Diffusion tensor imaging detects white matter abnormalities and associated cognitive deficits in chronic adolescent TBI

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Abstract

Primary objective—This study examined long-term alterations in white matter microstructure following TBI in adolescence using diffusion tensor imaging (DTI). It was hypothesized that white matter integrity would be compromised in adolescents with TBI and would correlate with measures of executive functioning and cognitive abilities.

Research design—This study employed whole-brain, voxel-wise, statistical comparison of DTI indices in youth of 12–17 years old (mean = 15.06) with TBI vs an age- and gender-matched cohort (mean age = 15.37).

Methods and procedures—This study scanned 17 adolescents with complicated-mild-to-severe TBI, 1–3 years after injury, and 13 healthy adolescents. Tract-Based Spatial Statistics (TBSS) was employed for DTI analysis.

Main outcomes and results—Overall diffusivity elevations were found in the TBI group with increases in axial diffusivity in the right hemisphere. White matter integrity was associated with word reading, planning and processing times in the TBI group, but not healthy controls.

Conclusions—The detected abnormalities in axial diffusivity may reflect neuronal regeneration and cerebral reorganization after injury. These findings provide tentative evidence of persistent white matter alteration following TBI in adolescence. Associations of DTI indices with cognitive

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performance following TBI provide tentative support for links between white matter integrity and performance post-TBI.

Keywords

Traumatic brain injury; adolescents; executive functioning; diffusion tensor imaging; diffuse axonal injury

Introduction

Paediatric traumatic brain injury (TBI), a common cause of acquired disability in youth [1], occurs mostly in adolescence and young adulthood [2, 3]. While basic cognitive functions such as motor and sensory processing mature in childhood, adolescence is a crucial period for development of higher level processing [4]. Executive function (EF) processing deficits are common after childhood TBI [5–8] with many studies demonstrating deficits in measures of working memory, attention, inhibition and cognitive control linked to injury severity [9–11].

Although the neuropsychological and behavioural consequences of paediatric TBI have been well documented, the neural substrates of these cognitive and behavioural deficits are less well understood. The rotational and shearing forces associated with TBI often result in multi-focal and diffuse axonal injuries which are not evident on Computed Tomography (CT) scans [12] or conventional T1 or T2 weighted magnetic resonance (MR) imaging. Diffusion tensor imaging (DTI) is an advanced MRI imaging technique that quantifies microstructural changes in white matter based on the mapping of *in-vivo* patterns of water diffusion using scalar maps of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Evidence from combined histological and DTI studies utilizing animal models of acute and subacute brain insult suggest that DTI variables can identify the primary axotomy and secondary demyelination arising from TBI [13–17]. Acutely, decreased FA was related to decreased white matter fibre directional coherence and decreased AD was associated with axon degeneration [13, 14, 16, 17]. In the sub-acute phase of TBI, AD returned to pseudo-baseline but increased RD was associated with secondary demyelination [14, 16, 17]. In the chronic phase of TBI, decreased FA and increased RD and MD have been consistently reported [18–21]. DTI variables have also been shown to be related to behavioural measures of executive functioning in chronic human TBI in both adult [20, 22] and paediatric [23–25] populations. In adult populations, relatively low FA [22] and high RD [20] in frontal white matter regions have been related to executive dysfunction. FA and MD values were predictive of executive and memory functioning in acute and chronic TBI [26]. Additionally, FA in the fornix has been associated with memory functioning [20, 27]. In paediatric populations, frontal white matter tract integrity was also associated with behaviour and planning [25], inhibition and switching [23], and prospective memory [24] performance. These works are part of a growing body of evidence showing that relationships between microstructural integrity of frontal white matter and EF performance can be mapped with DTI (see Zappalàet al. [28] for a review).

The objectives of this study were: (1) to characterize persistent deficits in white matter organization in adolescents between 1–3 years following complicated-mild-to-severe TBI using DTI and Tract-Based Spatial Statistics (TBSS) [29] and (2) to examine the relationship between white matter tract integrity and executive functioning skills. Previous reports with a similar cohort noted specific executive functioning deficits, despite otherwise normal cognitive performance [30]. It is hypothesized that the TBI group would exhibit lower levels of white matter organization and higher diffusivity compared to age-matched controls. It is also hypothesized that DTI measures in affected white matter tracts would correlate with measures of cognitive and executive function performance [20].

Patients and methods

Adolescents between the ages of 12–17 who had been hospitalized overnight with confirmed TBI were recruited. The injury classifications were defined by values of the Glasgow Coma Scale (GCS), where severe TBI was GCS <9, moderate TBI was GCS 9–12 and complicated-mild TBI was GCS 13–15, with evidence of abnormalities on imaging. The participants with TBI were recruited from a pool of families that had participated in ongoing research studies on adolescent TBI at a tertiary care children's hospital. All participants were at least 12-months post-injury to ensure that acute recovery was complete. A comparison group of typically-developing adolescents with no history of TBI or other neurological insults was recruited from the community. Groups were matched on age, gender and maternal education. Exclusion criteria included significant developmental delay, significant psychiatric or behaviour disturbance prior to injury and extreme vision or hearing impairments.

Study neuropsychological data and MR imaging were acquired in the chronic phase (mean time since injury: 1.94 years, range: 1.1–3.5 years). After obtaining informed consent, participants completed neuropsychological testing followed by the study MRI session. The study was approved by the local Institutional Review Board.

Clinical and structural imaging evaluation

All patients had a clinical CT scan at the time of injury (initial presentation) performed in standard fashion using axial plane and 5 mm slice thickness. Patients with identified injury on initial CT had follow-up CT exams between 24 hours and 1 week after injury. Clinical MRI examinations were performed in selected patients at variable intervals after injury (2 days –13 months). All available imaging (clinically obtained and study obtained, see below) was reviewed by a board-certified radiologist with experience with paediatric traumatic brain injury (JL).

Neuropsychological measures

General cognitive ability was estimated using the Word Reading sub-test of the Wide Range Achievement Test, Fourth Edition (WRAT-4) and the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4), respectively. Executive functioning domains of working memory, processing speed, inhibition, planning, reasoning and impulsivity as well as behavioural manifestations of executive abilities were also evaluated. The Working Memory (WMI) and

Processing Speed (PSI) Indices from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) [31] were administered to assess domains of executive abilities known to be vulnerable to TBI [25]. The Colour-Word Interference Test from the Delis-Kaplan Executive Function System [32] was used to assess verbal inhibition. The Tower sub-test from the Delis–Kaplan Executive Function System (D-KEFS [32]) was used to test the flexibility of thinking, inhibition, problem-solving, planning, impulse control, concept formation, abstract thinking and creativity in the spatial modality. The Behaviour Rating Inventory of Executive Function (BRIEF) [33] and self-report (BRIEF-SR) [34] questionnaires provided ratings of behavioural manifestations of EF in everyday contexts.

Study MR imaging

MRI scans were obtained using a 3T (Philips Medical Systems, Cleveland, OH) scanner. The imaging session lasted 50 minutes and involved acquisition of a T1-weighted anatomical scan, a DTI scan and four fMRI scans (the fMRI results were reported elsewhere [30]). High-resolution T1-weighted anatomical images were acquired with a 3D MPRAGE compatible sequence with the following imaging parameters: TR 8.1 ms, TE 3.7 ms, flip angle: 8°, in-plane resolution: 0.98×0.98 mm^2, slice thickness: 1 mm, matrix size: 252×250 (reconstructed to 256×256), 180 contiguous slices. Diffusion-weighted images were acquired with an EPI sequence with the following imaging parameters: TR 8799 ms, TE 88 ms, flip angle: 90°, slice thickness 2 mm, 72 contiguous slices. The geometry for data acquisition was slightly variable with Field-of-view ranging from 180×180 mm^2 to 201.6×201.6 mm^2 and in-plane resolution ranging from 1.73×1.73 mm^2 to 1.96×1.96 mm^2. A total of 33 volumes were acquired, consisting of one diffusion insensitive volume and 32 diffusion weighted volumes with gradients applied in non-collinear directions with a single b-value ($b = 1000$ s mm^{-2}).

DTI analysis

TBSS was utilized for voxel-wise analysis of the DTI variables across the white matter. Voxel-based analysis requires accurate correspondence of voxels between subjects. By projecting the DTI values from the estimated local centres of major white matter onto a 'skeleton' that is used as the basis of voxel-wise analysis, TBSS attempts to overcome the requirement of accurate alignment and smoothing issues of conventional voxel-based analysis. The TBSS pipeline consists of multiple pre-processing steps that optimize the correspondence between voxels at the centre of major white matter tracts. First, eddy current correction was performed by affine registration of the diffusion images with a non-diffusion-weighted reference scan. At each brain voxel a tensor, a symmetric 3×3 matrix of apparent diffusion coefficients along the Cartesian axes, was computed using standard linear least squares estimation [35] to model the directionality of water movement. Eigen decomposition of the tensor yields the eigenvalues $\lambda_1 > \lambda_2 > \lambda_3$, which are used to compute scalar maps of (AD = λ_1), (MD = ($\lambda_1+\lambda_2+\lambda_3$)/3),

$$\left(\mathrm{FA} = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}} \right)$$

and (RD = $(\lambda_2+\lambda_3)/2$) [36]. Voxel-wise registration is performed by exhaustive pairwise non-linear registration, using FNIRT [37, 38], of FA images to select the 'most typical' subject's FA image as the registration target [29]. We chose a study-specific template in order to minimize the amount of nonlinear distortion applied to the images. Additionally, using a real FA image as opposed to a blurred version of multiple subjects should preserve the sharpness of edges. The images were then linearly aligned to MNI152 space. Skeletonization of the major white matter tracts was performed by thinning the mean FA image, which was thresholded at FA > 0.2 in order to remove highly variable white matter tracts. Residual misregistration of the tract centres in the FA images with the skeleton was corrected by projecting maximal FA values onto the skeleton; the projected values were used for voxel-wise statistical comparison.

Non-parametric voxel-wise statistical comparisons were performed using permutation testing implemented by the 'Randomize' tool [39]; 5000 permutations were generated, leading to confidence limits on $p = 0.05$ of ±0.0062. After Family-Wise Error (FWE) correction for multiple comparisons and application of the Threshold-Free Cluster Enhancement (TFCE) method [40], voxels were considered statistically significant if $p <0.05$. The localization of significant voxels to white matter regions and tracts was performed by referencing the John Hopkins University (JHU) and International Consortium of Brain Mapping (ICBM) atlases [41], respectively. Cortical regions in close proximity to significant voxels in white matter were identified using a Montreal Neurological Institute (MNI) space Talairach atlas [42].

Multivariate linear regression using permutation testing with the 'Randomize' tool [39] was used to examine the relationships between DTI variables and the neuropsychological variables (as listed in Table I) within the TBI group, the control group and across both groups. Participant age at the time of the MRI scan was included in the linear models as a covariate to control for known variations of DTI parameters with age at scan [43, 44].

Results

Seventeen adolescents with TBI (mean age at scan = 15.06, range = 12–17) and 13 controls (CTL) (mean age at scan = 15.37, range 13–17) consented and produced usable imaging data. The groups did not differ significantly on ages at scan ($t = -0.54$, $p = 0.59$) or gender ($\chi^2 = 0.002$, $p = 0.96$). Age at scan, GCS scores, mechanisms of injury and image findings for the TBI group are displayed in Table II.

The TBI and CTL groups did not differ on measures of general intellectual ability, although there was a trend for poorer performance for word reading (WRAT-4) in the TBI group (see Table I). Adolescents with TBI had significantly higher behavioural ratings of executive dysfunction [BRIEF-GEC ($p = 0.02$, uncorrected)].

Group differences in DTI variables

Group comparison of the DTI variables (TBI vs CTL) identified several regions of elevated AD in the TBI group (TBI > CTL; $p < 0.05$, corrected) across the white matter on the TBSS skeleton (Figure 1). All clusters were lateralized to the right hemisphere. Regions of affected

white matter tracts include the right anterior corona radiata (rACR), genu of the corpus callosum (gCC), body of the corpus callosum (bCC), right superior corona radiata (rSCR), right posterior limb of the internal capsule (rPLIC), right cerebral peduncle (rCP) and white matter in close proximity to the medial frontal gyrus and precuneus in the right hemisphere. Further, trend-level differences in AD (TBI > CTL, $p < 0.1$ corrected) were also apparent in white matter in the left hemisphere, including portions of the bCC and lPCR. No group differences were identified in FA, MD or RD at corrected level.

Using the voxels identified as having abnormally high AD in the TBSS analysis, mean values for AD, MD, RD and FA were extracted for each participant. Figure 2 depicts the group-wise mean values for all DTI variables and shows a statistically significant increase in AD (as expected) and MD in the TBI group with non-significant differences for RD and FA. It should be noted that the p-value for FA (TBI > CTL) was significant prior to correction.

To more fully understand the genesis of the right lateralized findings, this study examined the pattern of white and gray matter injuries found in the imaging review (Table II). Of the eight participants that had identifiable parenchymal damage, each had at least one site of damage in the right hemisphere at either the sub-acute or late stage of TBI.

Associations of DTI abnormalities with cognitive ability and executive functioning

To investigate associations between white matter microstructure and neuropsychological performance, this study performed linear regression of the DTI variables with the neuropsychological variables (see Table I) across the skeleton and found no significant relationships between any pairs of variables. To assess the potential association with a less stringent level of correction for multiple comparisons, the data were re-analysed using the regions of the skeleton that contained significantly higher AD in the TBI group (see Figure 1). Figure 3(a) shows a significant correlation between FA and word reading score (WRAT-4) in the gCC/ rACR (558 voxels). Figure 3(b) reveals significant negative correlations of RD with the DKEFS Tower Total Achievement score (DKEFS-TOW-TAS) in the right SCR (42 voxels). Figure 3(c) shows a cluster with trend-level significance (150 voxels) that indicates a positive correlation between AD and WISC-IV PSI in the rACR. All of these associations were found only in the TBI group, but not in the CTL or combined group.

The other neuropsychological variables (PPVT-4, WISC-IV WMI, DKEFS-Colour word, BRIEF GEC, BRIEF-SR GEC) were not correlated to the DTI variables in the TBI, CTL or across both groups.

Discussion

This study used non-invasive neuroimaging techniques to investigate the magnitude of persistent white matter microstructure abnormalities in an adolescent cohort with TBI and to relate DTI measures of white matter microstructure organization to performance on measures of cognitive ability and executive functioning.

Consistent with the hypothesis, regions of elevated white matter diffusivity were found in adolescents with TBI more than 12 months after the initial injury. The finding of increased MD in the TBI group is suggestive of demyelination and axonal death that occurs with TBI [45]. The increase of AD for adolescents with chronic TBI agrees with cross-sectional studies of chronic injury that reported increased AD in patients compared to controls [20, 22]. However, longitudinal studies showed that recovery of AD only reached control levels after an initial decrease in the acute phase [46]. Expected decreases in FA and increases in RD compared to healthy controls were also observed but did not reach statistical significance in the present study. The weaker significance of these differences is perhaps not surprising given that the cohort sustained mostly mild injuries, whereas recent evidence suggests that significant decreases in FA may only be found following moderate-to-severe TBI [18].

Contrary to expectations, regions of increased AD following TBI found in the present study were predominantly evident in the right hemisphere. Most previous TBI studies have identified bilateral white matter damage [20, 22], although some studies of adult TBI have detected certain level of laterality [18, 47, 48]. One possible explanation for the current finding is the prevalence of shear injuries or contusions in the right hemisphere on initial scans (see Table II). This heterogeneous pattern of lateralized lesions, along with the potential influence of small sample size, may have contributed to the right lateralization of the TBSS findings. It should be noted that the clusters with significantly higher AD in TBI were located in deep white matter, while the lesions tended to be isolated in superficial white matter in closer proximity to the cerebral cortex. Thus, DTI may be sensitive to white matter microstructure abnormalities that are remote from the site of injury and resulting lesions identified by CT.

Statistically significant increases were observed in AD and MD in the TBI group and with no statistically significant increases of FA or RD. For a possible interpretation of the biological basis of these findings, this study turns to the literature on animal studies using DTI. Animal studies suggest that increased AD may reflect neuroplasticity mechanisms including peri-lesional cortical reorganization, dendritic or axonal sprouting and neurosynaptogenesis [49–51]. These neuroplasticity factors, particularly axonal sprouting, may explain the increased levels of AD following TBI compared to controls found here. An alternate explanation of the increased AD and MD is gliosis without neuronal regeneration. A study examining the recovery of peri-lesional tissue after stroke revealed proliferation of astrocytes (gliosis), in the cortex as well as in white matter, with no evidence of axonal regeneration [15]. Directionally coherent glial cells cause increases in FA (increased AD compared to RD) [13]. Although the mechanism of stroke is different to TBI and this was not a human study, the stroke model does demonstrate the brain recovery pathway from insult. The lack of axonal regeneration could explain the increase in MD and RD, while the gliosis may be the cause of the profound increase in AD, with the lack of axons contributing to the increased MD values. Alternatively, the simultaneous increases of AD and MD values may be caused by the preferential death of fibre populations orthogonal to the primary diffusion directions within voxels. It should be noted that the tensor model sometimes is insufficient to model crossing fibre populations presented in the majority of the white matter [52]. Further DTI-based TBI studies and investigation of crossing fibres using a non-tensor

based model, e.g. Q-ball or HARDI, may be required to ascertain whether axonal regrowth or death is more plausible. In conclusion, the complex relationships between the DTI variables, neuropathology precludes one from making categorical statements about the underlying biological causes of the results. However, the fact that DTI is able to detect significant differences even in children with mild TBI that does not produce poor academic and neurocognitive outcomes, despite conservative corrections, is evidence for the high sensitivity of the method.

The second objective was to examine the potential relationships between DTI variables and measures of cognitive functioning and EF. Due to the severe FWE correction applied across the whole skeleton and the small sample size, no significant associations were found between measures of cognitive functioning and EF and white matter integrity across the sample as a whole. In order to alleviate the severity of the multiple comparison correction, this study re-analysed the neuropsychological variables in the regions of elevated AD in the TBI group. Significant correlations were found between abnormal DTI indices and poor performance on several neuropsychological measures using this regionally specific analysis strategy. A positive correlation between FA and word-reading score (WRAT-4), where higher score means better performance, was found in the rACR and gCC. In general, word reading is not typically adversely affected by TBI and for this reason it is considered a 'hold skill' that may provide a possible measure of pre-injury functioning or cognitive reserve. As language skills, including reading, are primarily sub-served by the left hemisphere, it is likely that the correlations in the right hemisphere are driven mainly by the site of injury. As such, it is likely that the association between FA and word reading could be more diffuse and left-sided with a larger and more representative sample of adolescents with TBI.

Consistent with this hypothesis, lower RD was associated with higher DKEFS-TOW-TAS, which assesses problem-solving and planning, where a higher score means a better performance, across all subjects in the rSCR. Although a relationship was not seen with FA, as per the literature, a decrease in RD is indicative of increased myelination [17] and is often coupled with increased FA, which could have explained the relationship between white matter microstructure and performance on this task.

A positive correlation of AD with WISC-IV PSI was observed in the TBI group at trend-level significance. Processing speed has been shown to be impaired in TBI [25]. In this study, the cluster is located in the rCing, which contains projections to the frontal cortex. This finding may demonstrate the influence white matter microstructure has on performance, specifically in TBI patients, despite normal neuropsychological performance and mild injuries. However, given that the finding was not significant with correction, it must be interpreted with caution; recognizing the potential for a false positive finding.

Associations between the integrity of white matter microstructure based on DTI and neuropsychological functioning reported here should be treated with caution given the sample size and methodological limitations of the study. Despite these limitations on specific interpretations of the relationship of neuro-cognitive outcome measures to the DTI data, this study demonstrates the sensitivity of DTI as a non-invasive imaging tool in detecting subtle residual WM abnormalities in chronic stage TBI in adolescents. The results

presented in this study are preliminary and yet promising and add new value to the field. If such findings can be substantiated by a larger comprehensive study, then the DTI parameters examined here might collectively serve as an imaging biomarker to be translated into a clinical method for assessing WM damage from TBI. The tool could help clinicians for determining critical timing of intervention and for predicting outcome related to WM recovery at various stages of patient management.

Conclusion

This study augments the existing literature of DTI study of TBI by reporting abnormal white matter microstructure determined by DTI matrices as well as their association with cognitive functioning in a cohort of adolescents who sustained mostly complicated mild or moderate TBI. Consistent with the hypotheses, elevated diffusivity was observed in a series of WM regions in the TBI group. This study also presented evidence for the association between the elevated AD and the processing speed and executive function in the TBI group providing a snapshot of white matter tract recovery and its relationship with neuropsychological variables in chronic TBI.

Abbreviations White matter region abbreviations

ACR	anterior corona radiate
ALIC	anterior limb of the internal capsule
CP	cerebral peduncle
Cing	Cingulum
ExCAP	external capsule
gCC	bCC, sCC, genu, body, splenium of the corpus callosum
PCR	right posterior corona radiate
PLIC	posterior limb of the internal capsule
PTR	posterior thalamic radiation
RetroIC	retrolenticular part of the internal capsule
SCR	superior corona radiata
SS	sagittal stratum
TAP	tapetum. These regions in the left and right hemispheres were denoted using l or r prefixes, respectively. e.g
lPLIC	left posterior limb of the internal capsule

White matter tract abbreviations

ATR	anterior thalamic radiation
CST	cortico-spinal tract

Fmin	forceps minor
IFOF	inferior fronto-occipital fasciculus
SLF	superior longitudinal fasciculus
UF	uncinate fasciculus. These tracts in the left and right hemispheres were denoted using l or r prefixes e.g
lSLF	left superior longitudinal fasciculus

Magnetic Resonance Imaging abbreviations

EPI	Echo Planar Imaging
FSE	Fast Spin Echo
GRE	Gradient Echo
MPRAGE	Magnetization Prepared Rapid Gradient Echo
TE	echo time
TI	inversion time
TR, repetition time. **Neuropsychological tests**	PPVT, Peabody Picture Vocabulary Test Version 4
WRAT	Wide Range Achievement Test 4th Edition word reading sub-test
DKEFS	Delis-Kaplan Executive Function System
Tower	Tower Total Achievement Score
ISvCb	Interference/Switching minus colour baseline
WISC	Wechsler Intelligence Scale for Children 4th Edition
PSI	Processing Speed Index
WMI	Working Memory Index
BRIEF	Behaviour Rating Inventory of Executive Function
GEC	Global Executive Composite
SR	Self-Report

Other abbreviations

CT	Computed Tomography
FEW	Family-Wise Error
GCS	Glasgow Coma Score
ICBM	International Consortium of Brain Mapping
JHU	John Hopkins University

| MNI | Montreal Neurological Institute |
| **TBSS** | Tract-Based Spatial Statistics |
| **TFCE** | Threshold-Free Cluster Enhancement |

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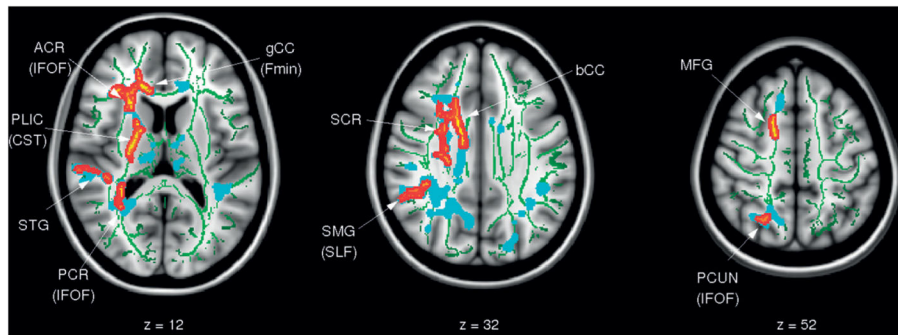
Figure 1.
Results of TBSS analysis comparing axial diffusivity (AD) between adolescents with TBI (TBI) and an age-gender matched control group (CTL)., Voxels with significant differences (TBI > CTL) are shown in red/yellow ($p < 0.05$ corrected) and blue ($p < 0.1$ corrected); the significant regions were ''thickened'' to enhance visualization. The results are overlaid onto the MNI152 T1 template and the white matter tract skeleton is shown in green.
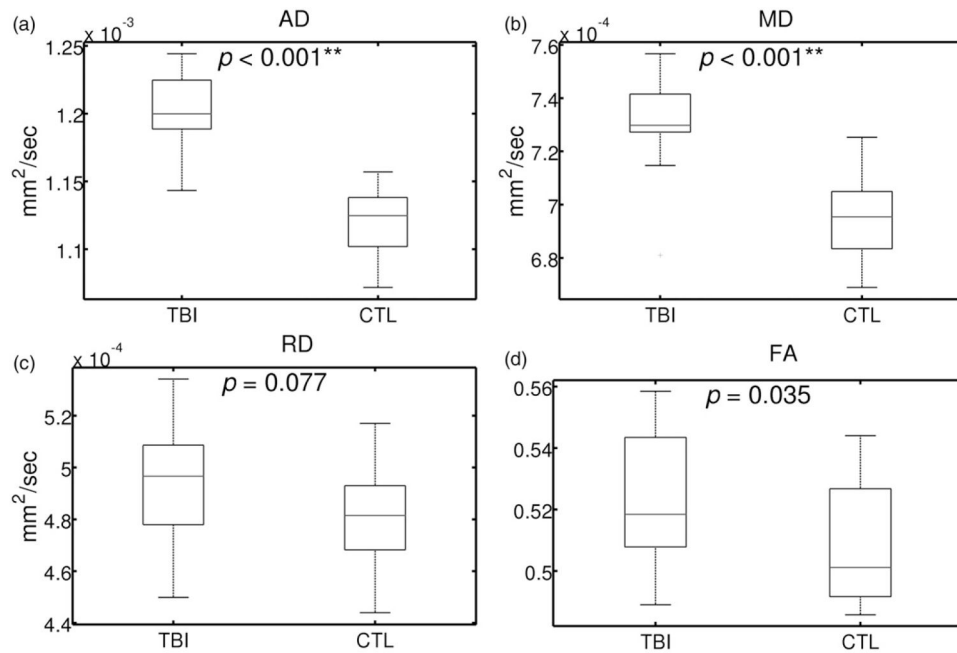
Figure 2.
Comparison of the DTI variables (i) AD, (ii) MD, (iii) RD, and (iv) FA between TBI and CTL groups using subject-wise mean values across all voxels in the significant cluster for AD (TBI >CTL) (see Figure 1) Group-wise mean values are denoted by horizontal lines. Significant differences between groups after correction for multiple comparisons are denoted by *($p < 0.05$), **($p < 0.01$). Note that AD (TBI > CTL) (i) is bound to be significant given that the ROI was chosen from voxels of significantly increased AD in the TBI group as determined by TBSS.
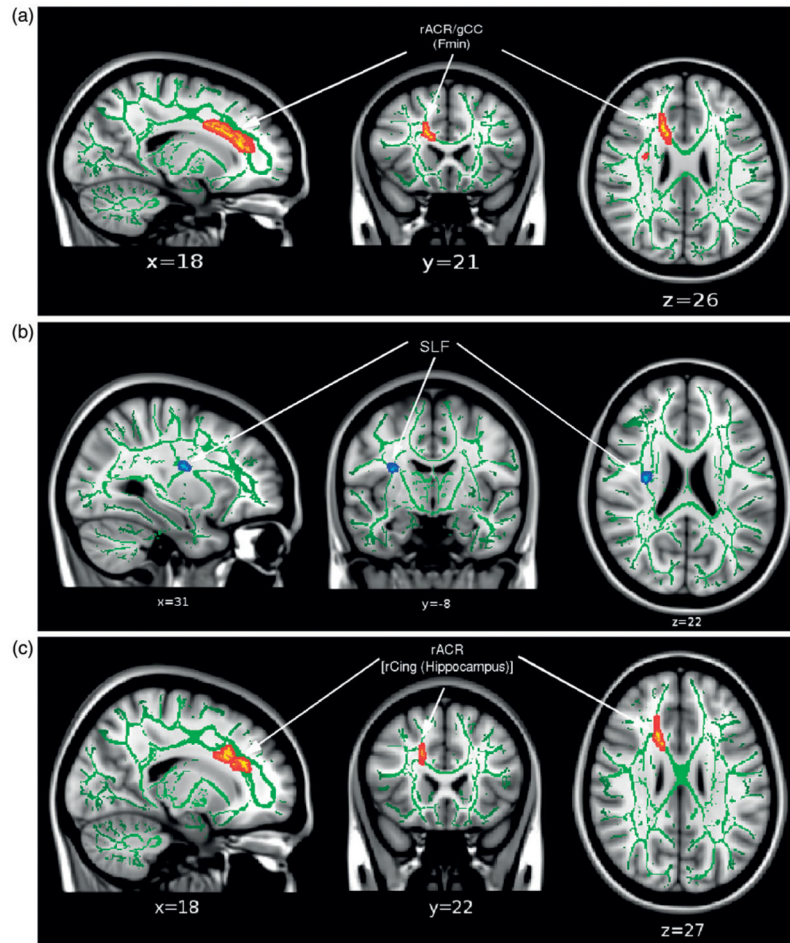
Figure 3.
Results of the TBSS regression analysis of FA with the WRAT-4 word reading subtest ($p < 0.05$, corrected) (i), RD with the DKEFS Tower Total Achievement Score ($p < 0.05$, corrected) (ii), and AD with the WISC-IV PSI score ($p < 0.1$, corrected) (iii) in the TBI group (positive correlation: red, negative correlation: blue). The significantly correlated regions were ''thickened'' to enhance visualization. The results are overlaid onto the MNI152 T1 template and the white matter tract skeleton is shown in green. The p-values are thresholded at $p < 0.05$ corrected over voxels that were reported as significant for AD (TBI > CTL) (see Figure 1).

Table I

Neuropsychological performance by group.

Measure	Direction of score	TBI (*n* =17)	CTL (*n* = 13)	*t*	*p* (unc.)	Cohen's *d*
PPVT-4	↑	101.29 (13.47)	105.15 (7.97)	−0.92	0.37	0.35
WRAT-4	↑	102.41 (16.73)	113.31 (17.46)	−1.74	0.09	0.66
DKEFS-Tower	↑	10.24 (2.25)	9.54 (2.79)	0.76	0.45	0.29
DKEFS-ISvCb	↑	9.94 (2.14)	9.54 (1.13)	0.62	0.54	0.23
WISC-IV WMI	↑	99.19 (8.84)	103.00 (14.09)	−0.89	0.38	0.35
WISC-IV PSI	↑	104.00 (15.62)	107.31 (15.52)	−0.57	0.57	0.22
BRIEF-SR GEC	↓	51.71 (11.37)	50.69 (11.21)	0.24	0.81	0.09
BRIEF GEC	↓	55.24 (15.16)	43.23 (8.08)	2.58	0.02*	0.98

In the 'Direction of score' column, ↑ denotes that a higher score means better performance, ↓ denotes that a lower score means better performance.

TBI, Traumatic Brain Injury group; CTL, Control group; PPVT, Peabody Picture Vocabulary Test Version 4; WRAT, Wide Range Achievement Test 4th Edition word reading sub-test; DKEFS, Delis-Kaplan Executive Function System; Tower, Tower Total Achievement Score; ISvCb, Interference/Switching minus colour baseline; WISC, Wechsler Intelligence Scale for Children 4th Edition; PSI, Processing Speed Index; WMI, Working Memory Index; BRIEF, Behaviour Rating Inventory of Executive Function; GEC, Global Executive Composite; SR, Self-Report.

Table II

Clinical characteristics and imaging findings for the TBI group.

ID	GCS	Age (years) At injury	When imaged	Classification	Mechanism of injury	Imaging findings
1	15	14.08	16.50	CM	Sport	Small R EDH haematoma, Normal brain
2	13	12.11	15.59	CM	Fall	Small L SDH, Normal brain
3	11	11.01	13.83	M	Fall	Normal
4	11	14.17	16.08	M	MVC	Normal
5	15	14.92	17.00	CM	Fall	Normal
6	15	14.00	16.00	CM	Fall	Bilateral anterior temporal contusions, R > L. Bilateral frontal contusions, R > L (inferior and orbital frontal)
7	11	12.50	14.25	M	Fall	L inferior frontal and right anterior temporal haemorrhagic contusions
8	8	16.33	17.59	M	MVC	Small R SDH, Normal brain
9	14	14.92	16.08	CM	Sport	R frontal haemorrhagic contusion, R > L superior frontal lobe, R temporal and R splenium haemorrhagic shear injuries
10	15	14.02	16.17	CM	MVC	Bilateral frontal, R > L haemorrhagic shear injury
11	15	14.02	16.08	CM	Fall	Small L EDH, Normal brain
12	13	12.05	14.33	CM	Fall	Bilateral temporal, L > R, and R frontal haemorrhagic contusions
13	10	13.10	14.83	M	Fall	Small R temporal contusion
14	3	12.02	13.59	S	Sport	Normal
15	15	10.90	12.00	CM	Fall	Small L SDH. Bilateral L > R inferior frontal contusions and temporal contusions
16	15	12.02	13.30	CM	Sport	R posterior temporal haemorrhagic contusion
17	13	11.06	12.90	CM	Ped vs MVA	Subarachnoid haemorrhage. Normal brain

MVC, motor vehicle collision; MVA, motor vehicle accident; SDH, subdural haematoma; EDH, epidural haematoma. All subjects had CT and research T1-weighted MPRAGE MRI sequences. Subjects 2, 6, 9, 10, 12, 13 and 15 had clinical MRI examinations. CM, Complicated-mild; M, moderate; S, severe.