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Article *in* Brain Injury · January 2021

DOI: 10.1080/02699052.2020.1859615

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BRAIN INJURY
https://doi.org/10.1080/02699052.2020.1859615

Dynamic changes in white matter following traumatic brain injury and how diffuse axonal injury relates to cognitive domain

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ABSTRACT

Objective: The goal is to evaluate longitudinally with diffusion tensor imaging (DTI) the integrity of cerebral white matter in patients with moderate and severe DAI and to correlate the DTI findings with cognitive deficits.

Methods: Patients with DAI (n = 20) were scanned at three timepoints (2, 6 and 12 months) after trauma. A healthy control group (n = 20) was evaluated once with the same high-field MRI scanner. The corpus callosum (CC) and the bilateral superior longitudinal fascicles (SLFs) were assessed by deterministic tractography with ExploreDTI. A neuropsychological evaluation was also performed.

Results: The CC and both SLFs demonstrated various microstructural abnormalities in between-groups comparisons. All DTI parameters demonstrated changes across time in the body of the CC, while FA (fractional anisotropy) increases were seen on both SLFs. In the splenium of the CC, progressive changes in the mean diffusivity (MD) and axial diffusivity (AD) were also observed. There was an improvement in attention and memory along time. Remarkably, DTI parameters demonstrated several correlations with the cognitive domains.

Conclusions: Our findings suggest that microstructural changes in the white matter are dynamic and may be detectable by DTI throughout the first year after trauma. Likewise, patients also demonstrated improvement in some cognitive skills.

ARTICLE HISTORY
Received 14 May 2020
Revised 24 October 2020
Accepted 1 December 2020

KEYWORDS
Brain injury; white matter; MRI; DTI; tractography; cognition

Introduction

Traumatic brain injury (TBI) is a complex public health issue worldwide because of its high prevalence, morbidity, and mortality (1,2). In the last decades, studies have demonstrated the vulnerability of cerebral parenchyma in the trauma scenario and also the social and economic burden associated with cognitive and psychological impairments in survivors (3,4).

Diffuse axonal injury (DAI) plays an essential role in TBI since it is present in almost half of the patients who need hospitalization and because it is related to brain dysfunctions (5–8). The widespread axonal injury leads to a loss of the brain connectiveness, causing cognitive, motor, and sensory deficits (9–11). Also, DAI is associated with the development of the chronic neurodegenerative traumatic disorder (12,13).

There are different and complex mechanisms involved in the pathophysiology of DAI. Histopathological studies have shown primary and secondary axonal lesions, inflammatory and regeneration processes accompanied by Wallerian degeneration and neuroplasticity that may be the related with the clinical and cognitive outcomes in patients with TBI (7,14). Computed tomography (CT) and conventional magnetic resonance imaging (MRI) are relatively insensitive for these microstructural changes. Nevertheless, diffusion tensor imaging (DTI) is an advanced MRI technique that is able to probe microstructural integrity by exploring the diffusion of water molecules in brain tissues (15–17). Therefore, we hypothesized that these abnormalities would be detectable by DTI metrics along the first year after trauma.

In the last decades, DTI has demonstrated its capability to study brain architecture, geometry and microstructure, and it has been used in the evaluation of several neurological conditions, including brain trauma (18,19). Among different DTI methods of analysis, tractography has been commonly used to parcellate and to assess the white matter tracts in patients with TBI, ranging from mild to severe trauma, and even in those without associated findings in conventional MRI (20–23).

Fibre tracts connect different regions of the brain in order to modulate neuronal impulses. The greatest white matter bundle in the human brain is the corpus callosum (CC), responsible to link homologous regions of both cerebral hemispheres, and also involved in motor, psychological and cognitive activities (24). The genu, body and splenium are the main CC

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subdivisions connecting the orbitofrontal regions, the fronto-parietal lobes and the occipital cortices, respectively. Another critical tract involved in different cognitive processes such as language, memory, emotions and attention is the superior longitudinal fasciculus (SLF), which connects Broca´s area (frontal lobe), Geshwind´s area (parietal lobe) and Wernicke ´s territory (temporal lobe) in the same brain hemisphere (25). Several studies have demonstrated the vulnerability of these brain tracts in the context of patients with traumatic brain injury (20,22,26,27). However, longitudinal studies assessing the dynamic changes of white matter in DAI are scant in the literature.

This study aims to longitudinally evaluate with DTI the integrity of the CC and the SLFs in patients with moderate and severe DAI at three moments during the first year after the traumatic event, and also in comparison with a matched healthy control group. In addition, correlations between DTI quantitative parameters and neuropsychological data will also be scrutinized.

Materials and methods

Patients

Selection criteria

This study was approved by the Institutional Review Board, and all individuals agreed to be in the study and signed the informed consent form. Patients included in this study were adult outpatients (ages between 18 and 55 years old) admitted to the Emergency Room of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil, due to moderate and severe head trauma according to Glasgow Coma Scale (GCS) scores of 3–12 at initial evaluation, and who met the following criteria: (1) clinical and tomographic diagnosis of DAI, (2) a Marshall score (28) of I, II or III based on CT evaluation, (3) had no focal lesions greater than 10 cm^3, (4) had no midline shift greater than 0.5 cm, (5) had no epidural hematomas that determined compression of the brain parenchyma, (6) had no previous head injury history with hospitalization.

Description of patient's sample

Initially, 225 patients with moderate and severe head trauma were admitted in Emergency Room, but 186 were excluded due to the presence of intra- or extra-axial hematomas or cerebral contusions larger than 10 mm at initial computed tomography examination. Of the 39 remaining individuals, 19 were excluded based on the following reasons: seven losses of follow-up; five individuals had exclusion safety criteria for MRI examination; five DTI artefacts; one patient deceased; and one patient developed epidural compressive hematoma.

For the 20 patients who met the selection criteria, demographic characteristics were as follows: 17 men and 3 women; mean age was 29.6 years (SD±6.8), 14 patients presented with moderate head trauma (GCS of 9–12), and 6 patients presented with severe trauma (GCS of 3–8). The majority of patients suffered motorcycle accidents (n = 10), while the others suffered car accidents (n = 6), running over (n = 3), and physical aggression (n = 1).

Brain imaging

Magnetic resonance imaging

Each patient had a 3.0 Tesla MRI of the brain performed on the same scanner (Intera Achieva, Philips Medical System, Best, The Netherlands) with an eight-channel head coil (Philips Medical System) at three timepoints: (1) 2 months after the trauma, (2) 6 months after the trauma and (3) 12 months after the trauma. A healthy age- and sex-matched control group of 20 individuals was also scanned once.

Anatomical imaging protocol was acquired in the sagittal plane with a 3D T1-weighted Fast Field Echo (3DT1-FFE) sequence covering the entire brain (180 slices), and the following parameters: inversion time (IT) = 700 ms; TR/TE = 6.2 ms/2.7 ms; flip angle = 8°; acquisition matrix = 240 x 240; field of view (FOV) = 240 x 240 × 180 mm; voxel resolution = 1 mm^3 (isotropic); slice thickness = 1.0 mm; completion time = 4 minutes. The susceptibility weighted image protocol consisted of principles of Echo Shifting with a Train of Observations (PRESTO) 3D-T1FFE sequence, axially acquired (a total of 230 slices – 1 mm thick), according to these specifications: TR/TE = 22/29 ms; flip angle = 10°; FOV = 220 x 182 mm; matrix = 224 x 224; voxel size = 0.98 x 0.98 × 1.0 mm; completion time = 3 minutes.

DTI data acquisition

DTI images were collected in the axial plane with gradients applied in 32 non-collinear directions. The entire brain was covered within 70 slices, 2 mm-thick each, with no gaps in between. One image with no diffusion weighting was obtained (b = 0 s/mm^2). Other parameters used were: TR/TE = 8500/61 ms; b value = 1000 s/mm2; matrix = 128 x 128; FOV ("field-of-view") = 256 x 256 mm; $2mm^3$ isotropic voxel; NEX = 1; completion time = 7 minutes.

Pre-processing

All data were pre-processed using the functional MRI brain (FMRIB) software library (FSL), version 5.0 (available at http://www.fmrib.ox.ac.uk/fsl/), following this sequence: brain extraction tool (BET), FMRIB's linear image registration tool (FLIRT) and correction of eddy current induced distortions (29,30). Motion correction was completed using the free toolbox ExploreDTI (A. Leemans, University Medical Center, Utretch, The Netherlands), by rotating the B-matrix in order to keep the orientation input accurate. Investigation for residuals and outliers of the diffusion tensor fit was done with the same software, ending on residual maps similar on all groups. Moreover, the same software was used for tensor calculation and fibre tracking (31,32).

Tractography

A whole-brain tractography was first automatically obtained in the native space using a brute-force approach of every pixel. Deterministic tractography technique was then achieved following a predesigned combination of specific procedures, which included positioning of multiple regions-of-interest (ROIs) on different planes, based on prior anatomical knowledge and previous studies (33,34). The FACT (fibre assignment by continuous tracking) algorithm was calculated with

a fractional anisotropy threshold of 0.25 and maximum angles of 30° for the CC and 60° for the SLF, equally applied to all subjects (35).

The CC was segmented in three parts: genu, body and splenium. According to the Hofer and Frahm's representation (36), the genu was defined as the one-sixth part of the anterior CC, while the splenium the last one-fourth and the body the residual part. The CC was virtually dissected following these steps: first, "SEED" ROIs were marked in the paramedian plane along the CC. To securely track fibres from left and right hemispheres, "AND" ROIs were traced in the midsagittal portion, and, finally, "NOT" ROIs were drawn in the axial and coronal planes in order to eliminate horizontally and vertically oriented fibres (e.g. cingulum and corticospinal tracts, respectively). To dichotomize the SLF fibres, two "SEED" ROIs were delineated in the coronal plane, and two "NOT" ROIS were used to the axial plane to exclude any tracks that had a vertical orientation (toward the corona radiata or the corticospinal fibres) (Figure 1).

The following average quantitative DTI parameters were extracted from each track: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD).

Neuropsychological tests

An experienced neuropsychologist (ALZ) performed specific tests to assess different cognitive domains. The patients were submitted to neuropsychological (NP) assessment only at timepoints 2 and 3 because of comprehension difficulties, mental confusion and agitation typically seen in the early post-trauma stage. The results of each test were converted into a Z-score according to age and years of education. On timepoint 2, three patients were not able to complete the NP tests. On timepoint 3, one patient had missing information concerning the IQ estimation.

The Hopkins verbal learning test (HVLT) evaluates the episodic verbal memory. It consists of immediate, late recall and later recognition of a list containing 12 words (37). The examiner reads the list and the patient is asked to repeat as many words as possible. This procedure is repeated two more times and then, 25 minutes after that, the participant is required to remember the words previously learned (later recognition).

The Victoria Stroop test assesses selective attention and inhibitory control. It consists of three cards. The first card has coloured dots, the second has random coloured nouns words, and the third has the name of the colours with mismatched ink's colour (38). The patient has to say aloud the colour of the ink of the dots, nouns, and coloured names in each card as fast as possible.

Phonologic fluency was assessed by the FAS test – where the patient is asked to say as many words as possible beginning with each letter F, A and S, for 1 min each letter. For the semantic verbal fluency assessment – using animals as a category, the patient has to say as many different animals as possible in one-minute interval (38).

Digit Span (DS) forward and backward (Wechsler Memory Scale 3rd edition, WAIS – III) evaluates the working memory (39). A digit sequence is presented at one digit per second rate. The sequence starts with a two span and increases as the participant repeats it correctly. After the DS forward, the

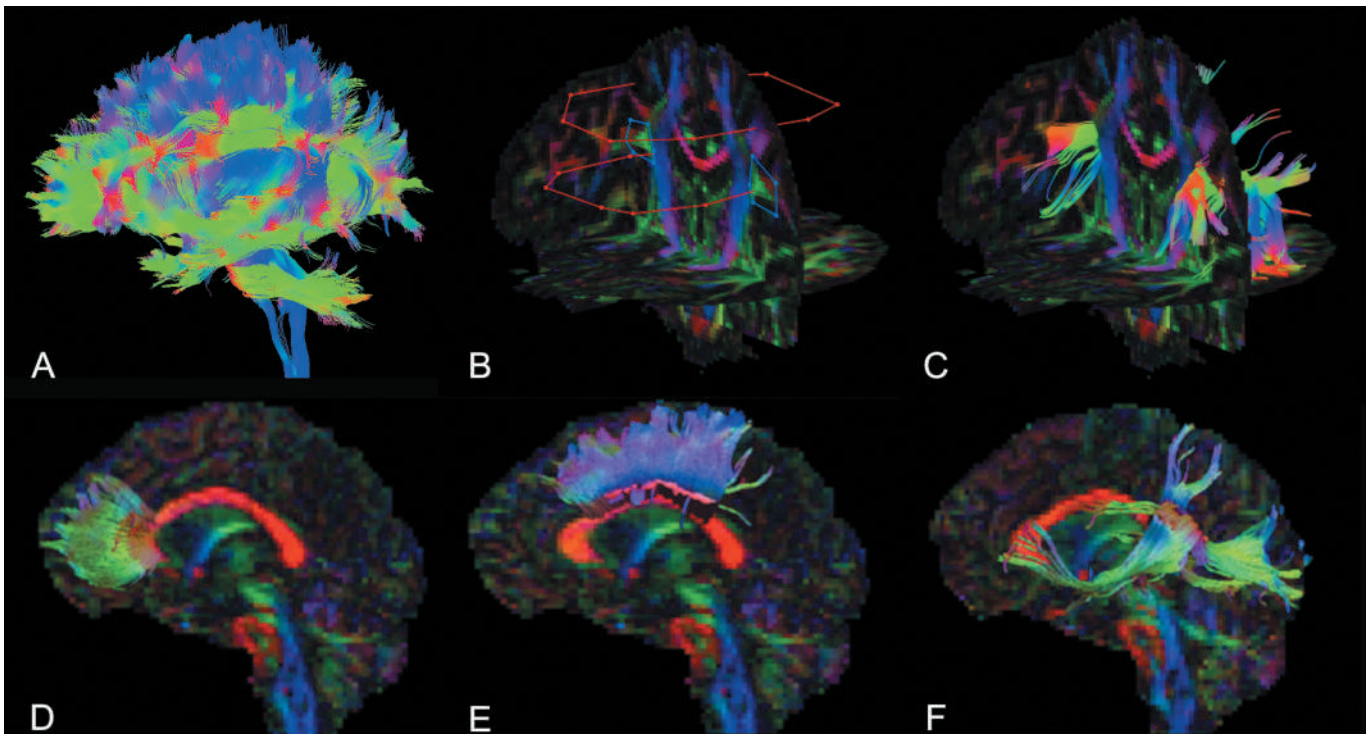

Figure 1. DTI-based tractography post-processing with ExploreDTI. (a), whole-brain tractography is first obtained with a brute-force approach. (b), SEED (in blue) and NOT (in red) ROIs placed in multiple planes of FA maps to virtually dissect the bilateral SLFs. (c). Three-dimensional representation of both SLFs on oblique view. (d, e and f) show the final results of segmentation of the CC in the lateral plane: genu, body, and splenium, respectively.

same procedure is repeated, but the digits are repeated in the backward sequence.

IQ estimation was calculated by combining the performance on both vocabulary and matrix reasoning tests present in the WAIS – III (39,40). The vocabulary test consists of the presentation of words and the patient is asked to define them. In the matrix reasoning test, a matrix of abstract pictures in which there is one picture missing is presented, and the patient has to choose one option that better suits the missing picture.

Statistical analyses

Statistical analysis was performed using IBM – SPSS statistics for Windows, version 25 (International Business Machines Statistical Package for the Social Sciences Inc., Chicago, IL, USA). A professional statistical expert was consulted for all analyses.

Initially, the data were inspected for outliers and distributional characteristics. There were no considerable asymmetries in all DTI quantitative samples or NP tests results.

Comparisons between the patients and the control group were performed with Student´s t-test. A generalized linear function test with robust standard error and unstructured correlation matrix was performed to evaluate changes over time of DTI parameters and neuropsychological tests. After that, the Benjamin-Hochberg procedure for repeated measures was performed. To calculate correlation coefficients, Pearson and Spearman's tests were used. Results were significant with p-value <0.05.

Results

Comparisons of the DTI parameters between patients and healthy controls

The DTI parameters (FA, MD, AD and RD) extracted from the CC and both SLFs in the control group and in the patients' group at all three timepoints can be seen in the supplementary Table S1.

In order to examine the early microstructural abnormalities after moderate and severe TBI, we compared the patients' group at timepoint 1 with the healthy controls (Figure 2). We found significant differences in various DTI parameters at all segments of the CC with lower FA values and higher MD and RD values in the patients' group ($p < .001$). There were no significant differences in AD in any CC segment when comparing both groups. For both SLFs, we found similar results as those found in the corpus callosum, except for AD in the right SLF, which also demonstrated significantly higher values in the patient's group ($p = .04$).

Changes in the DTI parameters along time

Table 1 summarizes the results from the generalized estimating equation (GEE) for the comparison of all quantitative DTI metrics in the patients group considering the three timepoints.

In the body of the CC, FA demonstrated a decrease between timepoints 1 and 2, and then a significant increase at timepoint 3 ($p = .02$). For both MD and AD, we also observed the same pattern of increasing values along time in the body ($p = .003$, p

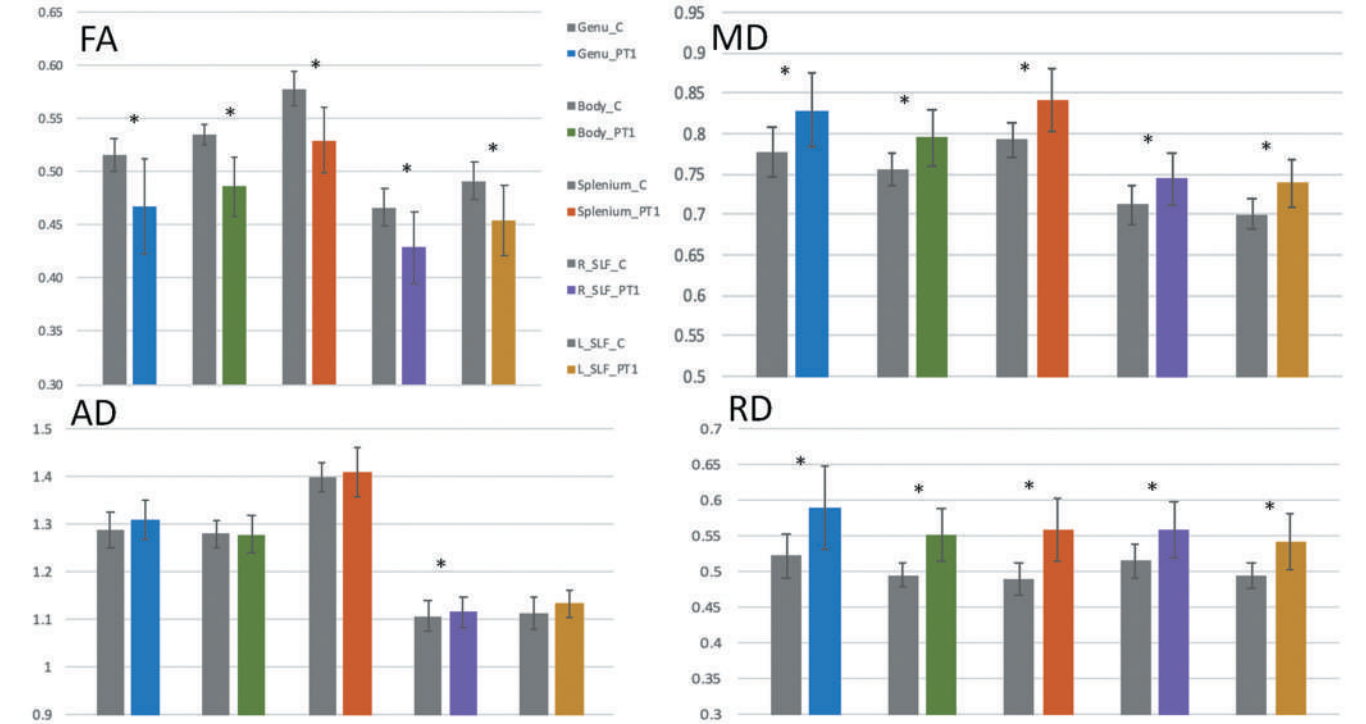

Figure 2. Column bar graphics exhibit the mean values with 95% confidence intervals (error bars) of DTI metrics (FA, MD, AD, RD) for the patients group at timepoint 1 (PT1) in each CC segment (genu in blue, body in green, splenium in orange) and both SLFs (right SLF in purple, left SLF in yellow). The corresponding parameters in the control group are shown in grey colour. MD, AD and RD are expressed in x 10^{-3} mm^2/s. Statistically significant differences ($p < .05$) obtained with Student´s t-test are indicated in the graphics with asterisks (*).

Table 1. Results obtained with generalized estimation equation to evaluate of DTI parameters in the patients group (n = 20) along timepoints 1, 2 and 3.

Tract	DTI metric	*p*-value
Genu	FA	.835
	MD	.063
	AD	.061
	RD	.181
Body	FA	*.020*
	MD	*.003*
	AD	*.025*
	RD	*.016*
Splenium	FA	.992
	MD	*<.001*
	AD	*<.001*
	RD	.070
Right SFL	FA	*.003*
	MD	.764
	AD	.575
	RD	*.035*
Left SLF	FA	*.035*
	MD	.231
	AD	.088
	RD	.180

Significant *p*-values are shown in italics.

Table 2. Z-scores computed for each cognitive domain and the statistical results after generalized estimated equation using time as a model of effect.

Cognitive domain	PT2	PT3	*p*-value
Memory	−2.478 ± 0.171	−1.980 ± 0.205	*.004*
Attention	−1.941 ± 0.249	−1.113 ± 0.251	*.001*
Verbal fluency	−1.348 ± 0.190	−1.239 ± 0.132	.473
Working memory	−0.424 ± 0.158	−0.425 ± 0.155	.993
IQ	−1.006 ± 0.141	−0.885 ± 0.144	.101

The results are shown in mean values ± standard deviations. PT2 and PT3 accounts for the patients groups at timepoints 2 and 3, respectively. Significant *p*-values are shown in italics.

= .025), and splenium ($p < .001$, $p < .001$), respectively. For RD, we found increasing values in the body of the CC ($p = .016$). There were no other significant changes in the DTI parameters in the genu of the CC (Figure 3).

We also found significant FA increases along time in both right and left SLFs ($p = .003$, $p = .035$, respectively), accompanied by a significant decrease for RD values in the right SLF ($p = .035$). No other significant changes over time for the other DTI parameters were observed in the SLFs (Figure 3).

Neuropsychological evaluation

Neuropsychological tests indicated deficits in all cognitive domains in the patients group as indicated by negative Z-scores at both timepoints 2 and 3. Along time, however, patients presented improvement of the performances on memory ($p = .004$) and attention ($p = .001$). Other domains such as verbal fluency, working memory and IQ estimation did not demonstrate significant changes throughout time (Table 2).

Correlations between DTI parameters and neuropsychological tests

There were several significant correlations between DTI parameters and the results of the neuropsychological tests at both timepoints 2 and 3. These results are summarized in the supplementary Table S2.

At timepoint 2, we found positive correlations of FA values in the genu of the corpus callosum with attention (R = 0.508, *p*

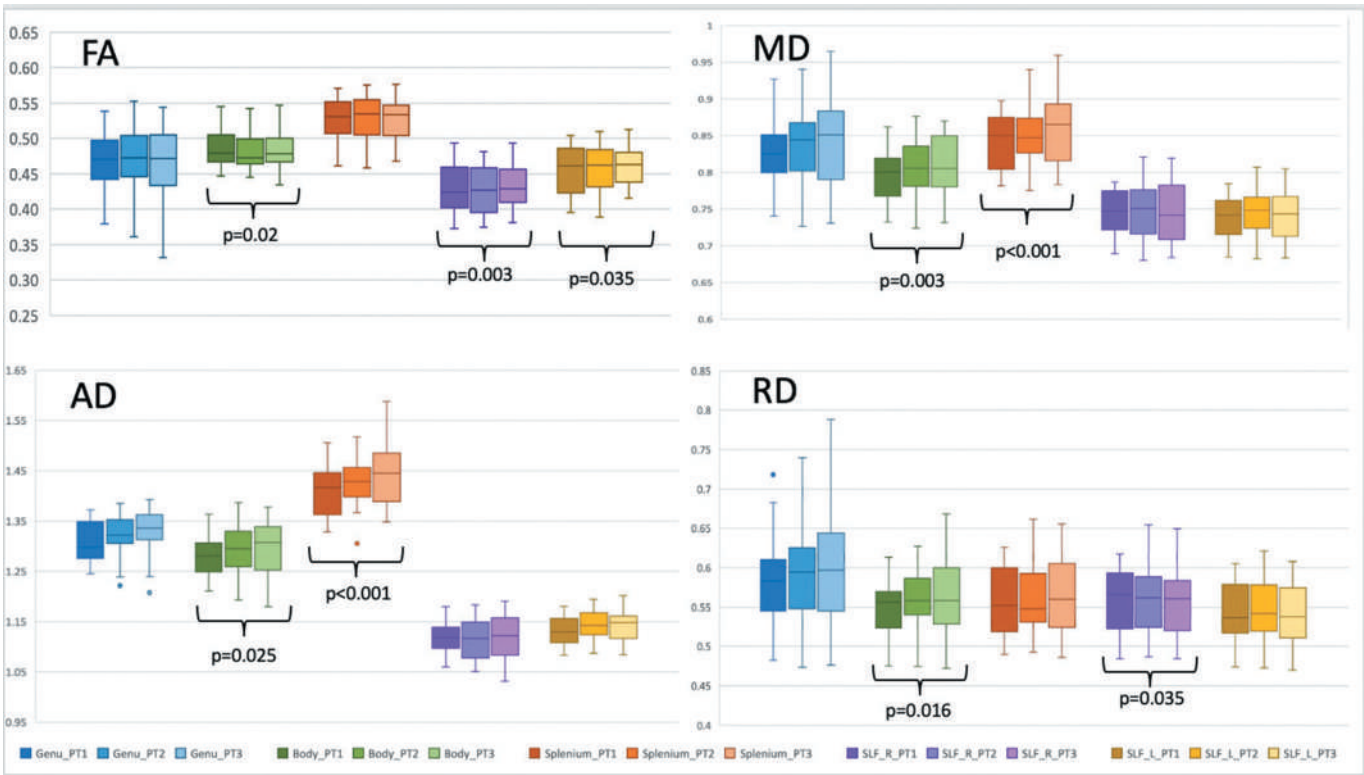

Figure 3. Box-plot graphics exhibit comparisons of DTI metrics (FA, MD, AD, RD) along time for the patients group in each CC segment and in both SLFs (genu in blue shades, body in green shades, splenium in orange shades, right SLF in purple shades, and left SLF in yellow shades). MD, AD and RD are expressed in x 10^{-3} mm^2/s. Statistically significant differences along time found with generalized linear function tests are indicated in the graphics with the corresponding *p*-values.

= .031), and in the splenium with attention (R = 0.496, p = .036) and working memory (R = 0.645, p = .003). There were also positive correlations of FA values in the right (R = 0.489, p = .039) and left (R = 0.6, p = .009) SLFs with IQ. In parallel, MD values in the genu correlated negatively with working memory (R = −0.456, p = .05), as well as in the splenium with attention (R = −0.594, p = .009), verbal fluency (R = −0.529 = p = .020), working memory (R = −0.494, p = .032) and IQ (R = −0.53, p = .024). MD values also correlated negatively with verbal fluency on left SLF (R = −0.481, p = .037). Moreover, RD values in the splenium were correlated negatively with attention (R = −0.549, p = .018), verbal fluency (R = −0.465, p = .045), working memory (R = −0.511, p = .032) and IQ (R = −0.597, p = .009); and in the left SLF with IQ (R = −0.479, p = .044). There was no evidence of correlations between AD at any regions studied and the neuropsychological results at timepoint 2.

At timepoint 3, FA values at the genu also demonstrated a positive correlation with the attention index (R = 0.514, p = .02). Correspondingly, RD values in the same site showed a negative correlation with the same cognitive domain (R = −0.445. p = .049). AD values in the left SLF showed a negative correlation with attention index (R = −0.620, p = .004). There were no other significant correlations between DTI metrics and the cognitive domains at timepoint 3.

Discussion

Our study demonstrates extensive diffusion abnormalities in the white matter, characterized by lower FA and higher MD, in all the evaluated segments in patients with DAI in comparison to healthy controls. This is coherent to the widespread feature of DAI following moderate and severe trauma and is in line with several previous works conducted in animal models and in humans (9,18–20,41–50).

FA is the most commonly used parameter in DTI studies to assess integrity and geometry of axonal fibres. High FA values (close to one) are observed in brain regions containing well-organized parallel axon arrays. On the other hand, brain regions with no internal directional organization are associated with low FA (close to zero). In contrast to FA, MD represents the overall water diffusion, regardless its direction, and is affected by both radial and axial diffusivities (51,52). It has been largely discussed which processes underlie the changes in RD and AD and how they should be interpreted (51–55). Based on mathematical models, observations of in vitro and in vivo experiments (51–53) and also studies with animal models (54,55), we think the more pronounced increments in RD found in our study are possibly associated with demyelination and neuroinflammation, particularly the water accumulation within the myelin sheath (intramyelinic oedema). There were also higher AD values in the patients' group, but this difference was significant only in the right SLF, which most likely reflects abnormalities in cell density and increase in extracellular space. Kinnunen et al. also found the same combination of abnormalities in DTI-derived scalar metrics using a voxelwise approach in patients with TBI in several brain regions, including the CC and SLFs (9). Our work reinforces the usefulness of both FA and MD as sensitive DTI biomarkers of microstructural damage in patients with DAI, even in otherwise normal-appearing parenchyma on conventional MRI.

The longitudinal evaluation of DTI parameters demonstrated that the diffusion abnormalities are not stationary, but also change into some extent along time after trauma. This was particularly evident in the body of the CC, that showed an initial decrease in FA values followed by an increase in the second phase post-injury, accompanied by an increase in MD, AD and RD in the overall study interval. There were also progressive increments in MD and AD values in the splenium. In the SLFs, there were progressive increases in FA mean values, accompanied by significant changes in RD in the right side. Indeed, several works demonstrated that, in addition to the primary axonotmesis directly caused by rotational forces at the moment of the impact, other pathological processes ensue afterwards. There is evidence of a late secondary pro-inflammatory response associated with deposition of myelin debris, overexpression of cytokines, synaptic dysfunction, activation of glial cells, and also deposition of anomalous proteins, such as Tau and beta-amyloid (56–59). On the other hand, in a search for homeostasis and regeneration, a continuous process of debris clearance and anti-inflammatory response is also triggered, with reparative mechanisms that contribute to a neurological recovery (60,61).

One study using a mouse model showed early isolated axonal injury, followed by demyelination, oedema, and persistent axonal damage up to one month after the experiment, which were accompanied by progressive changes in scalar indices, suggesting that DTI may indicate approximate timing of injury (43). Tissue reorganization have been detected to start as early as days after trauma and within 4 weeks, along with an increase in fibre density in affected regions in a rodent model (62). Other investigations conducted in humans that analyzed patients with TBI from mild to severe trauma also demonstrated FA changes from early phases up to several years after trauma (42,45,48). In addition to the continuing process of debris removal and neuronal regeneration, another reasonable explanation for the progressive increment in FA may be related to the vascular injury associated with DAI that causes local bleeding with haemoglobin degradation and iron deposition, which may also determine dynamic changes in FA values (63,64). Noninvasive methods such as DTI might be helpful to foster the understanding of the underlying complex pathophysiologic abnormalities and the microstructural anatomical substrates of the commonly observed cognitive deficits in patients with TBI.

Following recovery from transient loss of consciousness and partial or complete recuperation of acute neurological deficits caused by head trauma, survivors of DAI may present persistent disabilities, loss of productivity and impaired quality of life (1,2). Cognitive impairments depend on multiple variables, such as the trauma severity, rehabilitation and even genetic factors (65–67). A neuropsychological assessment indicated compromise of all cognitive functions in the patients' group in our study up to one year after trauma, but there was significant improvement of episodic verbal memory and attention domains along time. This is in agreement with a meta-analysis review of 39 cross-sectional TBI studies, which indicated that cognitive functions improve after

moderate to severe TBI but remains markedly impaired up to two years post-injury (67).

Moreover, we found significant correlations between DTI metrics and cognitive performances. There were positive correlations between FA values in the genu of the CC with attention at both evaluated phases, as well as negative correlation between MD values and working memory at timepoint 2. The mechanics of head trauma places the ventral and lateral surfaces of the frontal lobes in particular vulnerability for damage (68,69). Given the frontal projections of the genu, it is not surprising that executive functions mediated by these areas could be correlated with microstructural abnormalities as detected by DTI in our study. The splenium is also frequently injured in head trauma due to specific anatomical features such as its close proximity to the fixed falx that determines how the shearing forces propagates in this region. There were significant correlations between DTI indices extracted from the splenium and several cognitive domains, including attention, verbal fluency, working memory and IQ at six months post-trauma. Our results also indicated positive correlations between FA values in both SLFs and IQ at the same timepoint, in addition to negative correlations between the other DTI metrics and verbal fluency and IQ. The correlations were more pronounced in the left SLF, what may be related to the by far more prevalent functional language dominance in the left cerebral hemisphere (70). Furthermore, there were more pronounced correlations in our study at six-moths post-injury, suggesting this interval as the optimal timing of DTI data acquisition for evaluation of cognitive outcomes.

Other authors have also found correlations between DTI parameters and neurocognition. Hashim et al. evaluated 19 subacute (up to one year post-trauma) and chronic (from one up to five years post-trauma) patients with a voxelwise approach and found persistent functional loss in chronic TBI, and also correlations between diffusion indices with memory and visuomotor coordination test scores, but not with executive function (71). Another group conducted a longitudinal study with region-of-interest-based analysis at specific brain sites and demonstrated significant correlations with clinical outcomes up to 15 months after severe trauma (72). There is also evidence of associations between DTI indices and self-reported cognitive and emotional symptoms at 12 months post-injury in mild TBI (4). This study also pointed strongest effects in frontal regions including the forceps minor and the genu of the CC (4).

Lack of correlations between some DTI metrics and cognitive domains at specific sites in our study, especially in the body of the CC, may be related to the relatively low number of participants that are ideally required for correlational studies (73). Indeed, we have applied strict exclusion criteria in order to evaluate a very homogeneous group of patients with moderate and severe TBI with a pure presentation of DAI rather than evaluating patients with a broader spectrum of traumatic injuries, such as large intra-axial and extra-axial hematomas. Furthermore, another possible explanation is that distant rewiring and behavioural compensation may mediate spontaneous improvement of cognitive deficits after TBI. Although these mechanisms are not completely understood and do not represent true pathological recovery, it is supposed that second behaviour in intact circuits overtake the original cognitive function with associated shifts in anatomo-functional maps topography (74,75).

There are several methodological approaches to analyze DTI datasets. Region-of-interest analysis allows straightforward extraction of diffusion parameters from a predetermined area of the brain, but only a limited part of the cerebral structure is evaluated in two-dimensional images. Voxelwise analysis is broadly applied on research scenarios because it is suitable for global analyses of brain parenchyma and allows semi-automated comparison of large groups of patients. Some shortcomings of this approach, however, are the need for alignment and registration of brain volumes to a standard space, with its associated inaccuracies (15,18). Herein, rather than applying an exploratory evaluation prone to multiple error biases, we chose to evaluate with tractography the greatest inter-hemispheric commissure bundle and one long association tract that are known to link critical cortical regions and to modulate several cognitive functions.

Still, some caveats of the deterministic streamline tractography approach should be mentioned. This technique indirectly estimates fibre tract anatomy based on the main direction of water molecules diffusion in each voxel (in the order of millimetres), by far much bigger than the axonal diameter (in the order of microns). This assumption of homogeneous unidirectional vectors is unrealistic and gives erroneous estimations of fibre pathways in areas of crossing fibres. Furthermore, longer acquisition times and motion artefacts limit increases in spatial resolution. Other robust diffusion analysis techniques that soothe some of these limitations are evolving steadfastly, such as global probabilistic tractography, high angular resolution diffusion imaging (HARDI), q-ball imaging and diffusion kurtosis analysis (DKI) (15,18,75–77,78). So far, however, these approaches require more sophisticated processing algorithms and are less feasible for implementation in clinical settings to evaluate individual patients with TBI.

Finally, this study emphasizes the utility of DTI to obtain quantitative information about the white matter microstructure in patients with moderate and severe brain injury. Our results showed extensive and dynamic changes in DTI parameters throughout the first year after trauma. In parallel, patients also demonstrated better performance scores in different neuropsychological domains over time, which could be correlated with DTI metrics at particular brain sites, indicating the potential role of microstructural reorganization and neuroplasticity. DTI is a noninvasive method that could be helpful in monitoring progression of DAI and to select cognitively compromised patients for targeted therapies in the future.

Acknowledgments

We are also thankful to patients and volunteers who agreed to join this study.

Funding

This work was supported by FAPESP - Sao Paulo Research Foundation under Grants [2015/18136-1, 2016/05547-6 and 2017/17065-9].

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Declaration of interest

The authors have no conflicts of interest to declare.

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