Longitudinal White Matter Changes after Traumatic Axonal Injury

Alison M. Perez, Justin Adler, Nimay Kulkarni, Jeremy F. Strain, Kyle B. Womack, Ramon Diaz-Arrastia, and Carlos D. Marquez de la Plata

Abstract

Diffusion tensor imaging (DTI) has been useful in showing compromise after traumatic axonal injury (TAI) at the chronic stage; however, white matter (WM) compromise from acute stage of TAI to chronic stage is not yet well understood. This study aims to examine changes in WM integrity following TAI by obtaining DTI, on average, 1 d post injury and again approximately seven months post-injury. Sixteen patients with complicated mild to severe brain injuries consistent with TAI were recruited in the intensive care unit of a Level I trauma center. Thirteen of these patients were studied longitudinally over the course of the first seven months post-injury. The first scan occurred, on average, 1 d after injury and the second an average of seven months post-injury. Ten healthy individuals, similar to the cohort of patients, were recruited as controls. Whole brain WM and voxel-based analyses of DTI data were conducted. DTI metrics of interest included: fractional anisotropy (FA), mean diffusivity, axial diffusivity (AD), and radial diffusivity (RD). tract-based spatial statistics were used to examine DTI metrics spatially. Acutely, AD and RD increased and RD positively correlated with injury severity. Longitudinal analysis showed reduction in FA and AD (p < 0.01), but no change in RD. Possible explanations for the microstructural changes observed over time are discussed.

Key words: axonal injury; biomarkers; brain edema; diffusion tensor imaging; traumatic brain injury

Introduction

Traumatic axonal injuries (TAIs) are a common type of traumatic brain injury (TBI) involving rotational forces, occurring frequently after high-speed motor vehicle collisions and are predominantly characterized by extensive white matter damage. TAIs have serious detrimental effects on the integrity of white matter microstructure that often lead to cognitive impairments. Although studies have focused on the disruptions of TAI at the late chronic stage, there is a relative lack of understanding about what happens to white matter (WM) after TAI acutely.

Studies examining acute TAI, utilizing clinical protocols with fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), have demonstrated hyperintensities in diffuse subcortical WM regions corresponding to regions susceptible to lesions commonly seen in post-mortem histopathology studies. These acute FLAIR hyperintensities may reflect edema of cytotoxic or vasogenic origin, as water can invade either intracellular or interstitial spaces following brain injury, respectively. Additionally, these areas of hyperintensity are associated with hypointensity six months post-injury, a relationship that suggests intracranial volume loss and impairment in functional outcomes. While these clinically obtained images are useful, they do not inform us much about the WM microstructure after TAI.

Diffusion tensor imaging (DTI) has been useful in describing the microstructure compromise in the chronic stage of TAI. Several studies have reported patients months to years post-injury demonstrate increased water diffusion as measured by mean diffusivity (MD) and a reduction in the directionality of diffusion as measured by fractional anisotropy (FA) using DTI, suggesting either axotomy or demyelination. These findings, in conjunction with the apparent loss of subcortical WM volume, suggest the possibility that acute edema is an early marker of a deteriorating process that occurs after injury that ultimately leads to compromise to the integrity of axons at the chronic state. To date, very few studies have examined WM damage after human TAI in a longitudinal manner; however, the acute scans were collected, on average, within two months post-injury and smaller time windows are necessary to obtain a more thorough understanding in the evolution of WM damage.

This study examines white matter integrity, on average, one day of injury and again months later to explore the evolution of TAI. Through the investigation of DTI, this study will aid the...
understanding of the changes in the microstructure of white matter after TAI. Further, the study will examine the clinical utility of WM microstructure imaging biomarkers by examining their association between clinical markers in the acute and chronic stages.

Methods

Participants

Sixteen patients with traumatic brain injury (TBI) were recruited as part of a longitudinal observational study at the intensive care unit of Parkland Memorial Hospital. Thirteen patients participated in a longitudinal follow-up scan because three participants could not be contacted to participate at the second time point. All patients enrolled in this study sustained a closed-head TBI through a mechanism consistent with TAI, demonstrated acute subcortical white matter lesions visible on clinical MRI scans, and were at least 16 years old. Exclusion criteria included prior history of TAI, presence of focal lesions (including contusion, extra-axial hematoma, and intraparenchymal hemorrhages) with volume greater than 10 mL visible on cranial CT, midline shift, and preexisting neurologic/psychiatric conditions that may result in abnormal MRI findings and compromise cognitive functions (i.e., prior brain tumor, Alzheimer’s disease/mild cognitive impairment, human immunodeficiency virus encephalopathy, schizophrenia, etc.). Participants were taken from a convenience sample of ten healthy volunteers recruited to match the cohort of patients in age, gender, and ethnicity (Table 1). All healthy volunteers were cognitively normal and had no known history of neurocognitive disorders.

This study was approved by the institutional review board at the University of Texas Southwestern Medical Center at Dallas. Informed consent was obtained from all participants or their legally authorized representative. All research was conducted in concordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964).

Image acquisition

MRI data were collected using a General Electric Signa Excite 3.0 Tesla (T) scanner (GE Healthcare, Milwaukee, WI). Each patient was scanned twice (with the exception of three patients who could not be contacted to undergo scanning at the second time point) once within three days of the injury (mean, 1.11 days; standard deviation [SD], 0.66 days), and a second scan conducted post-injury (mean, 7.03 months; SD, 1.01 months). The DTI images were obtained using a single shot, spin-echo, echo-planar imaging sequence with field of view = 240 mm, slice thickness/gap = 3/0 mm, approximately 45 slices, repetition time = 12,000 msec, echo time = 75.5 msec, flip angle = 90°, number of excitations = 2, and a matrix of 128 × 128. The diffusion-sensitizing gradients were applied at a b value of 1000 sec/mm² per axis with 19 noncollinear directions and 3 b0 images. The acquisition time was 9 min with a voxel size of 2 × 2 × 3 mm³.

Image preprocessing

DTI images were skull-stripped using the Brain Extraction Tool (BET) from the FSL software package (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library). The images were then corrected for eddy currents using FSL’s Diffusion Toolbox. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and DTI tensor maps were calculated using FSL’s DTIFIT program.

Tract-based spatial statistics

Tract-based spatial statistics (TBSS) was used to examine white matter diffusion in a whole-brain voxel based manner. TBSS initially created a warp matrix to transform individual subjects into a common MN152 space (http://imaging.mrc-cbu.cam.ac.uk/ imaging/MniTalairach). The warp matrix is then applied to each individual subject and a mean image is derived from the subjects’ data. All aligned FA images are then averaged to create a mean FA image. The mean generated image that TBSS created was then used to form a core white matter skeleton. Each individual FA image was then projected onto a one-voxel width group mean skeleton template to represent the core white matter for the group. The core skeleton applies a given threshold of 0.2 as determined by previous TBSS methodology and searches for the highest FA values within the surrounding voxels. Voxel based analysis across subjects was carried out for all voxels with a threshold of FA ≥ 0.2 derived from the mean FA skeleton image. The core skeleton reduces the probability of noise from surrounding gray matter and registration artifacts to produce an analysis with fewer constraints from noise and morphing problems. The average FA value for the entire white matter skeleton for each patient was recorded for subsequent analysis. AD, MD, and RD data were processed using the same procedure for analysis. Two individual raters visually checked each step within the TBSS processing to ensure accuracy of the analysis.

Clinical measures

Acute injury severity measures include Glasgow Coma Scale (GCS) taken at the time of the acute scan, days spent in the intensive care unit (ICU), and days spent in the hospital.

Table 1. Significance Comparison of Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.00 36.80 15.28 17–60</td>
<td>25.50 29.11 11.29 17–58</td>
<td>23.00 28.56 12.14 16–58</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.00 16.10 3.42 11–21</td>
<td>13.00 13.14* 2.03 10–16</td>
<td>12.50 12.63 2.71* 5–16</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>60% 89%</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>90% 78%</td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>90%</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>GCS</td>
<td>4.50 6.81 4.56</td>
<td>3.00 3.93 4.55</td>
<td>7.00 8.87 6.63</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>1.00 (days)</td>
<td>1.11 (days)</td>
<td>0–3</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>3.00 (months)</td>
<td>7.03 (months)</td>
<td>1.01 6–9</td>
</tr>
</tbody>
</table>

NC, normal controls; SD, standard deviation; GCS, Glasgow Coma Scale; ICU, intensive care unit.
Chronic-stage outcome evaluations were administered approximately six months post-injury by a trained research coordinator and were supervised by a neuropsychologist; both the research coordinator and the neuropsychologist were blinded to imaging results. General functional recovery was measured using the Glasgow Outcome Scale-Extended (GOSE). GOSE scores range from 1 to 8, with higher scores suggesting better functional outcomes. Neuropsychological assessments were conducted at chronic stage scanning and included measures for processing speed, learning and memory, and executive function, and demographically corrected scores were utilized when available.

Processing speed was assessed by using performance on Trail Making Test A. Learning and memory was assessed using the California Verbal Learning Test-II. Learning was assessed by the total number of items learned across five trials, and memory was assessed by the number of words recalled after a 20-minute delay. Executive functions, defined as cognitive switching and selective attention, were assessed by using Trail Making Test B and Stroop interference condition, respectively.

Statistical analysis

Between-group differences for demographic variables were examined using independent samples t tests (Table 1). Chi-squared analysis was utilized to determine group differences for categorical variables such as gender and ethnicity. SPSS software was used (IBM Corp., Armonk, NY).

Independent samples t tests were used to examine differences in the mean values of FA, MD, AD, and RD whole-brain distributions between acute patients and controls and chronic patients and controls, and a paired sample t test was used to examine change in patients over time (p ≤ 0.05) using SPSS. Also, an exploratory analysis was conducted examining correlations between whole-brain averages of diffusivity measures, outcome measures, and neuropsychological assessments, also using SPSS. Due to the small sample size, there was not enough power in the analyses to correct for multiple comparisons; therefore, this correction was not done in order to find significant relationships between variables would not be seen otherwise.

TBSS analysis

The DTI images were analyzed with the “Randomise” statistical package in FSL. We conducted voxel wise cross-subject analysis with group comparisons including: normal versus acute, normal versus chronic, and acute versus chronic using a Monte Carlo analysis with 5000 permutations. Average skeletal voxels from mean DTI metrics were created to exclude both ventricles and gray matter using a strict 0.2 threshold. White matter skeletons were then used to create mean DTI metrics including FA, MD, AD, and RD for pairwise comparisons. Pairwise comparisons of acute and chronic data also were conducted in this manner. Significance levels were corrected for multiple comparisons using a family-wise error rate of p < 0.05 on the uncorrected TBSS output. The effect of age and gender were covaried from each comparison prior to each analysis.

Results

Demographics

Participants with TAI spent an average of 3.93 days in the ICU, as well as an average of 8.08 days in the hospital. On average, patients in this study experienced a moderate to severe TBI (mean GCS, 6.81). There were three patients included whose GCS scores fell in the mild injury severity range; however, they demonstrated subcortical white matter abnormalities on clinical imaging representing a complicated mild TAI. All groups were comparable in age, gender, and ethnicity although not in levels of education (Table 1).

Diffusion changes

In acute stages of TAI, average MD, AD, and RD values were significantly increased in patients, compared with controls (p < 0.05). Patients in the chronic stage had significantly lower FA than controls; however, AD, MD, and RD values were significantly higher in chronic patients than in controls (Figs. 1 and S1).
Pair-wise *t*-tests demonstrated significantly lower FA, MD, and AD in the chronic stage than in the acute stage of TAI patients (*p* < 0.05). While RD was numerically higher in chronic images, compared with acute images, this difference was not statistically significant.

**Spatial diffusion changes**

Group contrasts between controls and acute patients demonstrated widespread significant increases in AD, RD, and MD but no WM regions with significant decrease or increase in FA (Fig. 2). Group contrasts between controls and chronic patients demonstrated increased AD in most of WM skeletons. MD and RD also were significantly increased, compared with controls, specifically in several WM regions including the corpus callosum, internal capsule, brain stem, and centrum semiovale (Fig. 3). FA among the chronic patients was significantly decreased in the splenium of the corpus callosum, internal capsule, inferior longitudinal fasciculus, and uncinate fasciculus.

Within group analyses of diffusion parameters demonstrated significant reductions over time in FA within the corpus callosum, cingulum, fornix, and inferior fronto-occipital fasciculus/inferior longitudinal fasciculus (Fig. 4). Minimal MD increases were observed over time, and were noted in posterior callosal radiations and within the midbrain. AD was increased within various white matter regions including the corpus callosum, internal capsule, cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus (Fig. 3). There were no white matter regions with significant RD changes over time.

**Outcome**

On average, patients in this study demonstrate average functional and neurocognitive recovery at the chronic stage as measured by the GCS (mean, 6.81, SD, 4.56; Table 2). The majority of individuals in this study have GOSE scores suggestive of a good recovery (mean, 6.69, SD, 1.49).

**Correlation between DTI and outcome**

Acute RD was positively correlated with days in the ICU (*r* = 0.470; *p* = 0.038) and days in the hospital (*r* = 0.534; *p* = 0.020; Table 3). Chronic DTI metrics were not associated with acute injury measures; however, chronic FA was positively correlated with processing speed (*r* = 0.497; *p* = 0.042).

**Discussion**

This study explores the evolution of damaged WM by examining DTI changes obtained within the acute stage of injury and again at the chronic stage. Thirteen patients with complicated mild to severe TAI demonstrating subcortical white matter lesions without predominant cortical hemorrhagic lesions were examined longitudinally as they underwent serial neuroimaging scans over the course of the first seven months post-injury to better understand changes to WM integrity over time. Acute data were collected within an average of 24 hours post-injury, which is the earliest reported acquisition of DTI scans following TAI.12,17,20 The relatively short time frame offers unique insight about early changes in WM after TAI.

In the acute stage of TAI, patients exhibited an increase in white matter diffusivity (MD, AD, and RD) both globally and locally but acute FA was not changed because the increased values of AD and RD were proportional. This is consistent with acute neuroimaging studies examining FLAIR MRI.33–35 Consistent with our finding that mean FA values were not significantly different between acute patients and controls, there were no areas of white matter FA increases or decreases among acute patients. These data are slightly inconsistent with other neuroimaging studies, which found increased MD
FIG. 3. Diffusion tensor imaging (DTI) comparisons after traumatic axonal injury (TAI) of normal controls and chronic patients. A measure of fractional anisotropy demonstrates where normal controls show more diffusivity than chronic patients. All other DTI metrics demonstrate where normal controls show less diffusivity than chronic patients. Significant at $p < 0.05$ is shown in red; significant at $p < 0.01$ is shown in yellow. Green tracts are representative of skeleton created by tract-based spatial statistics. FA, fractional anisotropy; AD, axial diffusivity; MD, mean diffusivity; RD, radial diffusivity.

FIG. 4. Longitudinal diffusion tensor imaging (DTI) comparisons after traumatic axonal injury (TAI) of acute and chronic patients. Images shown depict instances where DTI measures of acute patients were more than that of chronic patients. Significant at $p < 0.01$ is shown in yellow. Green tracts are representative of skeleton created by tract-based spatial statistics. FA, fractional anisotropy; AD, axial diffusivity; MD, mean diffusivity; RD, radial diffusivity.
Healthy controls likely due to an initial decrease in RD.\textsuperscript{39,40} These findings as reflections of cytotoxic edema and inflammation.\textsuperscript{11,38} The discrepant finding with regard to FA may be explained by the timing of our respective scans, as the majority of scans in the present study were acquired within a day (all within three days) after injury, which may be too soon to detect the disproportionate changes in AD and RD required to produce increases or decreases in FA. Findings from the present study also are inconsistent with data from other research between DTI metrics and outcome measures. It is possible that a sample that included large hemorrhagic lesions in addition to subcortical white matter lesions may result in worse clinical outcomes. An evaluation of WM integrity over time in this cohort of TAI demonstrated patients underwent a general reduction in FA and AD with no significant change in RD. Essentially, patients' global FA decreased as a net result of an AD decrease and persistently elevated RD over the first seven months post-injury (Fig. S2). This finding is consistent with another longitudinal study of TBI-related WM changes,\textsuperscript{18} as they found FA decreases over time were driven by elevated RD and not by significantly depressed AD. Studies that have found elevated RD have interpreted this finding to suggest myelin is compromised causing reduced water restriction along WM bundles and resulting in greater diffusion perpendicular to axons.\textsuperscript{47–50} The mechanism that explains this finding is still unclear. However, speculatively, it is possible that edema in WM regions occurring soon after injury breaks down myelin over time through phagocytosis, and once the edema and inflammation resolve, the macrophages gradually disappear leaving behind a denuded (or partially denuded) axon. This process could explain why RD is elevated acutely and remains elevated, as an increase in RD suggests demyelination.\textsuperscript{50} The present study observed a decrease in AD over time, which is inconsistent with findings from Sidaros and colleagues showing that AD increased in select WM regions.\textsuperscript{19} Additionally, Sidaros and colleagues also found increases in FA (and stable RD) of certain WM regions, whereas FA in the present cohort declines over time. The difference between these findings may be explained in

### Table 2. Neuropsychological Testing at Chronic Stage of Traumatic Axonal Injury

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td>GOSE</td>
<td>7.00</td>
<td>6.69</td>
<td>1.49</td>
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<tr>
<td>Digit Symbol test score</td>
<td>43.33</td>
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<td>6.64</td>
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<td>Symbol Search test score</td>
<td>50.00</td>
<td>48.75</td>
<td>8.41</td>
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<tr>
<td>Stroop Reading test score</td>
<td>61.00</td>
<td>57.75</td>
<td>8.80</td>
</tr>
<tr>
<td>TMT A score</td>
<td>49.00</td>
<td>49.63</td>
<td>13.27</td>
</tr>
<tr>
<td>TMT B score</td>
<td>50.00</td>
<td>50.88</td>
<td>10.63</td>
</tr>
<tr>
<td>COWAT score</td>
<td>38.50</td>
<td>40.69</td>
<td>11.15</td>
</tr>
<tr>
<td>CVLT-II Total Learning test score</td>
<td>47.00</td>
<td>47.67</td>
<td>15.71</td>
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<tr>
<td>CVLT-II Long Delay Recall test score</td>
<td>45.00</td>
<td>45.33</td>
<td>14.31</td>
</tr>
</tbody>
</table>

**SD**, standard deviation; **GOSE**, Glasgow Outcome Scale-Extended; **TMT**, Trail Making Test A; **TMT B**, Trail Making Test B; **COWAT**, Controlled Oral Word Association Test; **CVLT-II**, California Verbal Learning Test II.

as well as decreased FA seven days post-injury.\textsuperscript{12,36,37} Conversely, other groups found increased FA and decreased diffusivity in concussive patients, compared with controls, and explained these findings as reflections of cytotoxic edema and inflammation.\textsuperscript{11,38} The discrepant finding with regard to FA may be explained by the timing of our respective scans, as the majority of scans in the present study were acquired within a day (all within three days) after injury, which may be too soon to detect the disproportionate changes in AD and RD required to produce increases or decreases in FA. Findings from the present study also are inconsistent with data from other research between DTI metrics and outcome measures. It is possible that a sample that included large hemorrhagic lesions in addition to subcortical white matter lesions may result in worse clinical outcomes. An evaluation of WM integrity over time in this cohort of TAI demonstrated patients underwent a general reduction in FA and AD with no significant change in RD. Essentially, patients' global FA decreased as a net result of an AD decrease and persistently elevated RD over the first seven months post-injury (Fig. S2). This finding is consistent with another longitudinal study of TBI-related WM changes,\textsuperscript{18} as they found FA decreases over time were driven by elevated RD and not by significantly depressed AD. Studies that have found elevated RD have interpreted this finding to suggest myelin is compromised causing reduced water restriction along WM bundles and resulting in greater diffusion perpendicular to axons.\textsuperscript{47–50} The mechanism that explains this finding is still unclear. However, speculatively, it is possible that edema in WM regions occurring soon after injury breaks down myelin over time through phagocytosis, and once the edema and inflammation resolve, the macrophages gradually disappear leaving behind a denuded (or partially denuded) axon. This process could explain why RD is elevated acutely and remains elevated, as an increase in RD suggests demyelination.\textsuperscript{50} The present study observed a decrease in AD over time, which is inconsistent with findings from Sidaros and colleagues showing that AD increased in select WM regions.\textsuperscript{19} Additionally, Sidaros and colleagues also found increases in FA (and stable RD) of certain WM regions, whereas FA in the present cohort declines over time. The difference between these findings may be explained in

### Table 3. DTI Association with Clinical Measures

<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FA</td>
<td>MD</td>
</tr>
<tr>
<td>Acute injury severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU days</td>
<td>−0.359</td>
<td>0.429</td>
</tr>
<tr>
<td>Hospital days</td>
<td>−0.473*</td>
<td>0.460*</td>
</tr>
<tr>
<td>Processing speed</td>
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<tr>
<td>Trails A</td>
<td>0.135</td>
<td>0.324</td>
</tr>
<tr>
<td>Stroop I</td>
<td>−0.031</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*p < 0.05

DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; ICU, intensive care unit.
part by the differences in the patients examined, as the present study includes only individuals with imaging evidence suggestive of subcortical white matter injury, an injury mechanism consistent with TAI (i.e., acceleration-deceleration), and minimal cortical involvement. This requirement allows for greater confidence in statements regarding predominant axonal compromise over time; however, limits the generalizability for TBI with significant and/or prominent cortical involvement. It is possible, but completely speculative at this juncture, that a decrease in AD to near normal levels may be explained by a reduction of edema that was present at the acute stage. A reduction in AD over time may be representative of a structural damage to the axon. The reduction in AD over time may also represent cytoskeletal disorganization as suggested by prior studies examining WM after TBI, as retraction balls which commonly form after axonal injury (i.e., Wallerian degeneration) may have formed over time and could be causing structural obstructions that reduce parallel diffusion.

The present study also is in contrast to findings from Mac Donald and colleagues, as they examined the effect of the controlled-cortical impact model on rodents longitudinally and found AD drops to lower than normal levels within hours of injury and for approximately four days before returning to normal levels. It should be noted that their study created cortical injuries and examined DTI metrics within pericontusional regions, and the difference in injury mechanism and location of injury may explain the different findings between their study and the present investigation, although, similarly, other studies using animal models of axonal injury also have shown decreased AD relative to controls. The present study may be a more accurate representation of what happens to humans after an acceleration-deceleration injury predominantly impacting white matter.

One limitation of this study is that the influence of scanner drift cannot be fully ruled out because the clinical scans were performed seven months apart. However, results from Takao and colleagues suggest scanner drift is negligible when using a skeltonized data. Another limitation is that TBSS is not ideal for use when WM is significantly compromised, as it is possible that the procedure excludes significantly compromised WM among patients and that the accurate identification of WM skeleton is negatively impacted by lesions in WM (Fig. S3).

This study examined the evolution of WM integrity from acute to chronic stages of TAI, typically represented in traumatic brain injuries without large hemorrhagic lesions or midline shift. The data from this study suggest complicated mild to severe TAI results in significant edema that eventually resolves leaving behind compromised WM microstructure. Further, the data suggest white matter compromise after TAI is a process involving demyelination of WM, as well as axonal damage that may be present as early as hours after injury but is better appreciated at the chronic stage. Further, this study demonstrates that very early measurements of perpendicular diffusion (RD) are related to the degree of injury severity, while the degree of parallel diffusivity at the chronic stage is a marker of axonal integrity that has implications for speed of neuronal connectivity. These findings implicating the use of DTI for early identification of individuals who may be candidates for neuroprotective agents, as reducing WM edema early after injury may result in less myelin damage in these regions and possibly less subsequent damage to the axon.

### Author Disclosure Statement

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