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Diffusion Tensor Imaging Biomarkers for Traumatic Axonal Injury: Analysis of Three Analytic Methods

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Abstract

Traumatic axonal injury (TAI) is a common mechanism of traumatic brain injury not readily identified using conventional neuroimaging modalities. Novel imaging modalities such as diffusion tensor imaging (DTI) can detect microstructural compromise in white matter (WM) in various clinical populations including TAI. DTI-derived data can be analyzed using global methods (i.e., WM histogram or voxel based approaches) or a regional approach (i.e., tractography). While each of these methods produce qualitatively comparable results, it is not clear which is most useful in clinical research and ultimately in clinical practice. This study compared three methods of analyzing DTI-derived data with regard to detection of WM injury and their association with clinical outcomes. Thirty patients with TAI and 19 demographically similar normal controls were scanned using a 3T magnet. Patients were scanned approximately eight months post-injury, and underwent an outcomes assessment at that time. Histogram analysis of FA and MD showed global WM integrity differences between patients and controls. Voxel-based and tractography analyses showed significant decreases in FA within centroaxial structures involved in TAI. All three techniques were associated with functional and cognitive outcomes. DTI measures of microstructural integrity appear robust, as the three analysis techniques studied showed adequate utility for detecting WM injury.

Keywords

DTI; DAI; Traumatic Brain Injury; memory; Tractography; cognitive outcomes

INTRODUCTION

Traumatic axonal injury (DAI) is common after brain trauma involving rotational acceleration-deceleration forces often produced by high-speed motor vehicle collisions. Clinically, TAI is inferred when patients' clinical presentation is worse than predicted based on unremarkable computed tomography (CT), as CT has shown to be very insensitive to shear injuries (Gentry, Godersky, & Thompson, 1988; Ogawa et al., 1992). Traditional magnetic resonance imaging (MRI) sequences are more sensitive than CT for WM lesions in

areas commonly affected by TAI, but remains a modest predictor of outcome likely due to insensitive detection of the diffuse injury (Diaz-Marchan, Hayman, Carrier, & Feldman, 1996; Marquez de la Plata et al., 2007). Diffusion Tensor Imaging (DTI), a magnetic resonance modality assessing the integrity of WM, has been used to study diseases affecting subcortical areas such as multiple sclerosis and HIV dementia (Budde et al., 2007; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007; Saindane et al., 2007; Schmierer et al., 2007; Thurnher et al., 2005; Wu et al., 2006). One of the DTI parameters used to characterize the integrity of WM is fractional anisotropy (FA) which measures the directionality of water diffusion in WM. Generally, studies have found FA is sensitive to WM integrity, as water diffuses in a relatively more anisotropic manner in intact WM and less so in compromised WM (Arfanakis et al., 2002; Huisman et al., 2004; Inglese et al., 2005). Furthermore, the mean amount of diffusion regardless of directionality [i.e., mean diffusivity (MD)] within particular white matter structures is also sensitive to compromise after TBI (Huisman et al., 2004; Inglese et al., 2005).

DTI has recently shown sensitivity to axonal damage in patients with chronic TAI using several methods (Benson et al., 2007; Newcombe et al., 2007; Xu, Rasmussen, Lagopoulos, & Haberg, 2007). Conventional region of interest (ROI) analysis involves selecting areas of a given voxel size within a known anatomic structure, and comparing a measure of diffusion for those regions between patients with lesioned WM and healthy controls. This approach has revealed greater FA and lower MD in intact subcortical WM regions among controls than patients with TAI (Benson et al., 2007; Huisman et al., 2004; Inglese et al., 2005; Saindane et al., 2007; Wu et al., 2006). However, conventional ROI analysis is poorly suited for routine clinical practice and research, as it requires an operator with expertise in neuroanatomy to place the ROIs for adequate intra- and inter-rater reliability, is time consuming, and involves some inherent subjectivity, introducing error.

Another ROI approach is diffusion tensor tractography (DTT), which reconstructs WM structures based on the anisotropy of water, and allows one to examine the integrity of these structures (Wang et al., 2008). This approach involves reconstructing WM fiber bundles by identifying neighboring voxels in the brain that reach a specified FA threshold and pass through the projected path of the structure of interest. The resulting reconstructed fiber bundles are the regions of interest from which FA or other DTI-derived parameters can be extracted. This procedure has been used to show the extent of WM injury in TBI as well as stroke, finding significant FA and MD differences in WM structures affected by the disease process (Lee et al., 2005; Wang et al., 2008; Xu et al., 2007). The corpus callosum (CC) is commonly affected by TAI (Gentry et al., 1988). Recently, Xu et al. (2007) found patients with chronic TBI demonstrated earlier termination of reconstructed CC fibers than healthy controls. However, this procedure has its own drawbacks, as operator error may be introduced when placing seed ROIs along the trajectory of a WM structure, and the procedure is relatively labor intensive which may further limit its clinical utility.

Whole-brain analysis of FA is also sensitive to WM injury. This procedure might involve segmenting all WM within the brain using a masking function, and examining the distribution of DTI-derived data for voxels within this mask. Benson et al. (2007) reported FA histogram properties (i.e., FA mean, peak, skewness, and kurtosis) were globally decreased in patients with very chronic TBI compared to healthy controls, and were significantly correlated with clinical severity measures [i.e., Glasgow Coma Score (GCS) and length of posttraumatic amnesia]. This approach to analyzing FA is automated, involves minimal operator subjectivity, and represents a much simpler and quicker method of measuring the overall extent of WM injury.

Voxel-based analyses (VBA) of FA is yet another method of determining the integrity of WM that may prove useful as a biomarker for TAI. This procedure does not involve a priori assumptions of affected WM; rather, it is a voxel by voxel comparison of FA values between two groups of brains. Voxel-based analysis is automated and objective, but requires spatial normalization and presents a biostatistical problem of multiple comparisons. Nonetheless, VBA may be preferred to other means of assessing WM integrity, as it examines the integrity of WM over the entire brain (an advantage over ROI-based methods and tractography) and may show injury to specific WM areas (an advantage over histogram analyses).

The ability of these approaches to measure differences between healthy and brain injured populations and to correlate with clinical outcome have not been evaluated in a single study. Such an investigation is critical to examine the clinical utility of these techniques and facilitate the identification of potential biomarkers of cognitive dysfunction following TBI. The present study aims to examine the utility of three methods that measure degree of WM injury eight months post-traumatic axonal injury, and their respective associations with functional and neurocognitive outcome. The authors hypothesize that all three analytic techniques will differentiate patients with TAI from uninjured controls. Furthermore, VBA and tractography are expected to show compromise in centroaxial white matter regions including the corpus callosum, fornix, and internal capsule among patients. Additionally, we expect global and regional white matter compromise to correlate highest with functional outcome, and expect integrity of reconstructed limbic structures to correlate best with learning and memory deficits.

METHOD

Participants

Thirty patients with TBI recruited prospectively as part of a longitudinal observational study at Parkland Memorial Hospital were included in this study. Inclusion criteria for TBI patients: 1) sustained closed head traumatic brain injury through a mechanism consistent with TAI (such as high-speed motor vehicle collision), 2) were at least 16 years old. Exclusion criteria were: 1) preexisting neurologic disorders or prior history of TBI, 2) presence of focal lesions (including contusion, extra-axial hematoma, and/or intraparenchymal hemorrhages) with volume greater than 10ml visible on cranial CT, 3) neurologic/psychiatric conditions which may result in abnormal MRI findings and compromise cognitive functions (i.e., prior brain tumor, Alzheimer's disease/mild cognitive impairment, HIV encephalopathy, schizophrenia, etc.). All patients demonstrated acute subcortical white matter lesions visible on T2 FLAIR MRI that resolved by the time the images for the present study were acquired (Ding et al., 2008). Nineteen healthy volunteers of similar age and gender were recruited as controls resulting in a cohort of controls who were demographically similar to the cohort of patients. All healthy volunteers had good general health and no known neurocognitive disorders.

This study was approved by the Institutional Review Board at UT Southwestern Medical Center at Dallas. Informed consent was obtained from all participants or their legally authorized representative.

Image Acquisition

MRI data were collected using a General Electric Signa Excite 3.0 Tesla (T) scanner (GE Healthcare, Milwaukee, Wisconsin) scanner. Each subject was scanned approximately eight months post-injury. The DTI images were obtained using a single shot, spin-echo, echo-planar imaging sequence with field of view (FOV) = 240 mm, slice thickness/gap = 3/0 mm,

approximately 45 slices, repetition time = 12000 milliseconds, echo time = 75.5 milliseconds, flip angle = 90°, number of excitations (NEX) = 2, and a matrix of 128 × 128. The diffusion-sensitizing gradients were applied at a b value of 1000 s/mm² per axis with 19 noncolinear directions and 3 b₀ images. The acquisition time was 9 minutes. The voxel size was 2 × 2 × 3 mm³ interpolated (scanner default) to 1 × 1 × 3 mm³. Three-dimensional (3D) T1-weighted structural FSPGR images were obtained with FOV = 240 mm, slice thickness/gap = 1.3/0 mm, approximately 130 slices, echo time = 2.4 milliseconds, TR = 8ms, flip angle = 25°, NEX = 2, and a matrix of 256 × 92, and an acquisition time of 6 minutes.

Image Preprocessing

DTI images were skull-stripped using Brain Extraction Tool (BET) of FSL software package (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library: <http://www.fmrib.ox.ac.uk/fsl/fdt>). The images were then corrected for eddy currents using FSL's Diffusion Toolbox. After tensor calculation, fractional anisotropy (FA), mean diffusivity (MD), and DTI color maps were calculated. The b₀ images, obtained from DTI datasets, were segmented using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). The FA and MD maps were normalized to a template brain in Montreal Neurological Institute (MNI) space using a 12 parameter linear registration process and a subsequent nonlinear registration procedure available through SPM5.

Histogram Based Analyses Preprocessing and Image Analysis—To retain high sensitivity, all B₀, FA, and MD images were analyzed in their native space. In-house MATLAB programs were written to threshold the b₀ segmented WM images at 86%, which is consistent with prior study using a similar technique (Anbeek, Vincken, van Osch, Bisschops, & van der Grond, 2004), and to create a global WM mask. Next, the WM mask was applied to FA and MD maps and voxel count normalization was performed. Last, individual and group histograms were plotted and their histogram characteristics (e.g. mean and skew) were calculated.

DTI Voxel Based Analysis Preprocessing and Image Analysis—Normalized FA maps for normal controls were averaged and smoothed with a 4mm full-width half maximum (FWHM) kernel to create a spatially normalized FA template. Subsequently, all FA maps (patients and controls) were normalized and smoothed with an 8mm kernel. Voxel-wise statistics were performed on these images using SPM5. A two-tailed two-sample t-test was performed between patient and control groups, restricting the analysis to WM voxels by using a normalized mask of WM derived from FSL's MNI Avg152, T1 2×2×2. A false discovery rate (FDR) correction was set to 0.05, and a minimum cluster size was defined as 50 voxels. WM lesion loads (i.e., the number of voxels showing below normal FA within each participants' brain) were calculated by conducting a series of t-tests between the pooled FA map of controls from the above step and each individual patient's FA map. The result of each t-test was a map of voxels with below-normal FA, and these identified voxels will be summed for each patient.

DTI Tractography Analysis—Tractography was performed with DTI Studio (Johns Hopkins Medical Institute, <http://lbam.med.jhmi.edu/>) utilizing the Fiber Assignment by Continuous Tracking algorithm (Mori, Wakana, Nagae-Poetscher, & van Zijl, 1999). WM fiber bundles were reconstructed using a minimum FA threshold of 0.25 and a maximum turning angle of 60 degrees. Fiber tracts were reconstructed using a multiple ROI approach, as the OR, CUT, and AND functions were used to select or exclude fibers that pass certain regions of interest on a color map, following the guidelines by Wakana, Jlang, Nagae-Poetscher, van Zijl, and Mori (2004). The multiple ROI approach increases accuracy and inter-rater reliability of the reconstructed tracks (Wang et al., 2008). Given two raters were

used to reconstruct white matter tracts, inter-rater reliability was assessed and ICC values ranged from 0.91 to 1.00 across all structures suggesting they were reliably reconstructed.

The reconstructed tracts were categorized as either 1) interhemispheric commissural, 2) limbic, or 3) association fibers. Interhemispheric commissural fibers consisted of WM tracts of the CC. Since CC is a large fiber bundle that connects various parts of the brain, it was parceled into 4 equal areas: CC₁ through CC₄ that correspond to the genu, anterior and posterior body, and splenium of the CC. Limbic fibers included WM tracts of the fornix body (FB), bilateral perforant path (PP), and cingulum (CI). Association fibers included bilateral uncinate fasciculi (UNC), inferior longitudinal fasciculi (ILF), and the inferior fronto-occipital fasciculi (IFO). Rigorously defined anatomical landmarks for ROI slice selection and placement were utilized to reduce subjectivity in fiber tracking. FA and MD were recorded for each tract.

Outcome Measures

Outcome measures were administered approximately eight months after injury by a research coordinator who completed standardized training, was supervised by a neuropsychologist, and was blinded to imaging results.

Functional Outcome—Overall patient functional outcome was measured using the Glasgow Outcome Scale – Extended (GOSE; Wilson, Pettigrew, & Teasdale, 1999), a structured interview that assesses various domains of functional abilities following brain injury. GOSE scores range from one to eight, where higher scores represent better outcomes.

Neuropsychological Outcome—Because processing speed (PS), learning and memory (LM), and executive function (EF) deficits are common after TBI (Brooks, Campsie, Symington, Beattie, & McKinlay, 1986; Levin, 1990; Mathias & Wheaton, 2007; McAllister, Flashman, McDonald, Brenna, & Saykin, 2002; Ylvisaker & Feeney, 1996), several neuropsychological measures of each of these domains were selected for analysis. We assessed PS by using the age corrected scores on the Digit Symbol Coding and Symbol Search subtests from the WAIS-III (Wechsler, 1997), and demographically corrected T-scores from the Trail Making Test A (TMT A; Reitan, 1958).

EF deficits were measured using Trail Making Test B (TMT B; Reitan, 1958), Controlled Word Association Test [COWAT; Benton, Hamsher, & Sivan, 1976], and Stroop interference condition (Dodril, 1978)]. Age, education, and gender corrected scores were analyzed for TMT B and COWAT.

LM was assessed using the California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 2000). Learning was measured using the T-score for the total number of items learned across 5 trials, and memory was assessed using the T-scores for long delay free recall. LM performance was age and gender corrected.

Statistical Analyses

Between-group differences for demographic variables were examined using independent samples t-tests ($p \leq 0.05$). Gender and ethnicity differences were tested using a χ^2 test for independence ($p \leq 0.05$) (Statistical Package for Social Sciences (SPSS v11.0; SPSS, Chicago, IL), as these data were categorical. Independent samples t-tests were used to examine differences in the mean and skewness of FA and MD distributions between patients and controls ($p \leq 0.05$). Mean FA and MD values for each reconstructed WM tract were examined for between group differences using independent samples t-tests ($p \leq 0.05$). Levene's test was used to test for equal variances between groups, and the appropriate

probability value associated with the independent samples t-test were used to determine between groups differences. Pearson correlations were used to determine the association between outcome measures and neuroimaging parameters ($p \leq 0.05$). A Spearman's correlation coefficient was used to examine associations between imaging metrics and GOSE, as the latter yields ordinal data ($p \leq 0.05$). False discovery rate (FDR) corrections were used on the correlations between the various reconstructed tracts and clinical outcome to correct for multiple comparisons (FDR, $p \leq 0.05$). None of the assumptions for the statistical tests used were violated.

RESULTS

Demography

Patients predominately suffered severe injuries, as the median GCS score was 3 (range = 3 – 15), and spent an average of eight days in the intensive care unit (range = 0 to 24 days). As expected there were no significant differences between patients and controls with regard to age or gender; however, controls were significantly more educated than patients. Approximately eight months after injury, patients were rated as having an upper moderate disability (GOSE = 6). Cognitively, as a group, patients performed in the low-average to average range on most neurocognitive tests, but demonstrated mild cognitive deficits (i.e., at least one standard deviation below the standardization sample's mean score) on a verbal fluency task, a test of delayed verbal recall, and a processing speed task.

Whole-Brain Histogram Analyses

Whole-brain WM mean FA was significantly lower among patients than normal controls. Furthermore, the distribution of FA values was more positively skewed for patients than controls. The average whole-brain WM MD value was greater among patients than normal controls, but the skewness of their distributions was not significantly different.

The mean value for the FA distribution among patients showed significant correlations with the GOSE, two of three PS measures, two of three EF measures, and both LM scores. FA skewness was negatively correlated with GOSE and the Stroop interference condition (see Table 3). The average MD of global WM among patients showed significant but modest correlations with GOSE, two of three PS measures, one of three EF measures, but none of the LM measures.

Voxel Based Analysis of FA

Between groups voxel based analysis of FA showed significantly lower values in centroaxial WM structures including the CC, posterior limb of the internal capsule, fornix, and corona radiata (FDR = 0.05) (See Figure 1). The voxel based analysis also revealed significant FA compromise in WM regions including the corticospinal tract, uncinate fasciculi, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, and superior longitudinal fasciculi fibers.

Patient lesion loads show significant statistical associations with functional outcome, one of three PS measures, both of the LM measures, but none of the EF measures (see Table 4).

Tractography-based Analyses

Patients FA and MD values of most reconstructed fiber tracts were statistically different as compared to controls (see Tables 5 and 6). FA values for several reconstructed fibers showed significant correlations with neurocognitive outcome including the CC, FB, bilateral ILF, and bilateral IFO (see Table 7). FA values for the CC, right ILF, and right IFO correlate

significantly with functional outcome. Furthermore, MD was not associated with outcome among any of the reconstructed tracts.

DISCUSSION

The present study examined the utility of three methods of measuring WM injury months after TAI. In general, the results suggest all three analytic techniques demonstrate similar levels of compromise in WM following TAI. Furthermore, each analytic technique supports the notion that measures of WM integrity are associated with clinical outcome.

Distribution Analysis of Global White Matter Changes Post-TAI

Using a histogram analysis, we examined the distribution of FA and MD, and noticed a shift in the distribution of FA among patients indicating a greater frequency of WM voxels with low FA values as compared to controls. Consequently, the distribution of MD values among patients was also shifted, but indicated a relatively greater frequency of higher MD values as compared to controls. These findings suggest microstructural WM changes occurring as a result of TAI are present approximately eight months post-injury, and can be identified using gross quantification of DTI-derived values of WM integrity. A post-hoc analysis of covariance, demonstrated all of the above group differences remained significant after accounting for variance associated with education, suggesting distribution analysis of WM integrity is not significantly influenced by level of education.

Histogram analysis findings from this study are consistent with prior investigations examining the distribution of global DTI-derived values among patients with TBI (Bazarian et al., 2007; Benson et al., 2007; Lipton et al., 2008). For example, Benson and colleagues (2007) found the shape of patient FA histograms were more peaked and skewed compared to controls; however, their sample was limited to individuals who on average suffered a TBI approximately three years prior to being scanned (range 3 days – 15 years). Interestingly, the present results are in contrast to Newcombe et al. (2007) who found WM FA histograms showed a slight leftward shift among patients, but the shape of the histograms between patients with TBI and controls were not statistically significantly different. One possible explanation for their failure to detect FA differences using the histogram approach may be related to how soon after injury they obtained their diffusion images, as they studied images acquired within a week of injury. Consequently, their diffusion measures may have been impacted by edema, which is common in the acute phase following moderate to severe TBI, whereas the present study of chronic diffusion imaging is not. The present study, to our knowledge, is the first to examine the distribution of whole brain WM among patients with relatively more severe TBI during a fairly early chronic phase; a time when swelling is likely resolved and the impact of injury to the axons is more readily observed. Additionally, the current results extend the use of FA distribution analysis from a marker of initial injury severity (Bazarian et al., 2007; Benson et al., 2007) to a marker of clinical outcome, as the results showed the mean (and to some extent skewness) of whole brain WM FA and MD distributions correlated with functional outcome and performance on certain cognitive tasks.

Voxel-Based Analysis of Regional White Matter Changes Post-TAI

The voxel-wise approach of examining the sensitivity of DTI for detecting regional compromise in WM among patients with TAI found significantly reduced FA in several major WM structures commonly implicated in diffuse axonal injuries among histopathologic and prior radiologic studies (Adams, Graham, Scott, Parker, & Doyle, 1980; Adams et al., 1982; Adams, Graham, Murray, & Scott, 1991; Gentry et al., 1988; Huisman et al., 2004; Marquez de la Plata et al., 2007; Nakayama et al., 2006; Xu et al., 2007) including the CC, posterior limb of the internal capsule, fornix, corona radiata, corticospinal tract, and

association fibers. Recent investigations employing voxel based analysis of diffusion tensor data have found reduced FA in several centroaxial WM structures among patients with mild to severe TBI (Bazarian et al., 2007; Bendlin et al., 2008; Lipton et al., 2008; Nakayama et al., 2006; Xu et al., 2007). For example, Nakayama and colleagues (2006) found significantly lower FA in the CC among patients with severe TAI, and confirmed these differences using an ROI analysis. Results from the present investigation are commensurate with Nakayama et al. (2006); however, given that we included patients with complicated mild and moderate injuries, it extends prior findings to less severe cases of TAI.

Voxel based analysis of DTI-derived data appears to have an advantage over a distribution-based analysis, as the former can identify regions of abnormal WM throughout the brain while the latter detects global WM abnormality but says nothing about the spatial location of the abnormalities. A valid concern regarding voxel-wise analyses is the risk of false positives due to the problem of multiple comparisons. The present study utilized three safeguards against Type I errors including reducing the number of voxels for comparison by restricting the analysis to voxels in WM using a standard WM mask, correcting the probability value for between group voxel-based analyses, and utilizing a minimum voxel size cluster threshold. Our analysis found significant between-group differences in expected WM regions using a fairly conservative false discovery rate correction of 0.05 and a minimum cluster size of 50 voxels, which excludes isolated voxels with decreased FA.

Another concern regarding VBA has to do with requiring spatial normalization, as it is necessary for voxel by voxel comparisons, but may introduce error especially for patients with significant focal lesions and/or atrophy. Patients in the current study had predominant subcortical WM injuries and were excluded if large focal lesions and/or significant midline shift were present. Voxel-based analyses of FA also lacks specificity in regions in which multiple WM structures run through. For example, the present study finds compromised FA in a region common to the uncinate fasciculus and the inferior fronto-occipital fasciculus, and it is not known which or whether both structures are truly compromised.

While the sensitivity of voxel-based analyses to WM compromise in moderately to severely injured cases of chronic TAI has been previously reported, the association between degree of WM compromise and outcome is novel. One study using DTI in moderate to severe cases of pediatric TBI utilized clinical data to characterize their sample's impairments compared to controls (Wozniak et al., 2007); however, we utilized clinical outcome data as continuous variables to correlate with the degree of WM compromise. Furthermore, Bazarian and colleagues (2007) examined a sample of five mild cases of TBI at the acute stage and found their whole brain WM measure correlated with early neurobehavioral test scores assessed 72 hours post-injury. Our results showed that greater WM compromise is associated with poorer functional outcome and poorer performance on a measure of PS, and measures of LM at the chronic stage. To our knowledge, this study is among the first to show DTI-derived WM integrity measures are associated with clinical outcomes among more severely injured adults with chronic TAI. These results suggest examination of regional WM integrity in an automated and unbiased manner at the chronic stage may be utilized as a biomarker for outcome after TAI. Given the association between measures of global WM integrity with clinical outcome, these results have important implications for future clinical research, as these techniques may someday be useful in trials of potential neuroprotective agents targeted at axonal injury, either as a means to select or stratify patients or as a marker for treatment outcome.

Tract-Specific White Matter Changes Post-TAI

Our tractography results demonstrated significant differences in the integrity of various WM structures between healthy controls and patients with TAI. The impact of TAI on

reconstructed WM tracts in this study resemble what is observed in histopathologic studies, such that the CC and fornix were negatively impacted by acceleration-deceleration type injuries. Furthermore, our results suggest DTI tractography is also sensitive to injury beyond the centroaxial structures, as association fibers and other limbic structures also showed evidence of compromise.

Interestingly, increased water diffusion (i.e., MD) occurring in the CC after injury was uniform throughout the structure; however, the directionality of water diffusion in the CC was minimally impacted in the anterior body of this structure. This finding may suggest the CC is not affected uniformly after TAI, and is supported by several studies of brain injury using conventional MRI and DTI measures (Adams et al., 1982; Gentry et al., 1988; Leclercq, McKenzie, Graham, & Gentleman, 2001; Rutgers et al., 2008; Wang et al., 2008). Rutgers and colleagues (2008) found FA in the genu and the splenium of the CC among moderately to severely injured patients was significantly lower compared to controls, but the body of the CC did not show significant compromise. Furthermore, the notion that the body of the CC was minimally affected by DAI is also supported by our VBA results, as the genu and splenium showed compromised FA, but the body of the CC was relatively spared.

Since memory impairment following TBI is common, we decided to reconstruct several limbic WM structures to determine whether compromise to these structures can be detected using DTI at the chronic phase. It is not surprising that the integrity of the reconstructed fornix was compromised, as this has been shown previously (Nakayama et al., 2006; Wang et al., 2008) however, the integrity of the perforant pathway and cingulum bundles also showed compromise in our study, which are novel findings in moderate to severe TBI among adults. Both the perforant pathway and the cingulum bundle play important roles in learning and memory, as they are afferents to the hippocampus and are involved in Papez circuit (Mark, Daniels, Naidich, & Hendrix, 1995). Furthermore, both structures are compromised among patients with Alzheimer's disease, a clinical population in which memory deficits are universal (Catheline et al., 2008; Hyman, Hoesen, Kromer, & Damasio, 1986). It is noteworthy that while the MD in reconstructed bilateral perforant pathway and cingulum bundles showed significant compromise as compared to controls, FA in these tracts were only significantly different for the right hemisphere and showed a strong trend toward significance in the left hemisphere. Our VBA results partially concur with these tractography findings, as they show significantly compromised FA in bilateral medial temporal lobes and in bilateral medial centrum semiovale consistent with compromise in the perforant pathway and cingulum bundle, respectively. The disparity between these two methods may be due to the lack of spatial specificity involved in VBA, as decreased FA in the left medial temporal lobes may actually reflect compromise to the uncinate fasciculus rather than the perforant pathway. In this regard, tractography has an advantage over VBA, as the former assesses the integrity to specific WM structures as opposed to regions.

The integrity of many limbic structures was positively associated with memory performance. Despite not showing large between group differences, the FA in the fornix was positively correlated with every neurocognitive measure obtained. Additionally, as expected, most of the reconstructed limbic fibers (4 of 5) correlated with a measure of verbal memory. Interestingly, performance on the CVLT-II among patients in this study was significantly correlated with reconstructed posterior CC fibers. This finding suggests damage to the splenium and posterior body of the CC after TAI negatively impact learning and memory of verbal information. This is not surprising, as the posterior half of the CC is known to have projections to the temporal lobe (Pannek et al., 2010). Furthermore, the posterior half of the CC is also heavily interconnected with the frontal lobes, which may explain why compromise in the posterior body and splenium is associated with decrement in PS and EF as well.

While tractography is useful for detecting compromise to several WM structures involved in TAI and was correlated with post-injury outcomes, the deterministic tractography procedure used in this study has its limitations. Deterministic tractography requires expertise in neuroanatomy and training with regard to using the software suite to draw reliable ROIs, as the procedure may introduce error when placing seed ROIs along the trajectory of a WM structure. Furthermore, the reconstruction of specific WM tracts is relatively more labor intensive in comparison to the other two analytic techniques studied, which may limit its clinical utility. Automated and atlas-based methods of analyzing DTI data to reconstruct WM tracts such as those proposed by Hagler et al. (2009) and Zhang, Olivi, Hertig, van Zijl, Mori, (2008) may reduce operator error or subjectivity involved with tractography and may therefore be better suited for future research. Additionally, a post-hoc analysis of covariance suggests the integrity of reconstructed WM tracts may be associated with education, as many of the p-values for between group differences in FA and MD decreased when education was used as a covariate; however, the FA of only 4 of 16 structures were no longer significantly different ($p < 0.05$) between patients and controls (3 of 16 tracts for MD) when controlling for education. These results suggest the impact of WM injury after TAI in this sample outweighs the influence of education on the integrity of reconstructed tracts.

Conclusion

The present study examined the utility of three methods to analyze DTI data to identify a biomarker of TAI that is both sensitive to WM changes and associated with clinical outcomes. Two of the analysis techniques are geared toward detecting WM changes occurring throughout the brain's white matter, and may be more robust than techniques requiring operator defined regions of interest, as they are almost entirely automated and are unbiased with respect to where WM changes may be found. The third technique reconstructs specific WM tracts using DTI-derived data and subsequently allows detection of microstructural compromise within these tracts. The three techniques produce qualitatively comparable results. All three analysis techniques identify TAI-related compromise to WM in the chronic stage following TBI, and many of the derived metrics were correlated with clinical outcomes. Clinicians and clinical investigators may wish to select an analysis technique that best suits their needs and resources. Generally, analysis of the frequency distribution of global WM using DTI-derived data is a much simpler and quicker method of measuring the extent of WM injury than the other methods used; however, it is less specific and does not convey information about particular WM regions or tracts. Voxel-based analyses of FA is an effective method of identifying microstructural compromise within WM regions, and has the advantage of not involving a priori assumptions of affected WM. Furthermore, this procedure may be more suitable for automation than deterministic tractography or conventional ROI analyses. While diffusion tensor tractography can detect compromise to commissural, limbic, and association fibers after TAI, the association between tractography-derived measures of integrity within limbic and association fibers and cognitive outcome is nonspecific. Given their sensitivity to microstructural WM compromise and relation to clinical outcome, all three analysis techniques show promise as markers to assist with selecting appropriate candidates for TAI-directed therapies or as potential markers of treatment outcome.

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Figure 1.

Note. The figure shows regions of significant between group FA differences superimposed on a standard template T1 image. UNC = Uncinate fasciculus, ILF = Inferior longitudinal fasciculus, CST = Corticospinal tract, IFO = Inferior fronto-occipital fasciculus, CING = Cingulum bundle, PLIC = Posterior limb of the internal capsule, CC-G = Corpus callosum genu, CC-S = Corpus callosum splenium, CR = Corona radiata. (FDR = 0.05, cluster threshold = 50 voxels).

Table 1

Participant Characteristics

	NC n=19			TBI n=30			p
	Median	Mean	SD	Median	Mean	SD	
Age	26.00	28.68	10.13	17 – 50	23.50	26.60	16 – 57
Education (Years)	16.00	15.72	3.14	11 – 21	12.00	11.83	5 – 16
Gender (% Male)	68%			70%			1.00
Ethnicity (% Caucasian)	58%			73%			0.26
Handedness (% Right)	100%			90%			0.11
GCS				3.00	5.97	4.19	
Days in ICU				4.00	8.28	7.68	
Days in Hospital				12.00	13.28	10.09	
Months to scan				8.00	7.88	1.86	
GOSE				7.00	5.97	1.97	
Digit Symbol T score				40.00	39.00	11.01	
Symbol Search T score				46.67	43.78	13.27	
TMT A T score				43.50	42.87	19.40	
TMT B T score				48.50	44.53	20.12	
COWAT T score				36.00	35.47	13.36	
Stroop T score				53.50	44.97	19.72	
CVLT-II Total learning T score				46.00	40.42	20.29	
CVLT-II Long delay recall T score				45.00	37.69	19.91	

Note. No significant differences between groups in age or gender.

NC = Normal Control. TBI = Traumatic Brain Injury. GCS = Glasgow Coma Scale. ICU = Intensive Care Unit. GOSE = Glasgow Outcome Scale Extended. TMT A = Trail Making Test A. TMT B = Trail Making Test B. COWAT = Controlled Oral Word Association Test. Stroop = Interference condition, CVLT-II = California Verbal Learning Test – Second Edition.

Table 2

Group Histogram Differences

FRACTIONAL ANISOTROPY					
		NC n=19		TBI n=27	
		Mean	SD	Mean	SD
	<i>p</i>				
Mean		0.42	0.02	0.38	0.03
					<0.001
Skewness		0.32	0.09	0.42	0.16
					0.024
MEAN DIFFUSIVITY (1*10 ⁻³ mm ² /sec)					
Mean		0.66	0.02	0.70	0.03
					<0.001
Skewness		0.42	0.41	1.08	1.38
					0.06

Note: NC = Normal Control; TBI = Traumatic Brain Injury

Association between Histogram derived Fractional Anisotropy, Mean Diffusivity, and Outcome Measures among Patients with TAI

Table 3

Domain	Outcome Measures	Fractional Anisotropy			Mean diffusivity (1×10^{-3} mm ² /sec)		
		Mean	Skewness	Mean	Mean	Skewness	Skewness
Functional Outcome	GOSE	0.48*	-0.38*	-0.44*			-0.01
	Digit Symbol T score	0.45*	-0.19	-0.44*			0.01
Processing Speed	Symbol Search T score	0.42*	-0.15	-0.42*			0.09
	TMT A T score	0.23	-0.15	-0.23			0.12
Executive Function	TMT B T score	0.49*	-0.31	-0.37			0.12
	COWAT T score	0.35	-0.26	-0.20			0.17
	Stroop T score	0.48*	-0.50*	-0.42*			0.16
Learning and Memory	CVLT-II Total learning T score	0.58**	-0.40	-0.33			0.13
	CVLT-II Long delay recall T score	0.61**	-0.29	-0.26			0.18

Note: Significant correlations

* = p<0.05,

** = p<0.005.

A nonparametric Spearman correlation used for GOSE, and Pearson correlations were used for all other variables.

TAI= Traumatic axonal injury, GOSE = Glasgow Outcome Scale Extended, TMT A= Trail Making Test A, TMT B= Trail Making Test B, COWAT= Controlled Oral Word Association Test, Stroop = Interference condition, CVLT-II = California Verbal Learning Test – Second Edition.

Table 4

Association between Fractional Anisotropy-Voxel-Based Lesion Load and Outcome Measures

OUTCOME		LESION LOAD (FDR, $p=0.05$)
Functional	GOSE	-0.40*
Processing Speed	Digit symbol T score	-0.41*
	Symbol search T score	-0.24
	TMT A T score	-0.30
Executive Function	TMT B T score	-0.27
	COWAT T score	-0.22
	Stroop T score	-0.17
Learning and Memory	CVLT-II Total learning T score	-0.44*
	CVLT-II Long delay recall T score	-0.54*

Note: Lesion load is defined as the number of voxels identified as having low FA values as compared to controls. VBA utilized FDR = 0.05, and a minimum voxel cluster threshold of 50 voxels.

* Significant correlation ($p<0.05$). A nonparametric Spearman correlation was used for GOSE, and Pearson correlations were used for other variables.

GOSE = Glasgow Outcome Scale Extended. TMT A= Trail Making Test A, TMT B= Trail Making Test B, COWAT= Controlled Oral Word Association Test, Stroop = Interference condition, CVLT-II = California Verbal Learning Test – Second Edition.

None of the correlations reached significance at $p<0.01$.

Table 5

Group Tractography Differences in Fractional Anisotropy

	NC n=19		TBI n=30		p
	Mean	SD	Mean	SD	
Inter-hemispheric commissural	CC	0.60	0.18	0.56	0.03 <0.001**
	CC ₁	0.58	0.02	0.54	0.03 <0.001**
	CC ₂	0.54	0.02	0.54	0.03 0.893
	CC ₃	0.54	0.04	0.50	0.06 0.007*
	CC ₄	0.63	0.03	0.58	0.05 <0.001**
Limbic	Fornix	0.58	0.05	0.53	0.08 0.036*
	PPL	0.47	0.04	0.46	0.04 0.167
	PPR	0.50	0.03	0.47	0.04 0.002**
	CIL	0.50	0.03	0.48	0.05 0.088
	CIR	0.49	0.03	0.46	0.05 0.008
Association fibers	UNCL	0.49	0.03	0.45	0.03 <0.001**
	UNCR	0.50	0.02	0.46	0.04 <0.001**
	ILFL	0.51	0.03	0.48	0.03 0.001**
	ILFR	0.50	0.03	0.47	0.03 <0.001**
	IFOL	0.55	0.02	0.50	0.04 <0.001**
	IFOR	0.54	0.02	0.49	0.04 <0.001**

Note: Significant group differences,

* =p<0.05

** =p<0.005

CC=Corpus Callosum, CC₁=CC genu, CC₂=CC anterior body, CC₃=CC posterior body, CC₄=CC splenium, PPL= Perforant Pathway left, PPR=Perforant Pathway Right, UNCL= Uncinate fasciculus left, UNCR= Uncinate fasciculus right, CIL= Cingulum Left, CIR= Cingulum Right, ILFL= Inferior Longitudinal Fasciculus Left, ILFR= Inferior Longitudinal Fasciculus Right, IFOL= Inferior Frontal-occipital Fasciculus Left, IFOR= Inferior Frontal-occipital Fasciculus Right.

Table 6

Group Tractography Differences in Mean Diffusivity

	NC n=19		TBI n=30		p
	Mean	SD	Mean	SD	
CC	21.81	0.67	23.87	2.57	<0.001**
CC ₁	20.09	0.81	24.13	2.73	0.005**
CC ₂	22.09	1.03	24.68	2.69	<0.001**
CC ₃	22.48	1.45	24.68	2.69	0.001**
CC ₄	21.47	1.00	23.73	2.78	<0.001**
Formix	33.96	2.76	34.93	3.31	0.309
PPL	21.01	1.08	22.67	2.15	0.001**
PPR	20.79	0.87	22.37	2.14	0.005**
CIL	20.36	0.91	22.13	2.78	0.012*
CIR	20.02	0.97	22.07	2.74	0.001**
UNCL	21.52	0.60	23.36	2.33	<0.001**
UNCR	21.88	0.90	23.36	2.27	0.011*
ILFL	21.56	0.78	23.77	2.50	0.001**
ILFR	21.56	0.71	23.77	2.45	<0.001**
IFOL	21.56	0.78	23.80	2.61	<0.001**
IFOR	21.61	0.70	23.67	2.56	<0.001**

Note: Significant group differences

* p<0.05

** p<0.005

CC=Corpus Callosum, CC₁=CC genu, CC₂=CC anterior body, CC₃=CC posterior body, CC₄=CC splenium, PPL= Perforant Pathway left, PPR=Perforant Pathway Right, UNCL= Uncinate fasciculus left, UNCR= Uncinate fasciculus right, CIL= Cingulum Left, CIR= Cingulum Right, ILFL= Inferior Longitudinal Fasciculus Left, ILFR= Inferior Longitudinal Fasciculus Right, IFOL= Inferior Frontal-occipital Fasciculus Left, IFOR= Inferior Frontal-occipital Fasciculus Right.

Table 7
Association between Tractography Derived Fractional Anisotropy and Outcome Measures among Patients with TAI.

	GOSE	Processing Speed			Executive Function			Learning and Memory	
		Digit Symbol	Symbol Search	TMT A	TMT B	COWAT	Stroop	CVLT-II Total learning	CVLT-II Long delay recall
Inter-hemispheric commissural	CC	0.41*	0.50*	0.48*	0.38	0.51*	0.47*	0.64*	0.66*
	CC ₁	0.40*	0.20	0.24	0.09	0.15	0.07	0.40	0.31
	CC ₂	0.29	0.33	0.33	0.31	0.32	0.09	0.34	0.34
	CC ₃	0.19	0.50*	0.58*	0.41	0.58*	0.52*	0.54*	0.63*
	CC ₄	0.23	0.57*	0.55*	0.51*	0.51*	0.54*	0.66*	0.70*
Limbic	Fornix	0.20	0.70*	0.72*	0.65*	0.73*	0.60*	0.62*	0.65*
	PPL	0.21	0.41	0.35	0.38	0.27	0.02	0.08	0.29
	PPR	0.13	0.48*	0.48*	0.35	0.40	0.20	0.38	0.52*
	CIL	0.28	0.33	0.40	0.30	0.38	0.34	0.62*	0.60*
	CIR	0.14	0.20	0.21	0.23	0.22	0.31	0.40	0.46*
Association fibers	UNCL	0.31	0.33	0.40	0.20	0.23	0.14	0.26	0.17
	UNCR	0.20	0.27	0.20	0.16	0.11	-0.04	0.05	0.41
	ILFL	0.20	0.42*	0.42*	0.32	0.44*	0.25	0.50*	0.49*
	ILFR	0.42*	0.64*	0.58*	0.55*	0.65*	0.43*	0.54*	0.64*
	IFOL	0.39	0.52*	0.53*	0.33	0.49*	0.28	0.57*	0.48*
	IFOR	0.46*	0.67*	0.56*	0.52*	0.55*	0.37	0.59*	0.64*

* Note: Significant correlations at a false discovery rate of 5%, corresponding to a p-value < 0.023. A nonparametric Spearman correlation was used for GOSE, and Pearson correlations were used for other variables.

TAI= Traumatic axonal injury, CC=Corpus Callosum, CC₁=CC genu, CC₂=CC anterior body, CC₃= CC posterior body, CC₄=CC splenium, PPL= Perforant Pathway left, PPR=Perforant Pathway Right, UNCL= Uncinate fasciculus left, UNCR= Uncinate fasciculus right, CIL= Cingulum Left, CIR= Cingulum Right, ILFL= Inferior Longitudinal Fasciculus Left, ILFR= Inferior Longitudinal Fasciculus Right, IFOL= Inferior Fronto-occipital Fasciculus Left, IFOR= Inferior Fronto-occipital Fasciculus Right, GOSE = Glasgow Outcome Scale Extended, TMT A= Trail Making Test A, TMT B= Trail Making Test B, COWAT= Controlled Oral Word Association Test, Stroop = Interference condition, CVLT-II = California Verbal Learning Test – Second Edition.

All neuropsychological test scores reported are normalized T scores.