed using IBM SPSS (version 25, IBM, New York, NY), MATLAB (Mathworks, MA, USA). Age, gender, and Fazekas score were used as covariates in all statistical analyses, and a confidence interval of 95% was considered to evaluate the significance of the results. Moreover, results were corrected for multiple comparisons using the false discovery rate (FDR). Partial Spearman's correlation was performed to investigate the relationships between anisotropy and diffusivity metrics with GOSe. Additionally, a group-level analysis with bootstrapping was performed to compare the relationship between anisotropy and diffusivity measures with GOSE in patients with $\text{GOSE} \geq 7$ and $\text{GOSE} < 7$. This group-level analysis was performed to adjust for the unevenness of GOSE among the patients with mTBI.

Results

Comparison of anisotropy and diffusivity measures between patients with mTBI and OI controls

Tract-based spatial statistics

Patients with mTBI showed significantly lower FA compared to controls along the WM skeleton (Figure 1). In addition, MD and RD were significantly higher in patients with mTBI compared to controls in many WM regions (Figure 1). No difference was found in AD between patients and controls. The significant clusters were further analyzed using the JHU WM atlas and regions belonging to each cluster are defined (Supplementary Tables 1-3). To differentiate between differences related to small vessel disease and the traumatic brain injury, we performed additional statistical analyses in patients with mTBI without any WM hyperintensities compared to the control subjects without any WM hyperintensities (Fazekas grade 0). The differences in MD and RD remained significant, but there were no differences in FA (Figure 2).

Region of interest analyses

ROI-based analyses showed lower anisotropy and higher diffusivity in numerous WM regions in patients with mTBI compared with OI controls. Furthermore, patients with mTBI had lower FA in pontine crossing tract ($p = 0.044$), superior corona radiata R ($p = 0.017$), and cingulum (hippocampus) R ($p = 0.048$) (Supplementary Table 4). Higher MD, RD, and AD were observed in patients with mTBI compared with OI controls in the middle cerebellar peduncle, pontine crossing tract, superior cerebellar peduncle (L, R), corticospinal tract L, inferior cerebellar peduncle R, external capsule (R, L), cingulum (hippocampus) L, uncinate fasciculus R (Supplementary Table 4). Although lower anisotropy and higher diffusivity measures were found in patients with mTBI compared to OI controls, none of the statistically significant results could survive FDR method when corrected for the number of regions ($N=48$) by using age, gender, and Fazekas score as covariates in statistical analyses. Details of these measures in each of the 48 studies ROIs are demonstrated in Supplementary Table 4.

Directional analysis

The directional analysis was performed to describe in more detail the principal orientation of the diffusion tensor in the significant voxels of the WM skeleton. We found 4 distinguished clusters within the WM skeleton voxels that had similar average fiber orientations. These directional-dependent clusters of significant changes were similar in FA, MD, and RD, as shown in (Figure 3).

Association with outcome

After correcting for multiple comparisons, FA showed weak positive association with outcome in the left cerebral peduncle (Spearman's $\rho = 0.2$, $p = 0.009$) and left retrolenticular part of internal capsule (Spearman's $\rho = 0.34$, $p = 0.002$); MD showed negative weak association with outcome in the left superior longitudinal fasciculus (Spearman's $\rho = -0.35$, $p = 0.001$); RD showed negative weak association with outcome in the right posterior limb of internal capsule (Spearman's $\rho = -0.4$, $p < 0.001$), left cingulum (cingulate gyrus) (Spearman's $\rho = -0.37$, $p = 0.001$), and the left superior longitudinal fasciculus (Spearman's $\rho = -0.39$, $p < 0.001$).

In the group-level analysis, patients with mTBI with GOSE ≥ 7 showed significantly lower RD in left superior longitudinal fasciculus ($p < 0.001$) and the left cingulum (cingulate gyrus) ($p < 0.001$) after correcting for multiple comparisons using FDR (Supplementary Figure 1).

Furthermore, higher FA and lower MD and RD were moderately associated with better outcome in all clusters that have similar average fiber orientations. FA was positively correlated with GOSe in orientation-dependent clusters with Spearman's ρ values of 0.46, 0.45, 0.45, and 0.45 for clusters 1, 2, 3, and 4 respectively. Lower MD was moderately associated with better outcome (Spearman's ρ values of -0.48, -0.42, -0.37, and -0.45). Similarly, RD showed negative moderate association with GOSe (Spearman's ρ values of -0.53, -0.50, -0.51, and -0.53).

Discussion

We found WM abnormalities in several brain regions in patients with chronic mTBI compared to OI controls. Patients with mTBI had lower FA and higher MD and RD values compared to controls. No significant differences were found between patients and controls in AD, suggesting that diffusivity is more increased in perpendicular direction rather than along the axons. Higher FA, lower MD, and lower RD were weakly or moderately associated with better outcome in patients with mTBI. Furthermore, four directional dependent clusters were found indicating that WM alterations following mTBI were more prominent in specific fiber orientations. Similar associations were observed in FA, MD, and RD with patients' outcome in all the directional-dependent clusters. Higher anisotropy and lower diffusivity were weakly or moderately associated with better outcome.

Our results of finding lower anisotropy as well as higher diffusivity measures are in accordance with previous studies^{40,41,45,58}. Decreased FA may reflect compromised myelination and axonal integrity^{24,59-62}, or alternatively, reduced density of myelinated axons⁶³. Demyelination is shown to attribute to increased RD at the chronic stage²¹. Thus, our findings may indicate axonal degeneration⁶¹, and demyelination⁶⁴ in the chronic stage of mTBI²¹. Microstructural changes observed in the chronic stage of the injury could also indicate a combination of primary and secondary injury caused by Wallerian degeneration^{11,65}.

WM abnormalities were identified in numerous brain regions by diffusion measurements using either TBSS or ROI-based approach. Several of these regions such as corpus callosum (CC), internal/external capsule, and corona radiata are among commonly found brain regions that are known to be susceptible to brain injury and are often reported by researchers to be affected after TBI^{66,67}. Inglese et al has showed that CC and external capsule are affected following mTBI⁶⁸. Furthermore, CC consisting of genu, body, and splenium has been in particular, of interest in TBI research and it is shown that the splenium part of the CC is affected more than body or genu^{66,69}. The susceptibility of these regions to

brain injury stems from the structural relationship that these regions have with the skull and other brain structures e.g. the relationship between CC and falx cerebri ^{69,70}.

No differences were found in FA between patients with mTBI and OI controls with the Fazekas score of zero. This difference compared to the whole sample may be due to smaller sample size, but could also indicate that the differences in FA were related to the WM hyperintensities. To verify this, we compared the results using a stricter significance threshold in the whole sample to the results with the smaller sample size. The results concerning the FA, MD, and RD in the whole sample using a lower significant threshold of $P < 0.025$ are similar to the results in the smaller sample without WM hyperintensities (using $P < 0.05$), which indicates that the differences in the results may indeed be related to the different sample size. Directional susceptibility analysis showed four orientation-dependent clusters in which WM changes were present. However, more studies are necessary to investigate whether this was due to the prevalence of these orientations in the FA skeleton or an indication of directional susceptibility of the WM alterations related to mTBI.

DTI methods suffer from limitations such as susceptibility to partial volume effects and incapability of detecting complex fiber configurations ^{71–74}. TBSS approach can, however, reduce the partial volume effects related to non-WM signal through the use of a skeletonization technique ⁴³. Other limitations in TBSS have been thoroughly discussed in Bach et al ⁷⁵. Recently, it has also been suggested that using healthy controls rather than patients with acute orthopedic injuries would lead to a better detection of microstructural differences between patients and controls ⁷⁶.

Better understanding of the processes involved in axonal injury could be one step ahead to facilitate accurate prediction of prognosis of TBI. Recent methodological advances, such as multi-shell diffusion MRI methods ^{77–79}, and fiber-specific measures for density ⁸⁰, may provide more specific information about the underlying pathophysiology. However, majority of these methods are not suitable for the single-shell data used in this study.

Studying a well-characterized patient cohort is one important strength of this study. During the prospective recruitment process, the inclusion and exclusion criteria for patients with mTBI and orthopedic controls were rigorously controlled. In case of patients with mTBI, we excluded patients in whom the TBI criteria were uncertain because of confounders, whereas in case of orthopedic controls, we excluded patients who had any signs (post-traumatic amnesia, loss of consciousness or confusion) or suspicions of head injuries. The presence of any kind of indirect impacts on the head cannot be completely excluded, but given the clinical reality, the control group can be considered as appropriate non-TBI control group with orthopedic injuries as possible. However, with regard to the study limitations, it is noteworthy to mention that the current cohort of patients with mTBI, cannot be considered to represent cases with mTBI on a larger scale because the mildest cases were often discharged before possibility for recruitment and we only recruited those with presenting with indications for head CT. There were even five patients who presented with intracranial mass lesions necessitating hematoma evacuation later but had GCS of 13-15 as their worst score upon admission, thus meeting the criteria for mTBI. As another limitation, we only correlated the WM changes with functional outcome using the GOS-e scale. Correlating the alterations in the WM with psychiatric symptoms and neuropsychological test results would have perhaps revealed interesting associations, but we consider these analyses to be beyond the scope of this article.

Conclusion

In conclusion, our study showed that mTBI is weakly or moderately associated with WM changes following mTBI. The changes in the chronic stage were present bilaterally in several WM regions, most prominently in CC, internal and external capsule, and corona radiata. Furthermore, we showed that these WM changes are weakly or moderately associated with long term outcome.

In addition, several significant clusters of WM alterations in specific fiber orientations were found and these orientation-dependent clusters correlated with outcome. This suggests that WM alterations following mTBI are susceptible to the average fiber orientation.

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Figure legends

Figure 1. Voxel-wise analysis of diffusion-weighted images shows significantly decreased fractional anisotropy (FA) and increased mean (MD) and radial diffusivity (RD) in patients with mild traumatic brain injury in the chronic stage compared with orthopedically injured controls. Significant voxels are overlaid on T₁-weighted MR image.

Figure 2. Voxel-wise analysis of diffusion-weighted images shows significantly increased mean (MD) and radial diffusivity (RD) in patients with mild traumatic brain injury without any WM hyperintensities in the chronic stage compared with orthopedically injured controls. Significant voxels are overlaid on the T₁-weighted MR image.

Figure 3. Directional analysis of the significant microstructural differences in the chronic stage of TBI compared to control subjects. The number of voxels within the white matter skeleton that showed significant differences between patients with mild TBI and controls, is mapped onto the unit sphere according to the principal fiber orientation in the corresponding voxel. Using k-means clustering method, four distinguished clusters of significant changes in fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) are found that have similar fiber orientations. Anterior-Posterior (A-P); Left-Right (L-R); Superior-Inferior (S-I).

Table 1: Demographic and characteristics of mild traumatic brain injury and orthopedic control subjects.

Characteristic	mTBI (n=85)	Orthopedic controls (n=30)	P-value
Age (mean[SD] years)	47 (20)	50 (20)	0.472*
(min – max)	(18 – 84)	(22 – 90)	
Sex (number[%])			0.026**
Male	59 (69)	14 (46.7)	
Female	26 (31)	16 (53.3)	
Glasgow Coma Scale (number[%])			
GCS = 13	3 (3.5)	-	
GCS = 14	21 (24.7)	-	
GCS = 15	61 (71.8)	-	

Cause of injury (number[%])

Road Traffic accident	27 (31.8)	-
Incident fall	43 (50.6)	-
Other non-intentional injury	5 (5.9)	-
Violence/assault	8 (9.4)	-
Other	2 (2.4)	-

Marshall grade (number[%])

No visible pathology	48 (56.5)
Diffuse injury II	22 (28.2)
Diffuse injury III (swelling)	2 (2.4)
Diffuse injury IV (shift)	1 (1.2)

Evacuated mass lesion 5 (5.9)

Non-evacuated mass lesion 5 (5.9)

extended Glasgow Outcome Scale (GOSE)

GOSE = 8 31 (36.5) -

GOSE = 7 29 (34.1) -

GOSE = 6 11 (12.9) -

GOSE = 5 3 (3.5) -

GOSE = 4 5 (5.9) -

GOSE = 3 5 (5.9) -

Missing 1 (1.2) -

WM hyperintensity Fazekas score (number[%])

Absent	49 (57.6)	21 (70)	0.50**
Punctate foci	17 (20)	6 (20)	
Beginning confluence	14 (16.5)	2 (6.7)	
Large confluent areas	5 (5.9)	1 (3.3)	

*student t-test significance; ** Chi-square significance.

Figure 1. Voxel-wise analysis of diffusion-weighted images shows significantly decreased fractional anisotropy (FA) and increased mean (MD) and radial diffusivity (RD) in patients with mild traumatic brain injury in the chronic stage compared with orthopedically injured controls. Significant voxels are overlaid on T1-weighted MR image.

193x171mm (600 x 600 DPI)

Figure 2. Voxel-wise analysis of diffusion-weighted images shows significantly increased mean (MD) and radial diffusivity (RD) in patients with mild traumatic brain injury without any WM hyperintensities in the chronic stage compared with orthopedically injured controls. Significant voxels are overlaid on the T1-weighted MR image.

262x187mm (600 x 600 DPI)

Figure 3. Directional analysis of the significant microstructural differences in the chronic stage of TBI compared to control subjects. The number of voxels within the white matter skeleton that showed significant differences between patients with mild TBI and controls, is mapped onto the unit sphere according to the principal fiber orientation in the corresponding voxel. Using k-means clustering method, four distinguished clusters of significant changes in fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) are found that have similar fiber orientations. Anterior-Posterior (A-P); Left-Right (L-R); Superior-Inferior (S-I).

508x255mm (96 x 96 DPI)

Supplementary Table 1: The brain regions in the clusters with significant differences in fractional anisotropy ($P < 0.05$, corrected for family-wise error rate) between patients with mild traumatic brain injury in the chronic stage and orthopedic control subject in tract-based spatial statistics analysis. The regions according to JHU white matter atlas with at least 5 % cluster volume or peak significance are included in the table.

Cluster size (voxels)	Regions in the cluster (% of the cluster)	mTBI	Control	P-value
2654	Superior corona radiata L* (12.96)	0.521 ± 0.082	0.60 ± 0.08	0.031
	Body of corpus callosum (33.04)			
	Splenium of corpus callosum (26.04)			
	Superior corona radiata R (14.62)			
	Posterior corona radiata R(6.29)			
1937	Retrolenticular part of internal capsule L* (11.15)	0.60 ± 0.07	0.64 ± 0.07	0.034
	Anterior limb of internal capsule L (12.91)			
	Posterior limb of internal capsule L (21.22)			

	Superior corona radiata L (11.20)			
	External capsule L (29.32)			
469	Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) L* (57.99)	0.63 ± 0.08	0.68 ± 0.07	0.037
	Posterior thalamic radiation (include optic radiation) L (39.87)			
310	Superior longitudinal fasciculus L* (100)	0.48 ± 0.09	0.52 ± 0.08	0.033
204	Retrolesional part of internal capsule L* (38.72)	0.64 ± 0.05	0.67 ± 0.06	0.034
	Posterior corona radiata L (27.45)			
	Posterior thalamic radiation (include optic radiation) L (33.82)			
168	Superior longitudinal fasciculus L*(100)	0.62 ± 0.09	0.68 ± 0.06	0.032
120	External capsule L* (90.83)	0.56 ± 0.08	0.59 ± 0.07	0.04
	Retrolesional part of internal capsule L (9.17)			
74	Cerebral peduncle L* (100)	0.74 ± 0.06	0.77 ± 0.04	0.038
34	Anterior limb of internal capsule L* (100)	0.35 ± 0.07	0.39 ± 0.09	0.039

24	Splenium of corpus callosum* (100)	0.68 ± 0.06	0.72 ± 0.06	0.037
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* Region with the maximum significance in the cluster.

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Supplementary Table 2: The brain regions in the clusters with significant differences in mean diffusivity ($P < 0.05$, corrected for family-wise error rate) between patients with mild traumatic brain injury in the chronic stage and orthopedic control subject in tract-based spatial statistics analysis. The regions according to JHU white matter atlas with at least 5 % cluster volume or peak significance are included in the table.

Cluster size (#voxels)	Regions in the cluster (% of the cluster)	mTBI ($\times 10^{-3}$ mm ² /s)	Control ($\times 10^{-3}$ mm ² /s)	P-value
5933	Uncinate fasciculus L* (0.89)	0.76 $\pm$ 0.11	0.69 $\pm$ 0.15	0.019
	Body of corpus callosum (12.54)			
	Splenium of corpus callosum (18.62)			
	Anterior limb of internal capsule L (7.26)			
	Posterior limb of internal capsule L (7.74)			
	Retrolenticular part of internal capsule L (6.69)			
	Anterior corona radiata L (9.00)			
	Superior corona radiata L (8.19)			
	Posterior thalamic radiation (include optic radiation) L (0.62)			
	External capsule L (12.74)			
3379	Cerebral peduncle R* (6.51)	0.85 $\pm$ 0.12	0.79 $\pm$ 0.11	0.027
	Anterior limb of internal capsule R (8.35)			

	Posterior limb of internal capsule R (11.63)			
	Retrolenticular part of internal capsule R (9.06)			
	Anterior corona radiata R (14.80)			
	Superior corona radiata R (13.76)			
	External capsule R (16.54)			
740	Inferior cerebellar peduncle R* (18.65)	0.73 ± 0.10	0.65 ± 0.10	0.024
	Middle cerebellar peduncle (53.92)			
	Medial lemniscus R (4.60)			
	Superior cerebellar peduncle R (22.84)			
655	Middle cerebellar peduncle* (74.81)	0.61 ± 0.06	0.54 ± 0.06	0.033
	Inferior cerebellar peduncle L (20.46)			
	Superior cerebellar peduncle L (4.73)			
217	Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) L* (95.85)	0.77 ± 0.11	0.71 ± 0.10	0.020
162	Superior longitudinal fasciculus L* (100)	0.73 ± 0.10	0.70 ± 0.09	0.026

157	Superior longitudinal fasciculus L* (96.18)	0.71 ± 0.12	0.67 ± 0.12	0.035
113	Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) L* (1.77)	0.77 ± 0.11	0.73 ± 0.11	0.034
	Posterior thalamic radiation (include optic radiation) L (98.23)			
86	Superior cerebellar peduncle L* (86.05)	0.76 ± 0.08	0.71 ± 0.06	0.038
	Medial lemniscus L (13.95)			
77	Posterior thalamic radiation (include optic radiation) L* (100)	0.81 ± 0.14	0.77 ± 0.08	0.034
66	Superior longitudinal fasciculus L* (100)	0.70 ± 0.11	0.66 ± 0.10	0.037
53	Middle cerebellar peduncle* (81.13)	0.69 ± 0.09	0.65 ± 0.08	0.039
	Pontine crossing tract (a part of MCP) (18.88)			
48	Superior longitudinal fasciculus L* (100)	0.70 ± 0.10	0.66 ± 0.09	0.037
45	Anterior corona radiata R* (88.89)	0.78 ± 0.11	0.73 ± 0.10	0.038
	Genu of corpus callosum (11.11)			

41	Medial lemniscus R* (100)	0.73 ± 0.14	0.68 ± 0.14	0.039
20	Anterior corona radiata L* (100)	0.74 ± 0.09	0.70 ± 0.09	0.037
18	Superior longitudinal fasciculus L* (100)	0.71 ± 0.09	0.69 ± 0.09	0.038
17	Superior longitudinal fasciculus R* (100)	0.73 ± 0.08	0.67 ± 0.09	0.034
17	Anterior corona radiata R* (100)	0.73 ± 0.10	0.70 ± 0.10	0.035
17	Anterior limb of internal capsule L* (100)	0.77 ± 0.13	0.72 ± 0.13	0.031
16	Superior longitudinal fasciculus L* (100)	0.70 ± 0.12	0.66 ± 0.15	0.038
16	Posterior limb of internal capsule R* (100)	0.68 ± 0.08	0.63 ± 0.08	0.031
15	Superior longitudinal fasciculus L* (100)	0.71 ± 0.09	0.65 ± 0.08	0.037
14	Splenium of corpus callosum* (78.57)	0.82 ± 0.10	0.77 ± 0.11	0.034
	Posterior thalamic radiation (include optic radiation) L (21.43)			
13	Posterior corona radiata R* (100)	0.79 ± 0.11	0.75 ± 0.08	0.038

13	Cerebral peduncle R* (30.77)	0.72 ± 0.07	0.70 ± 0.05	0.036
	Posterior limb of internal capsule R (69.23)			
12	Anterior corona radiata L* (100)	0.73 ± 0.11	0.68 ± 0.10	0.042
10	Superior longitudinal fasciculus L* (100)	0.73 ± 0.11	0.69 ± 0.09	0.026
* Region with the maximum significance in the cluster.				

Supplementary Table 3: The brain regions in the clusters with significant differences in radial diffusivity ($P < 0.05$, corrected for family-wise error rate) between patients with mild traumatic brain injury in the chronic stage and orthopedic control subject in tract-based spatial statistics analysis. The regions according to JHU white matter atlas with at least 5 % cluster volume or peak significance are included in the table.

Cluster size (voxels)	Regions in the cluster ((% of the cluster)	mTBI ($\times 10^{-3} \text{ mm}^2/\text{s}$)	Control ($\times 10^{-3} \text{ mm}^2/\text{s}$)	P-value
8592	Uncinate fasciculus L* (0.65)	0.55 ± 0.11	0.49 ± 0.13	0.017
	Body of corpus callosum (9.23)			
	Splenium of corpus callosum (13.90)			
	Posterior limb of internal capsule L (5.96)			
	Anterior corona radiata L (7.68)			
	Superior corona radiata R (5.24)			
	Superior corona radiata L (7.29)			
	External capsule L (9.85)			
1225	Posterior limb of internal capsule R* (4.49)	0.39 ± 0.07	0.35 ± 0.09	0.033
	Anterior limb of internal capsule R (18.53)			
	Anterior corona radiata R (28.98)			

	Superior corona radiata R (17.47)			
	External capsule R (28.57)			
	Superior fronto-occipital fasciculus (could be a part of			
	anterior internal capsule) R (1.88)			
	Uncinate fasciculus R (0.08)			
310	Superior longitudinal fasciculus L* (98.39)	0.53 ± 0.10	0.49 ± 0.06	0.019
216	Superior longitudinal fasciculus L* (99.54)	0.44 ± 0.12	0.37 ± 0.07	0.019
204	Posterior thalamic radiation (include optic radiation)	0.49 ± 0.08	0.43 ± 0.08	0.042
	R* (78.92)			
	Sagittal stratum (include inferior longitudinal			
	fasciculus and inferior fronto-occipital fasciculus) R			
	(21.08)			
178	Cingulum (hippocampus) R* (100)	0.49 ± 0.10	0.43 ± 0.05	0.042
164	Superior cerebellar peduncle R* (17.68)	0.58 ± 0.13	0.50 ± 0.11	0.047
	Middle cerebellar peduncle (26.83)			

	Medial lemniscus R (6.71)			
	Inferior cerebellar peduncle R (48.78)			
147	Middle cerebellar peduncle* (100)	0.51 ± 0.09	0.46 ± 0.08	0.047
90	Superior longitudinal fasciculus R* (91.11)	0.62 ± 0.17	0.56 ± 0.14	0.033
	Superior corona radiata R (8.89)			
76	Fornix (cres) / Stria terminalis (cannot be resolved with current resolution) L* (100)	0.58 ± 0.11	0.54 ± 0.12	0.024
72	Superior longitudinal fasciculus L* (100)	0.52 ± 0.10	0.46 ± 0.09	0.026
68	Posterior thalamic radiation (include optic radiation) L* (100)	0.54 ± 0.17	0.45 ± 0.08	0.034
57	Superior longitudinal fasciculus R* (100)	0.50 ± 0.11	0.46 ± 0.09	0.045
53	Cingulum (cingulate gyrus) L* (54.72)	0.46 ± 0.07	0.41 ± 0.07	0.027
	Splenium of corpus callosum (45.28)			
50	Splenium of corpus callosum* (80)	0.40 ± 0.09	0.36 ± 0.10	0.045

	Posterior corona radiata R (20)			
49	Cingulum (cingulate gyrus) R* (81.63)	0.46 ± 0.09	0.41 ± 0.07	0.043
	Splenium of corpus callosum (18.37)			
46	Posterior thalamic radiation (include optic radiation) R* (100)	0.53 ± 0.14	0.49 ± 0.10	0.038
40	Superior longitudinal fasciculus L* (100)	0.51 ± 0.10	0.48 ± 0.09	0.027
32	Superior longitudinal fasciculus R* (100)	0.45 ± 0.10	0.42 ± 0.09	0.040
32	Middle cerebellar peduncle* (100)	0.32 ± 0.06	0.27±0.05	0.050
27	Cingulum (hippocampus) R* (100)	0.47 ± 0.07	0.45 ± 0.08	0.045
25	Anterior limb of internal capsule L* (100)	0.64 ± 0.15	0.58 ± 0.14	0.030
23	Cingulum (hippocampus) L* (100)	0.46 ± 0.09	0.42 ± 0.07	0.022
17	Cingulum (cingulate gyrus) L* (100)	0.44 ± 0.09	0.39 ± 0.07	0.027
16	Superior longitudinal fasciculus L* (100)	0.45 ± 0.10	0.42 ± 0.09	0.046

16	Anterior corona radiata R* (100)	0.54 ± 0.11	0.51 ± 0.09	0.033
16	Posterior limb of internal capsule R* (100)	0.52 ± 0.09	0.46 ± 0.08	0.033
15	Cingulum (cingulate gyrus) L* (100)	0.39 ± 0.08	0.37 ± 0.07	0.031
15	Superior longitudinal fasciculus L* (100)	0.45 ± 0.09	0.39 ± 0.08	0.031
13	Superior longitudinal fasciculus L* (100)	0.56 ± 0.12	0.53 ± 0.13	0.035
13	Posterior corona radiata R* (100)	0.56 ± 0.14	0.52 ± 0.13	0.022
12	Cerebral peduncle R* (100)	0.40 ± 0.09	0.37 ± 0.07	0.033
11	Superior longitudinal fasciculus R* (100)	0.48 ± 0.08	0.45 ± 0.09	0.043
11	Cingulum (cingulate gyrus) R* (100)	0.45 ± 0.08	0.41 ± 0.08	0.043
11	Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) L* (100)	0.62 ± 0.28	0.58 ± 0.12	0.024
*Region with the maximum significance in the cluster.				

Supplementary Table 4. Fractional anisotropy and diffusivity (mean, radial, and axial) measures in patients with mild traumatic brain injury (mTBI) at the chronic stage and orthopedic control subjects in 48 regions according to JHU white matter atlas.												
Region	FA		MD ($\times 10^{-3}$ mm ² /s)				RD($\times 10^{-3}$ mm ² /s)		AD($\times 10^{-3}$ mm ² /s)			
	mTBI	Control	mTBI		Control		mTBI	Control	mTBI		Control	
	mean(SD)		mean(SD)				mean(SD)		mean(SD)			
		P ^a			P ^a				P ^a		P ^a	
		P ^b			P ^b				P ^b		P ^b	
Middle cerebellar peduncle	0.37(0.03)	0.38(0.03)	0.169	0.6(0.03)	0.58(0.02)	0.002	0.44(0.03)	0.42(0.02)	0.003	0.91(0.04)	0.89(0.03)	0.021
		0.046				p<0.001*			p<0.001*			0.012
Pontine crossing tract (a part of MCP)	0.42(0.03)	0.43(0.03)	0.044	0.75(0.04)	0.73(0.03)	0.097	0.58(0.04)	0.56(0.03)	0.035	1.1(0.06)	1.09(0.06)	0.549
		0.013				0.02			0.006*			0.289
Genu of corpus callosum	0.51(0.04)	0.52(0.05)	0.229	1.17(0.14)	1.15(0.13)	0.477	0.88(0.15)	0.84(0.14)	0.409	1.77(0.13)	1.75(0.13)	0.702
			0.091			0.244			0.204			0.421
Body of corpus callosum	0.57(0.06)	0.58(0.06)	0.175	0.96(0.1)	0.93(0.1)	0.254	0.63(0.12)	0.61(0.12)	0.257	1.61(0.07)	1.59(0.08)	0.443
			0.07			0.112			0.111			0.29
Splenium of corpus callosum	0.66(0.04)	0.68(0.04)	0.119	0.86(0.06)	0.83(0.06)	0.053	0.48(0.08)	0.45(0.07)	0.088	1.61(0.06)	1.58(0.08)	0.140
			0.03			0.01			0.018			0.066
Fornix (column and body of fornix)	0.30(0.10)	0.32(0.13)	0.334	1.91(0.42)	1.87(0.48)	0.596	1.65(0.47)	1.61(0.54)	0.584	2.44(0.33)	2.41(0.35)	0.645
			0.205			0.473			0.455			0.572

Corticospinal tract R	0.40(0.03)	0.41(0.03)	0.821	0.67(0.04)	0.66(0.03)	0.3	0.49(0.04)	0.47(0.03)	0.299	1.04(0.05)	1.03(0.06)	0.526
			0.36			0.175			0.134			0.525
Corticospinal tract L	0.41 (0.03)	0.43(0.03)	0.188	0.72(0.04)	0.69(0.03)	0.012	0.52(0.04)	0.5(0.03)	0.018	1.1(0.05)	1.08(0.06)	0.108
			0.048			0.007			0.006*			0.71
Medial lemniscus R	0.53(0.04)	0.54(0.06)	0.583	0.78(0.06)	0.78(0.13)	0.640	0.53(0.07)	0.52(0.14)	0.645	1.3(0.07)	1.3(0.12)	0.698
			0.226			0.919			0.856			0.936
Medial lemniscus L	0.54 (0.04)	0.54(0.06)	0.674	0.78(0.06)	0.8(0.19)	0.174	0.52(0.07)	0.54(0.21)	0.190	1.3(0.07)	1.32(0.18)	0.189
			0.781			0.363			0.431			0.286
Inferior cerebellar peduncle R	0.33(0.04)	0.34(0.05)	0.437	0.64(0.07)	0.6(0.04)	0.060	0.48(0.09)	0.45(0.05)	0.105	0.94(0.07)	0.91(0.06)	0.045
			0.173			0.018			0.031			0.021
Inferior cerebellar peduncle L	0.40(0.05)	0.42(0.06)	0.275	0.88(0.12)	0.84(0.07)	0.092	0.7(0.14)	0.65(0.08)	0.096	1.26(0.11)	1.22(0.09)	0.127
			0.108			0.042			0.039			0.084
Superior cerebellar peduncle R	0.52(0.04)	0.53(0.04)	0.643	1.08(0.09)	1.01(0.1)	0.007	0.76(0.09)	0.7(0.09)	0.021	1.71(0.12)	1.63(0.14)	0.006
			0.257			0.002*			0.005*			0.004
Superior cerebellar peduncle L	0.51(0.03)	0.52(0.04)	0.524	1.18(0.1)	1.11(0.11)	0.049	0.87(0.1)	0.81(0.11)	0.075	1.8(0.13)	1.73(0.15)	0.051
			0.216			0.021			0.026			0.038
Cerebral peduncle R	0.57(0.04)	0.58(0.05)	0.537	0.81(0.03)	0.79(0.03)	0.079	0.51(0.05)	0.49(0.05)	0.157	1.41(0.06)	1.39(0.07)	0.267
			0.214			0.015			0.032			0.183
Cerebral peduncle L	0.57(0.04)	0.58(0.04)	0.284	0.79(0.03)	0.78(0.03)	0.085	0.5(0.05)	0.48(0.04)	0.098	1.38(0.07)	1.37(0.07)	0.524
			0.125			0.025			0.03			0.415

1													
2	Anterior limb of	0.49 (0.04)	0.51(0.05)	0.241	0.77(0.08)	0.74(0.07)	0.246	0.54(0.08)	0.52(0.08)	0.246	1.23(0.09)	1.2(0.07)	0.339
3													
4	internal capsule R			0.06			0.039			0.041			0.074
5													
6	Anterior limb of	0.49 (0.05)	0.51(0.05)	0.201	0.78(0.16)	0.74(0.08)	0.157	0.55(0.17)	0.52(0.09)	0.187	1.23(0.14)	1.19(0.08)	0.117
7													
8	internal capsule L			0.103			0.109			0.138			0.074
9													
10	Posterior limb of	0.58(0.03)	0.59(0.03)	0.067	0.74(0.05)	0.71(0.04)	0.021	0.47(0.04)	0.44(0.04)	0.017	1.28(0.06)	1.25(0.06)	0.096
11													
12	internal capsule R			0.018			0.003*			0.002*			0.021
13													
14	Posterior limb of	0.58(0.04)	0.60(0.03)	0.112	0.73(0.09)	0.71(0.05)	0.131	0.46(0.1)	0.44(0.05)	0.143	1.27(0.08)	1.25(0.06)	0.161
15													
16	internal capsule L			0.062			0.088			0.104			0.1
17													
18	Retrolenticular part of	0.52(0.03)	0.54(0.03)	0.136	0.84(0.09)	0.81(0.08)	0.150	0.59(0.09)	0.55(0.08)	0.138	1.35(0.09)	1.32(0.1)	0.236
19													
20	internal capsule R			0.046			0.038			0.036			0.073
21													
22	Retrolenticular part of	0.55(0.04)	0.56(0.03)	0.170	0.82(0.12)	0.79(0.1)	0.165	0.56(0.12)	0.53(0.1)	0.172	1.34(0.12)	1.32(0.11)	0.188
23													
24	internal capsule L			0.084			0.122			0.121			0.157
25													
26	Anterior corona radiata	0.39(0.05)	0.40(0.05)	0.126	0.85(0.11)	0.82(0.1)	0.322	0.67(0.11)	0.64(0.11)	0.278	1.2(0.09)	1.18(0.09)	0.490
27													
28	R			0.035			0.083			0.068			0.164
29													
30	Anterior corona radiata	0.39(0.06)	0.40(0.06)	0.183	0.84(0.12)	0.81(0.1)	0.329	0.66(0.13)	0.64(0.11)	0.289	1.19(0.1)	1.17(0.09)	0.488
31													
32	L			0.074			0.103			0.091			0.175
33													
34	Superior corona radiata	0.45(0.04)	0.46(0.04)	0.017	0.76(0.08)	0.73(0.08)	0.311	0.56(0.08)	0.54(0.07)	0.170	1.14(0.09)	1.12(0.09)	0.715
35													
36	R			0.003			0.057			0.025			0.228
37													
38													
39													
40													
41													
42													
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Superior corona radiata	0.46(0.04)	0.47(0.04)	0.057	0.76(0.1)	0.74(0.1)	0.335	0.57(0.1)	0.55(0.09)	0.235	1.15(0.11)	1.14(0.11)	0.626
L			0.021			0.153			0.097			0.369
Posterior corona radiata R	0.44(0.05)	0.46(0.05)	0.195	0.89(0.13)	0.86(0.14)	0.924	0.67(0.13)	0.64(0.14)	0.797	1.32(0.13)	1.3(0.14)	0.825
			0.051			0.266			0.225			0.388
Posterior corona radiata L	0.43(0.05)	0.45(0.05)	0.259	0.88(0.13)	0.86(0.15)	0.801	0.68(0.13)	0.65(0.15)	0.699	1.29(0.14)	1.27(0.15)	1.000
			0.089			0.275			0.237			0.391
Posterior thalamic radiation (include optic radiation) R	0.52(0.06)	0.54(0.05)	0.342	0.92(0.11)	0.89(0.1)	0.502	0.64(0.12)	0.61(0.11)	0.490	1.49(0.09)	1.46(0.1)	0.641
			0.087			0.099			0.105			0.167
Posterior thalamic radiation (include optic radiation) L	0.51(0.06)	0.53(0.06)	0.339	0.99(0.14)	0.96(0.12)	0.614	0.64(0.12)	0.61(0.11)	0.531	1.55(0.13)	1.53(0.12)	0.842
			0.118			0.248			0.213			0.403
Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) R	0.48(0.04)	0.49(0.04)	0.131	0.91(0.1)	0.88(0.09)	0.305	0.67(0.11)	0.64(0.1)	0.259	1.39(0.11)	1.36(0.09)	0.480
			0.051			0.124			0.104			0.241
Sagittal stratum (include inferior longitudinal fasciculus	0.45(0.04)	0.46(0.04)	0.081	0.98(0.15)	0.96(0.15)	0.668	0.75(0.15)	0.73(0.15)	0.567	1.44(0.15)	1.43(0.16)	0.887
			0.033			0.493			0.396			0.733

1													
2	and inferior fronto-												
3	occipital fasciculus) L												
4													
5													
6	External capsule R	0.38(0.03)	0.39(0.03)	0.189	0.81(0.08)	0.77(0.06)	0.044	0.64(0.08)	0.61(0.06)	0.062	1.13(0.08)	1.1(0.06)	0.035
7				0.054			0.006			0.01			0.005
8													
9													
10	External capsule L	0.39(0.05)	0.40(0.03)	0.052	0.81(0.16)	0.77(0.07)	0.058	0.64(0.17)	0.6(0.07)	0.065	1.15(0.14)	1.11(0.07)	0.049
11				0.03			0.045			0.053			0.035
12													
13	Cingulum (cingulate	0.43(0.04)	0.44(0.05)	0.184	0.77(0.04)	0.76(0.05)	0.389	0.58(0.05)	0.56(0.06)	0.230	1.14(0.05)	1.14(0.07)	1.000
14	gyrus) R			0.085			0.124			0.063			0.736
15													
16													
17	Cingulum (cingulate	0.47(0.04)	0.48(0.05)	0.112	0.75(0.04)	0.74(0.05)	0.207	0.54(0.05)	0.52(0.05)	0.082	1.18(0.06)	1.17(0.08)	0.908
18	gyrus) L			0.044			0.078			0.022			0.751
19													
20													
21	Cingulum	0.35(0.05)	0.37(0.04)	0.048	0.91(0.14)	0.86(0.11)	0.119	0.75(0.15)	0.69(0.12)	0.110	1.22(0.12)	1.18(0.11)	0.178
22	(hippocampus) R			0.022			0.035			0.035			0.049
23													
24													
25	Cingulum	0.34(0.05)	0.36(0.04)	0.052	0.93(0.16)	0.87(0.09)	0.022	0.78(0.17)	0.71(0.1)	0.024	1.24(0.14)	1.18(0.08)	0.028
26	(hippocampus) L			0.019			0.008			0.009			0.012
27													
28													
29													
30													
31	Fornix (cres) / Stria	0.42(0.07)	0.43(0.07)	0.369	1.12(0.22)	1.08(0.2)	0.324	0.89(0.25)	0.85(0.23)	0.368	1.58(0.19)	1.53(0.16)	0.255
32	terminalis (cannot be			0.211			0.169			0.204			0.119
33	resolved with current												
34	resolution) R												
35													
36													
37													
38	Fornix (cres) / Stria	0.45(0.07)	0.47(0.06)	0.208	1.01(0.25)	0.95(0.19)	0.122	0.78(0.27)	0.72(0.21)	0.139	1.47(0.21)	1.41(0.17)	0.102
39	terminalis (cannot be			0.153			0.125			0.139			0.107
40													
41													
42													
43													
44													
45													
46													

resolved with current												
resolution) L												
Superior longitudinal fasciculus R	0.44(0.04)	0.46(0.04)	0.230 0.077	0.77(0.07)	0.75(0.06)	0.314 0.053	0.58(0.07)	0.55(0.07)	0.302 0.058	1.15(0.06)	1.13(0.06)	0.477 0.101
Superior longitudinal fasciculus L	0.45(0.05)	0.46(0.04)	0.127 0.051	0.75(0.07)	0.73(0.07)	0.166 0.047	0.56(0.08)	0.54(0.07)	0.142 0.042	1.13(0.06)	1.11(0.07)	0.373 0.14
Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) R	0.43(0.07)	0.44(0.07)	0.633 0.256	0.8(0.18)	0.78(0.17)	0.827 0.444	0.61(0.18)	0.6(0.19)	0.860 0.465	1.17(0.16)	1.15(0.15)	0.768 0.426
Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) L	0.42(0.07)	0.43(0.08)	0.322 0.159	0.85(0.26)	0.83(0.28)	0.804 0.706	0.66(0.26)	0.65(0.29)	0.789 0.676	1.21(0.25)	1.2(0.26)	0.840 0.776
Uncinate fasciculus R	0.43(0.04)	0.45(0.04)	0.368 0.21	0.8(0.07)	0.76(0.07)	0.063 0.011	0.6(0.08)	0.57(0.07)	0.098 0.021	1.19(0.08)	1.15(0.08)	0.087 0.021
Uncinate fasciculus L	0.42(0.04)	0.44(0.04)	0.084 0.52	0.79(0.08)	0.75(0.07)	0.003 p<0.001*	0.6(0.08)	0.56(0.06)	0.007 0.002*	1.17(0.09)	1.12(0.09)	0.003 0.001

1													
2	Tapetum R	0.35(0.06)	0.36(0.07)	0.871	1.75(0.23)	1.74(0.24)	0.655	1.49(0.24)	1.47(0.26)	0.766	2.29(0.21)	2.29(0.21)	0.465
3				0.534			0.794			0.735			0.941
4													
5													
6	Tapetum L	0.26(0.05)	0.27(0.05)	0.489	2.14(0.22)	2.14(0.24)	0.684	1.91(0.24)	1.91(0.25)	0.835	2.59(0.21)	2.61(0.23)	0.422
7				0.355			0.999			0.874			0.718
8													
9													

^a Significance level when age, gender, and Fazekas score were used as covariates; ^b Significance level when age and gender were used as covariates; **Bold** numbers indicate statistically significant difference. *Regions that remain significant after correcting for multiple comparisons using false-discovery rate at p<0.05.

Supplementary Figure 1. Radial diffusivity in the left superior longitudinal fasciculus (A) and the left cingulum (cingulate gyrus) (B) in patients with mild traumatic brain injury (mTBI). Patients with mTBI are divided into two groups based on their outcome measured by extended Glasgow Outcome Scale (GOSE). P-values indicate statistically significant difference between the patient groups in each region.

152x101mm (500 x 500 DPI)