Published in final edited form as:

J Head Trauma Rehabil. 2008 ; 23(4): 197–208. doi:10.1097/01.HTR.0000327252.54128.7c.

Diffusion Tensor Imaging in Relation to Cognitive and Functional Outcome of Traumatic Brain Injury in Children

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Abstract

Objective—To investigate the relation of white matter integrity using diffusion tensor imaging (DTI) to cognitive and functional outcome of moderate to severe traumatic brain injury (TBI) in children.

Design—Prospective observational study of children who had sustained moderate to severe TBI and a comparison group of children who had sustained orthopedic injury (OI).

Participants—Thirty-two children who had sustained moderate to severe TBI and 36 children with OI were studied.

Methods—Fiber tracking analysis of DTI acquired at 3-month postinjury and assessment of global outcome and cognitive function within 2 weeks of brain imaging. Global outcome was assessed using the Glasgow Outcome Scale and the Flanker task was used to measure cognitive processing speed and resistance to interference.

Results—Fractional anisotropy and apparent diffusion coefficient values differentiated the groups and both cognitive and functional outcome measures were related to the DTI findings. Dissociations were present wherein the relation of Fractional anisotropy to cognitive performance differed between the TBI and OI groups. A DTI composite measure of white matter integrity was related to global outcome in the children with TBI.

Conclusions—DTI is sensitive to white matter injury at 3 months following moderate to severe TBI in children, including brain regions that appear normal on conventional magnetic resonance imaging. DTI measures reflecting diffusion of water parallel and perpendicular to white matter tracts as calculated by fiber tracking analysis are related to global outcome, cognitive processing speed, and speed of resolving interference in children with moderate to severe TBI. Longitudinal data are needed to determine whether these relations between DTI and neurobehavioral outcome of TBI in children persist at longer follow-up intervals.

Keywords

children; cognition diffusion tensor imaging; global outcome; traumatic brain injury

In This Article, we present a brief overview of the current approach to brain imaging in the clinical management of traumatic brain injury (TBI) in children. Following this introduction, we describe diffusion tensor imaging (DTI), an innovative magnetic resonance imaging (MRI) modality that has recently been utilized in TBI research and has the potential for clinical application in the near future. In addition, we present data from a recent study in which we analyzed DTI findings in relation to cognitive and functional outcome of moderate to severe TBI in children.

CURRENT CLINICAL BRAIN IMAGING OF CHILDREN WITH TBI

Current clinical management of acute TBI in children utilizes computed tomography (CT) scan to characterize the neuropathology and indications for neurosurgical intervention because this imaging technique is sensitive to expanding mass lesions and brain swelling that require urgent intervention. Other advantages of CT scan include its brevity, cost-effectiveness, and compatibility of the scanner environment with intensive care support equipment. However, disadvantages of CT scan include its insensitivity to axonal injury and radioactive burden that limits nonurgent, repeat imaging to assess residual neuropathology at follow-up and for research. Consequently, postacute clinical brain imaging of children with persistent sequelae of TBI often utilizes MRI rather than CT scan. MRI findings frequently include lesions at the gray white interface and in white matter regions such as the splenium of the corpus callosum^{1,2} consistent with gliosis. Blood products are also often seen on MRI as punctuate hemorrhagic lesions. However, there is growing evidence that more advanced imaging modalities can demonstrate pathology that appears normal on conventional MRI.^{3,4}

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging, which assesses myelination in vivo, is based on the characteristic of myelin sheaths and cell membranes of white matter tracts that restrict the movement of water molecules. As a result, water molecules move faster parallel to the major axis of nerve fibers rather than perpendicular to them. This characteristic, which is referred to as anisotropic diffusion and is measured by fractional anisotropy (FA), is determined by several factors including the thickness of the myelin sheath and of the axons as well as the organization of the fibers and properties of the intracellular and extracellular space around the axon. FA ranges from 0 to 1, where 0 represents maximal isotropic diffusion (eg, free diffusion in all directions) and 1 represents maximal anisotropic diffusion, that is, movement parallel to the major axis of a white matter tract. Areas with high FA such as the corpus callosum appear brighter, whereas tissue with low FA (eg, gray matter) appears darker on FA maps derived from DTI. Isotropic diffusion of water in multiple directions is measured by the apparent diffusion coefficient (ADC) and other measures of diffusivity. In general, measures of diffusivity such as ADC are inversely related to FA, though this relationship can be complex and influenced by differential changes in one or more eigenvalues.

Developmental studies of DTI have disclosed that FA increases with age in infants and children, potentially reflecting myelination, increased organization of white matter tracts, increased axonal diameter or alterations in the intracellular/extracellular ratio.^{5,6} In school-aged children age-related increases in FA have been reported in the white matter of prefrontal cortex, the internal capsule, corpus callosum, and the connections by which visual information is transferred from visual association cortex to more anterior regions.⁷ However, exceptions to this trend include nonsignificant differences between school-aged children and young adults in FA for the centrum semiovale and cortical gray matter,⁸ and other data⁶ showing that FA may even decrease with age in cortical gray matter. Corresponding to age-related increases in FA, the ADC decreases in white matter and some gray matter regions with age as diffusion becomes increasingly anisotropic, because of either increased fiber size, density, or

myelination.⁹ Changes in the intracellular environment, including a greater concentration of membranes and increased ratio of cell membrane-surface to cell volume ratio have been cited to explain the age-related decrease in ADC.¹⁰ However, exceptions to this age-related trend in ADC have been noted, including the finding of Snook et al⁸ that ADC in cortical gray matter did not significantly differ between school-aged children and young adults. Consistent with the use of DTI to estimate maturation of brain's white matter tracts, investigators have found that FA is related to cognitive skills in children. Olesen et al¹¹ found in typically developing children that FA in left frontal subregions, the corpus callosum, and left temporal-occipital region was related to working memory and left temporal FA was related to reading ability. These relations between white matter maturation and cognitive ability were still present after covarying for age, implying that individual differences in brain development were not entirely attributable to chronologic age. Similar to the results for working memory, age-related increases in speed of reaction time (RT) on a go/no-go task of response inhibition were directly related to increased FA and lower diffusivity in frontostriatal fibers of school-aged children and young adults.¹² Taken together, developmental DTI findings indicate that age-related, increased anisotropic diffusion in task-relevant fiber systems is strongly associated with improved working memory and response inhibition in children, adolescents, and young adults. An implication of these studies is that DTI has the potential to characterize white matter injury in brain regions affected by TBI in children.

APPROACHES TO ANALYSIS OF DTI

Three approaches to analysis of DTI have been used in published studies. The first approach is region of interest (ROI) analysis, which involves operator-dependent, manual outlining of the specific ROI. The ROI method has been used in several studies of DTI in patients with TBI, including adults^{13–15} and children.¹⁶ More recently, fiber tractography (FT) has been used to measure the integrity of white matter tracts, including the corpus callosum.^{3,17,18} FT is performed by defining 1 or more ROI, and computing likely fiber patterns (on the basis of the pattern of anisotropy or diffusivity in contiguous voxels) that pass through or between the specified region or regions. Measures such as mean FA or ADC can be calculated on the basis of these results. Although the ROI method is useful for testing hypotheses regarding the relation of white matter injury in a specific neuroanatomic region to outcome variables, FT is less operator dependent and generally includes a more homogeneous and larger sample of tissue that results in more robust findings.¹⁸ The third approach to DTI analysis is voxel-based analysis of whole-brain DTI data, which is useful for identifying regions that differ in diffusion among groups when no specific neuroanatomic area is hypothesized to be affected.¹⁸ Although the voxel-based approach may be less sensitive than other methods of DTI analysis¹⁸ and potentially suffers from limitations associated with the imperfect spatial normalization process and multiple comparison, which may lead to a higher error rate (see Snook et al [Snook, 2007 #5664] for further comparison of DTI methodologies), it is useful for exploratory studies of between-group differences when there is no ROI hypothesized to be of particular interest.

APPLICATIONS OF DTI IN STUDIES OF TBI

Pathological processes that alter the microstructure such as loss or disorganization of fibers because of breakdown of myelin and downstream nerve terminals,¹⁹ neuronal swelling or shrinkage, and increased or decreased extracellular space, could affect diffusion or anisotropy. With adverse immediate and delayed effects of acceleration/deceleration head trauma on cerebral white matter, DTI has been shown to be sensitive to a wide range of acute TBI severity. Investigation of DTI in 5 adults with mild TBI¹³ who were scanned within 24 hours postinjury indicated that FA was reduced in white matter that appeared normal on conventional MRI, including regions highly vulnerable to shearing effects of axonal injury such as anterior and posterior corpus callosum, and the anterior and posterior limbs of the internal capsule.

Arfanakis et al¹³ also found that FA was marginally lower in the external capsule relative to an uninjured comparison group. These findings were corroborated by another cross-sectional DTI study of 20 acute and 26 patients with chronic, mild TBI,¹⁴ which also reported that ROI analysis was more sensitive than a whole brain, voxel-based approach. Follow-up DTI has shown that reductions in FA were present in the corpus callosum for periods extending to 5 years after injury.^{14,20,21} The white matter specificity of DTI has been supported by the finding that FA in thalamus and putamen¹⁵ is minimally affected by TBI. In regard to the validity of DTI as a measure of TBI severity, investigators have reported a positive correlation of FA in the internal capsule and splenium with the GCS score, that is, adults with less severe TBI had higher FA reflecting relative integrity of white matter.¹⁵

Few studies have utilized DTI to characterize white matter injury after TBI in children. In 2 patients with hemiparesis secondary to TBI,²² DTI revealed microstructural injury to the right cerebral peduncle of the midbrain in the first patient and the posterior limb of the internal capsule of the second patient. In contrast, conventional MRI failed to detect either finding. In a DTI study of pediatric TBI, Wilde et al¹⁷ performed DTI fiber tracking analysis in the corpus callosum of 16 children who had sustained moderate to severe TBI ranging from 1 to 10 years earlier and in demographically matched, typically developing children. Children with TBI had lower FA in all corpus callosum regions and FA within the patient group was directly related to both functional outcome and cognitive processing speed. Although Wilde et al demonstrated that DTI FT was highly sensitive to white matter injury and related to long-term recovery, the investigators did not present an analysis of diffusivity and there was marked heterogeneity in the interval from injury to imaging.

To extend knowledge about DTI in pediatric TBI, we concurrently acquired DTI findings and outcome data in a larger, prospective sample of children at 3 months postmoderate to severe TBI whom we recruited during their initial hospitalization. The goals of this study were to characterize the effect of TBI on the microstructure of the cerebral white matter using advanced DTI methods to analyze both FA and ADC for a wider range of ROIs and in relation to cognitive and global outcome measures. In addition, we modified a composite measure of DTI²³ and explored its potential use for data reduction and to efficiently characterize overall white matter status. Here we also analyzed the relation of this composite DTI measure to evidence of diffuse axonal injury (DAI) seen on MRI. For comparison, we recruited and imaged children who sustained an orthopedic injury (OI), an approach that controlled for preinjury risk factors including behavioral features that predispose to injury and nonspecific effects of traumatic injury such as posttraumatic stress.

METHODS

Subjects

Diffusion tensor imaging was acquired without sedation in 2 groups of children and adolescents, including 32 patients who had sustained moderate to severe TBI and 36 patients who had a mild OI, which involved an extremity not involving the head and did not result in motor deficit. The rationale for including the OI group was to better control for risk factors that predispose to traumatic injury and the nonspecific effects of injury such as stress.²⁴ Both groups were prospectively recruited from Level 1 trauma centers and children's hospitals in Houston, Dallas, and Miami, and underwent DTI at about 3-month postinjury. Table 1 summarizes the demographic and clinical features of the groups. Within the TBI group, an injury was considered severe if the postresuscitation Glasgow Coma Scale (GCS)²⁵ score was 3 to 8, moderate if the score was 9 to 12 or 13 to 15 in patients whose CT scan during the initial hospitalization showed an intracranial contusion or hematoma. Inclusion of this "complicated" mild TBI subgroup was based on the finding that global outcome and cognitive sequelae of these patients approximate findings in patients with moderate impairment of consciousness.

²⁶ Exclusion criteria included contraindications to undergoing MRI and preinjury schizophrenia or bipolar disorder, pre-existing neurological disorder, and history of mental deficiency.

DTI acquisition

At all sites, Philips 1.5T Integra scanners were used with similar platforms to better ensure compatibility of the data across centers. Transverse multislice spin echo, single shot, echo planar imaging sequences were used (10150.5 ms TR, 90 ms TE, 2.7 mm slices, 0 mm gap). A 256 mm FOV (RFOV = 100%) was used with a measured voxel size of $2.69 \times 2.69 \times 2.7$ mm and a reconstructed voxel size of $2.00 \times 2.00 \times 2.7$ mm. Diffusion was measured along 15 directions, one of the standard manufacturer settings (number of b -value = 2, low b -value = 0, and high b -value = 860 s/mm²). To improve signal to noise ratio, high- b images were acquired twice and averaged. Each acquisition took approximately 5 minutes 45 seconds and 55 slices were acquired.

DTI analysis

DTI fiber tracking analysis of ROI—Operators who analyzed the DTI were not given any information concerning the outcome data. The Philips diffusion affine registration tool²⁷ was used to remove shear and eddy current distortion and head motion prior to calculating FA maps with Philips fiber tracking 4.1V3 Beta 4 software. ROIs were drawn manually using the protocols described below, then the automated Philips 3-dimensional fiber tracking tool²⁰ was utilized to determine fiber tracks passing through ROIs. Mean FA and ADC of the fiber system, which was automatically generated by the software, was used as the quantitative measure for DTI variables. The algorithm for fiber tracking is based on the Fiber Assignment by Continuous Tracking method.²⁸ For each of the ROIs listed below, we used standard parameters where tracking terminated if the FA in the voxels decreased below 0.2 or if the angle between adjacent voxels along the track was larger than 41.4 degrees. Philips software generated an automatic mean FA and ADC for each of the ROIs. The rationale for proposing the following ROIs is based in part on previous research, which identified these regions as especially vulnerable in patients with TBI.²²

Corpus callosum—Four measures on the basis of fiber projections from the corpus callosum included: (1) genu-frontal, (2) body-parietal, (3) splenium-occipital, and (4) total corpus callosum. The boundaries of the corpus callosum ROIs were based on a protocol originally developed by Witelson²⁹ and previously adapted for use with DTI by our laboratory.¹⁷ ROIs were drawn on FA color maps in the sagittal plane, using coregistered $b = 0$ images to cross check boundaries as necessary.

Internal capsule—Four measures on the basis of fiber projections from the internal capsule were utilized: (1) right anterior limb; (2) left anterior limb; (3) right posterior limb; and, (4) left posterior limb. ROIs were drawn on FA color maps in the axial plane using boundaries similar to those described by Mori et al.²⁸

Frontal lobes—Measures of frontal white matter were performed on both the right and left hemispheres. These ROIs were drawn in the coronal plane, on a slice just anterior to the first slice where the genu of the corpus callosum was visible. A line extending from the interhemispheric fissure at a point just inferior to the corpus callosum to the lateral orbital sulci formed the boundaries between the dorsolateral (superior to this line) and ventromedial (inferior to this line) regions. Right and left sides were calculated separately, and all white matter within the boundaries was included.

Temporal lobes—Measures of temporal white matter were performed in the right and left hemispheres in the sagittal plane, with the ROI drawn around the temporal white matter including the temporal stem to include the inferior longitudinal fasciculus.

Composite scores—We included a modified composite score²³ to facilitate data reduction and to explore an efficient index of white matter injury. Consistent with the view¹⁹ that axonal injury is typically multifocal or diffuse, a composite score encompassing multiple regions is potentially useful in characterizing overall injury to the white matter microstructure. To investigate the potential usefulness of composite DTI measures for data reduction and later clinical application,²³ we calculated composite variables for FA and ADC. To calculate the FA composite, each ROI in each TBI patient was compared with the corresponding mean FA of the OI group for this region. In view of the developmental increase in FA with myelination,^{5,7} we first subdivided each group according to age older or younger than 12 years. If a child with TBI had an FA for an ROI that fell 1.5 SD or more below the mean FA for the corresponding age subgroup, the TBI patient received a score of “1.” This procedure was repeated for each ROI and the sum score was taken as the composite FA score with higher FA composite scores reflecting more severe white matter injury. A composite score for ADC was generated using similar methodology with the exception that abnormality was defined as 1.5 SD above the mean. For each composite, the range of score was 0 to 11, as 11 regions were included. We selected 1.5 SD (approximately 86.6% of the data fall between $M - 1.5$ SD and $M + 1.5$ SD in a normally distributed data set) as a criterion because 2.0 SD (including 95.4% of data) corresponded to more extreme scores, which we thought would be too restrictive in this initial study. The ROIs included in the composite FA and ADC scores are listed in Table 2. Total corpus callosum and the frontal subregions were not used in the composite score, as these would have provided redundant data. Figure 1 illustrates FT that was used in each region that we included in the composite score.

Intrarater and interrater agreement—To examine intrarater agreement, each patient’s DTI variables were measured twice; intraclass correlation coefficients exceeded 0.98 for all DTI indices. Interrater agreement was also assessed by measurement of the corpus callosum by 2 different raters in 10% of the cases in both groups; intraclass correlation coefficients again exceeded 0.98.

Functional outcome and cognitive measures

Assessment of functional outcome at 3 months postinjury using a modified Glasgow Outcome Scale³² and evaluation of both cognitive processing speed and resistance to interference³³ were performed within 2 weeks of imaging.

Glasgow outcome scale (GOS)—We modified the GOS for use with children by reviewing the child’s academic achievement in school, psychosocial function, and adaptive activities at home.³⁴ A research assistant supervised by one of the investigators graded the GOS on the basis of a structured interview with the parent and the results of neuropsychological testing. The research assistant who graded the GOS had no knowledge of the DTI results.

Flanker task of cognitive processing speed and interference—To measure cognitive processing speed, we used the Flanker Task³³ in which a horizontal arrow pointing to the left or to the right (Figure 2) appeared on each trial. The child was asked to quickly press the button on the right or the left consistent with the direction that the arrow was pointing. Task conditions included baseline, facilitation, interference, and no-go. Under the baseline condition, the arrow was flanked by horizontal dashes, which provided no cue to the child as to which button to press. The interference condition consisted of flanker arrows that pointed in the direction opposite to the central arrow. In the no-go condition, the flanker stimuli were

“X”s, which signaled the child to withhold response to the central arrow. Although a facilitation condition was included in which the flanker arrows pointed in the same direction as the central arrow, this condition did not impose demands on inhibition and was not analyzed in this study. There were 112 trials, including 28 trials of each task condition, which were randomly interspersed. With the exception of the no-go condition in which the child was instructed to withhold responding, RT for trials with correct responses was the primary performance measure. However, accuracy was recorded for all conditions and error rate was analyzed for the no-go condition.

Statistical analysis

Group comparisons on demographic variables were done using *t*-tests for continuous variables, and χ^2 tests for categorical variables. Spearman rank correlation was used to evaluate the relation of GCS to the DTI composite scores within the TBI group. We also used the Spearman rank-order correlation coefficient to evaluate the relation of error rate in performance to the DTI variables, because the distribution of error data was highly skewed. Logistic regression was used to evaluate the relation of the DTI composite scores to GOS score, and interpretation in terms of odds ratio was provided. Repeated measures ANCOVA model was used to analyze the relation of FA and ADC to cognitive processing speed for baseline and interference conditions. Age at injury was controlled in the model if it was significant.

RESULTS

Demographic and injury variables

The patients with TBI were older than OI patients ($t(66) = -2.49$, $P = .0154$). Chi-square analysis revealed no significant differences between the groups on gender ($\chi^2_1 = 0.085$, $P = .771$). Fisher exact test revealed no significant difference between the groups on ethnicity ($P = .178$), but the higher proportion of left-handed children in the OI group was marginally significant ($P = 0.058$). Socioeconomic level³⁵ of the family did not differ between the groups, ($t = -0.03$, $P = .978$). High velocity injury mechanisms such as motor vehicle crashes were more frequent in the TBI than OI group (Table 1) ($\chi^2_1 = 8.90$, $P = .003$). Time between injury and assessment did not differ between the groups ($t = 0.61$, $P = .542$).

DTI composite and region of interest analysis of FA and ADC

Significant group differences were found in all ROIs (Table 2 and Table 3) for both FA and ADC, where white matter FA was reduced and ADC was increased in the patients with TBI relative to the OI group. Data on the means and SD for these measures are also presented in Table 2 and Table 3. A single TBI patient had substantially lower FA in the splenium of the corpus callosum than other TBI participants because of the presence of gliotic lesions in the occipital lobes, from which fibers would project through the splenium of the corpus callosum (interestingly, the patient did not have a lesion in the splenium of the corpus callosum itself). This increased the SD for TBI group on this measure, though exclusion of this individual did not change the differences between groups. With calculation of the composite FA and ADC scores on the basis of the distribution of FA and ADC in the OI group, analysis of the composite scores was confined to the TBI group. The mean composite score for FA was 4.875 (SD = 3.480; median = 5.00, range = 0–11), and the mean composite score for ADC was 3.813 (SD = 3.306; median = 2.00, range = 0–11). Figure 3 illustrates tractography in the combined regions included in the composite score in a child with TBI (composite scores of 7 for both FA and ADC) and an age- and gender-equivalent OI patient.

Relation of DTI composite score to signs of diffuse axonal injury on MRI

To identify DAI on the basis of MRI findings, we identified TBI patients with at least one lesion in the white matter or gray-white junction, which had been coded by the project neuroradiologist as gliosis, shearing injury, or any combination of these pathologies with other pathologies. According to this criterion, 25/32 (78.13%) of the TBI patients and no OI patients had evidence of DAI. Comparison of the composite FA score showed that it was higher (ie, more pathological) in the DAI subgroup (mean = 5.800, SD = 3.175, median = 6.00, range = 0–11.00) than the non-DAI subgroup (mean = 1.571, SD = 2.440, median = 1.00, range = 0–7.00), $t(30) = -3.25$, $P = 0.003$. Similarly, the ADC composite score was also higher in the TBI patients with evidence of DAI (mean = 4.440, SD = 3.330, median = 3.00, range = 1.00–11.00) than those without indications of DAI (mean = 1.571, SD = 2.149, median = 1.00, range = 0–6.00), $t(30) = -2.14$, $P = .040$. In addition, we identified diffuse edema in one of the TBI patients.

Relation of DTI composite score to GCS

Within the TBI group, the composite FA score was significantly correlated with severity of acute impairment of consciousness as reflected by the postresuscitation GCS score (Spearman $\rho = -0.44$, $P = .011$). Here a higher GCS score indicates milder impairment of consciousness whereas a higher composite FA denotes more extreme deviation in the pathological direction from the mean of the OI group implying more severe injury to the white matter microstructure. There was also a significant relation between the composite ADC score and GCS (Spearman $\rho = -0.48$, $P = .005$), indicating that overall injury to the white matter microstructure, increased with severity of acute TBI.

Relation of DTI findings to global outcome

This analysis was confined to the TBI group because the composite DTI scores were based on deviation from the mean in the OI group and 92% of the OI group had a good recovery. Figure 4a plots the probability of attaining a good recovery at 3 months postinjury against the composite FA score for children in the TBI group. Here the composite FA score reflects the number of ROIs in which the child's FA falls 1.5 SD below the corresponding mean of the OI group, ie, a high composite score reflects more severe white matter injury. High composite FA scores were inversely related to the probability of the child attaining a good recovery by 3 months post-TBI ($\chi^2_1 = 10.11$, $P = .002$), indicating that with each 1-unit increase on the composite score, the odds of attaining a good recovery are 0.67 times lower. Similarly, the ADC composite score relates to the probability of recovery, $\chi^2_1 = 6.48$, $P = .011$, showing that the odds of achieving good recovery are 0.744 times lower with each unit increase in this composite score (Figure 4b). Total corpus callosum FA ($\chi^2_1 = 16.11$, $P < .001$) and ADC ($\chi^2_1 = 3.97$, $P = .047$) were also related to the GOS at 3 months, with higher FA and lower ADC relating to better outcome.

Cognitive Processing Speed and Interference Effects on Flanker Task. Table 4 shows the descriptive statistics for performance on the Flanker task. It is seen that mean cognitive processing speed tended to be faster in the TBI patients than the OI group, but the differences did not reach significance for either the baseline ($F_{1,52} = 0.26$, $P = .614$) or interference ($F_{1,50} = 0.41$) condition, with age at injury controlled. There was also no significant between-group difference in error rate under the no-go condition (Wilcoxon nonparametric test, $P = .128$).

DTI findings in relation to cognitive processing speed and interference on Flanker task

Composite DTI scores—In the following analyses, lower RT reflects greater cognitive efficiency, whereas higher composite FA and ADC scores reflect more severe white matter injury. The composite FA score in the TBI group was significantly correlated with RT in the baseline (Spearman $\rho = 0.39$, $P = .049$) condition, but only a trend in the predicted direction was found in the interference condition (Spearman $\rho = 0.37$, $P = .067$) and percentage of errors on no-go condition (Spearman $\rho = 0.36$, $P = .071$). There were no significant correlations between the composite ADC score and RT in either condition.

CORPUS CALLOSUM AND PREFRONTAL CORTEX ROIS

Corpus callosum subregions

In the following analyses, higher FA and lower ADC indicate better preservation of white matter integrity. The relation of FA in the genu of the corpus callosum to RT under baseline and interference conditions of the Flanker task significantly differed between groups. There was a significant group by FA interaction on baseline RT ($F_{1,48} = 5.48$, $P = .023$), where increased FA was related to decreased RT in the TBI group ($t(48) = -2.59$, $P = .013$), but not in the OI patients. There was a similar interaction of group by FA for the interference condition ($F_{1,48} = 4.78$, $P = .034$), also revealing a significant negative relation between these variables in TBI group ($t(48) = -2.29$, $P = .027$), but not in the OI group. The relation of FA to RT did not differ between the baseline and interference conditions, $F_{1,48} = 0.04$, $P = .836$. For percentage of errors on the no-go condition, there was a significant negative relation (higher percentage of errors was associated with lower FA) for the TBI group (Spearman $\rho = -0.44$, $P = .034$), but only a trend for a positive relation in the OI group (Spearman $\rho = 0.37$, $P = .054$).

A similar pattern was also evident in the analysis of the body of corpus callosum, with a significant group by FA interaction for baseline ($F_{1,48} = 5.69$, $P = .021$) and interference ($F_{1,48} = 6.93$, $P = .011$). Here again, the FA was significantly related to both baseline ($t(48) = 3.00$, $P = .004$) and interference ($t(48) = -3.50$, $P = .001$) RT in patients with TBI, but not in OI patients. Again, the relation of FA to RT did not significantly differ by condition, $F_{1,48} = 0.26$, $P = .612$. For percentage of errors on the no-go condition, there was a trend toward a positive relation (higher percentage of errors was associated with higher FA) for the OI group (Spearman $\rho = 0.34$, $P = .081$), but no significant relation in the TBI group.

For the splenium of the corpus callosum, FA was negatively related to RT in both groups of patients for interference RT ($t(49) = -2.23$, $P = .031$), but did not reach significance for baseline RT ($t(49) = -1.83$, $P = .074$). As with the genu and body, the relation between FA and RT did not differ between the baseline and interference conditions, $F_{1,49} = 0.96$, $P = .332$. The overall effect of FA on RT was significant ($F_{1,49} = 4.29$, $P = .044$). For percentage of errors on the no-go condition, there was no significant relation to FA for either group. No significant relations were found between ADC in the corpus callosum subregions and any of the Flanker variables.

Frontal regions—As with the corpus callosum, we found a significant group by FA interaction in the left dorsolateral frontal region ($F_{1,48} = 7.18$, $P = .010$). FA was significantly related to both baseline ($t(49) = -2.94$, $P = .005$) and interference RT ($t(49) = -2.02$, $P = .024$) with longer RT associated with lower FA in patients with TBI, but not in the OI group. The relation of FA to RT in the TBI group did not differ between the baseline and interference conditions ($F_{1,48} = 1.25$, $P = .270$). For percentage of errors on the no-go condition, there was significant negative relation to FA in the TBI group in the left dorsolateral frontal region (Spearman $\rho = -0.45$, $P = .029$) such that higher FA was related to lower percentage of errors.

However, there was only a trend in the positive direction in the OI group (Spearman $\rho = 0.38$, $P = 0.054$). No significant relations were found between Flanker baseline and interference RTs and either FA or ADC for the other frontal regions including right dorsolateral, and the ventromedial areas.

Temporal regions—We found no significant relations between FA or ADC in the temporal region and performance on the Flanker task.

DISCUSSION

Developmental studies using DTI have shown that the measures of FA and diffusivity are related to age and interpreted as surrogate markers of myelination.⁶ However, other determinants of age-related changes in FA and ADC have been described, and the lack of age-related change in FA and ADC in cortical gray matter has been reported.⁸ Investigations^{6,10} of adult TBI^{3,15,36} and initial reports in pediatric TBI^{15,16} have documented that DTI can noninvasively characterize injury to the microstructure of the cerebral white matter including brain regions that appear normal on conventional MRI.³⁷ Caution is advised in the interpretation of these findings as evidence for traumatic axonal injury in patients, but histological confirmation of DTI in animal models of TBI has been reported.³⁸ In this study we showed that a composite of FA representing findings from multiple brain regions was related to severity of acute TBI and to global outcome measured at 3 months postinjury. This finding was also confirmed for the corpus callosum, the largest white matter tract in the brain. To the extent that traumatic axonal injury is implicated as a major pathological mechanism mediating TBI because of closed head trauma,³⁹ it is parsimonious to view our findings as reflecting a continuum of axonal injury in the TBI group. Convergent with this interpretation, TBI patients whose MRI results were consistent with DAI had composite FA and ADC scores indicating severe disruption of white matter microstructure. This view is consistent with the predominantly high velocity traumatic forces (eg, motor vehicle crashes) associated with TBI,⁴⁰ whereas sports injuries were more common in the OI group.

Our findings indicate that cognitive processing speed was also related to the integrity of white matter microstructure in the TBI patients as measured by DTI, including regions of the corpus callosum and frontal cortex. In contrast, corresponding DTI-cognition relations were not significant for temporal regions. Dissociations between the groups were also present as relations between DTI indices and cognitive performance in TBI patients were frequently not seen in the OI group. With evidence that slowed cognitive processing speed is a core deficit resulting from TBI⁴¹ that contributes to problems in performing a wide range of tasks, our finding that baseline processing speed on the Flanker Task was slowed as FA decreased extends previous reports in the pediatric TBI population. Moreover, we also found that interference RT was also related to FA. However, we found no significant group differences in processing speed under the baseline and interference conditions of the Flanker task. Although this finding is apparently at odds with our previous report of diminished resistance to interference in children with TBI,⁴² the previous study utilized typically developing children as a comparison group whereas this study recruited children who had sustained traumatic OI. As noted by other investigators,³⁵ Patients with OI control more effectively for risk factors that predispose to injury as compared with typically developing, uninjured children. In general, the relation of DTI to cognitive processing speed was more robust in the patients with TBI than the OI group, possibly reflecting the effects of traumatic axonal injury.

We also observed dissociation in results for FA and ADC with the former more consistently related to the cognitive measures. Within the Flanker task conditions, cognitive processing speed was the variable most consistently related to DTI findings and error rate under the no-go condition was the least sensitive. This pattern is consistent with the view that cognitive

processing speed is highly sensitive to traumatic axonal injury.⁴¹ As noted earlier, the distribution of errors was highly skewed and many children had no or few errors on the no-go condition. Taken together, the results of this study support the potential application of DTI for providing biomarkers of white matter injury that are sensitive to the neurobehavioral sequelae of TBI in children. With the caveat that DTI data are acquired from children with similar demographic background to provide a developmental frame of reference, this noninvasive brain imaging technique could be utilized clinically to evaluate the effects of TBI on white matter tracts in children to facilitate diagnosis and monitor recovery. Acquisition of DTI using a conventional MRI scanner and the satisfactory reliability of DTI analysis that can be achieved by FT are anticipated to enhance dissemination of this imaging modality.

Limitations of this study include its cross-sectional design. Longitudinal DTI could elucidate the effects of TBI on development of white matter in children and the relation to changes in cognition. The volume of white matter increases throughout childhood and extends to early adulthood,^{43,44} but the effect of TBI on this trajectory is unknown. Assets of our study include the good reliability in the DTI analysis, both within and between examiners. In addition, we demonstrated a relation between DTI measures of white matter integrity and both cognitive and functional outcome data. Behavioral assessment of the patients was done independently of the DTI analysis, thus mitigating examiner bias. In comparison with enrollment of typically developing, uninjured children in our previous investigation of DTI,¹⁷ recruitment of children who sustained OI in this study better controls for preinjury risk factors²⁴ that predispose to injury and are potentially related to brain maturation.

Acknowledgements

This research was supported by grant NS-21889 awarded to Harvey S. Levin, PhD by the National Institute of Health. We gratefully acknowledge the assistance of Summer Lane and Lori Cook for their assistance in patient recruitment and Stacey K. Martin for her assistance in manuscript preparation. We acknowledge the generous support of Mission Connect of the TIRR Foundation.

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Figure 1.

Regions included in the composite DTI score using FT, overlaid on a $b = 0$ image. Regions included in our analysis included (a) subregions of the corpus callosum such as the genu, body, and splenium; (b) the anterior and posterior internal capsules (both right and left sides); and (c) the frontal and temporal lobes. Color in the fiber tracts reflects the direction in which fibers are coursing: lateral or right-left (red), anterior-posterior (green), or superior-inferior (blue).

—	—	→	—	—	Baseline
←	←	→	←	←	Interference
→	→	→	→	→	Congruent
X	X	→	X	X	No-go

Figure 2.

Flanker: Display of the Flanker task conditions, including baseline, interference, congruent or facilitation, and no-go. Descriptions of these conditions are provided in Methods.

Figure 3.

Illustration of DTI tractography results for the regions of interest included in the composite score in a child with TBI and an age-equivalent OI patient. Note that despite the absence of large areas of focal abnormality on T1-weighted structural imaging in both the axial and the sagittal planes in the TBI patient (a–b) as compared with the OI patient (d–e), tractography demonstrates both a diminished number of fibers and intensity of color in the fibers in several areas of the brain, corresponding to the decreases in FA and increases in ADC that were observed quantitatively. The composite scores of the child with TBI were 7 (out of 11) for both FA and ADC, indicating FA in 7 areas was 1.5 SD lower (and ADC was 1.5 SD higher) than the mean for the OI comparison group. Regions where abnormality was detected for FA include the splenium and body of the corpus callosum, the right and left temporal lobes, left frontal lobe, and the right and left posterior internal capsule. Regions of abnormality for ADC included the splenium and body of the corpus callosum, the left temporal lobe, right and left frontal lobes, and the right and left posterior internal capsule. The paucity of fibers that is most apparent in the more superior and posterior aspects of the brain of the child with TBI (as indicated with arrows) is consistent with the thinning of the body of the corpus callosum and the small shear lesion in the splenium. However, even regions as the frontal and temporal lobes were impacted on quantitative analysis.

Figure 4.

a–b. Probability graph demonstrating the percent chance of obtaining a good recovery versus a poor recovery on the basis of composite FA (a) and ADC (b) in the TBI group. For the Glasgow Outcome Score (GOS), a score of 1 indicates Good Recovery, a score of 2 reflects Moderate Disability, and a score of 3 indicates Severe Disability. The scale also includes ratings for vegetative state and death, but only surviving children capable of participating in cognitive testing were included in our cohort. The prediction lines reflect the percent chance of obtaining good (GOS = 1) or poor (GOS ≥ 2) recovery on the basis of DTI composite score.

Table 1

Demographic and injury variables*

	TBI group (n = 32) (mean ± SD)	OI group (n = 36) (mean ± SD)
Age, y	13.75 ± 2.73 (range = 7–17)	12.12 ± 2.65 (range = 7–16)
Gender	23 males, 9 females	27 males, 9 females
Ethnicity	12 Caucasian, 15 Hispanic, 4 African American, 1 Other	9 Caucasian, 12 Hispanic, 12 African American, 3 Other
Handedness	31 right-handed, 1 left-handed	29 right-handed, 7 left-handed
Social composite index	−0.02 ± 0.83 (range = −1.83–1.44)	−0.03 ± 0.78 (range = −1.49–1.55)
Initial GCS score	7.37 ± 4.06 (range = 3–15)	N/A
Mechanism of injury	17 motor vehicle accident, 4 RV, 2 bicycle accident, 3 pedestrian vs motor vehicle, 4 fall, 1 sports-related, 1 other	7 motor vehicle accident, 1 RV, 2 bicycle accident, 2 pedestrian vs motor vehicle, 9 fall, 1 hit by falling object, 13 sports-related, 1 other
Postinjury interval for scanning and testing, days	124.09 ± 29.56 (range = 76–230)	128.53 ± 29.97 (range = 82–216)
DAI injury	25 had DAI, 7 had no DAI	No DAI

* GSC = Glasgow Coma Scale; RV = Recreational Vehicle; DAI = Diffuse Axonal Injury.

Table 2

Group differences on DTI regions of interest: FA *

Variable	TBI Mean (SD)	OI Mean (SD)	t	P value	Effect size
Corpus callosum					
Total	0.425 (0.031)	0.464 (0.023)	6.05	<.0001	1.19
Genu	0.426 (0.029)	0.468 (0.026)	6.29	<.0001	1.22
Body	0.409 (0.044)	0.453 (0.025)	5.04	<.0001	1.07
Splenium	0.455 (0.461)	0.497 (0.027)	4.47	<.0001	0.980
Frontal lobes					
Right ventromedial	0.360 (0.024)	0.389 (0.027)	3.81	.0003	0.864
Left ventromedial	0.359 (0.030)	0.378 (0.036)	2.33	.0230	0.559
Right dorsolateral	0.352 (0.035)	0.378 (0.025)	4.04	.0002	0.906
Left dorsolateral	0.358 (0.023)	0.379 (0.026)	3.52	.0008	0.805
Temporal lobes					
Right	0.393 (0.030)	0.425 (0.027)	4.63	<.0001	0.994
Left	0.397 (0.025)	0.422 (0.025)	4.04	.0001	0.896
Internal capsule					
Right anterior limb	0.368 (0.030)	0.392 (0.020)	3.73	.0005	0.845
Left anterior limb	0.374 (0.025)	0.397 (0.018)	4.20	<.0001	0.926
Right posterior limb	0.454 (0.030)	0.481 (0.019)	4.29	<.0001	0.948
Left posterior limb	0.461 (0.034)	0.487 (0.017)	3.96	.0003	0.896

* SD = standard deviation; OI = orthopedic injury; TBI = traumatic brain injury.

Effect sizes are reported for Cohen's d , where $d \geq .80$ indicates a large effect size; 0.50–0.79 indicates a moderate effects size.^{30,31}

Table 3

Group differences on DTI regions of interest: ADC*

Variable	TBI Mean (SD)	OI Mean (SD)	t	P value	Effect size
Corpus callosum					
Total	0.988 (0.084)	0.927 (0.046)	-3.62	<.0007	0.832
Genu	0.915 (0.036)	0.868 (0.046)	-4.79	<.0001	1.01
Body	0.980 (0.091)	0.913 (0.058)	-3.58	.0008	0.820
Splenium	1.037 (0.202)	0.949 (0.056)	-2.39	.0225	0.588
Frontal lobes					
Right ventromedial	0.888 (0.041)	0.851 (0.027)	-4.22	<.0001	0.938
Left ventromedial	0.872 (0.028)	0.848 (0.035)	-3.02	.0036	0.707
Right dorsolateral	0.868 (0.038)	0.834 (0.022)	-4.30	<.0001	0.951
Left dorsolateral	0.857 (0.030)	0.838 (0.030)	-2.61	.0114	0.619
Temporal lobes					
Right	0.907 (0.065)	0.884 (0.050)	-1.63	.1077	0.397
Left	0.893 (0.057)	0.861 (0.049)	-2.48	.0156	0.589
Internal capsule					
Right anterior limb	0.855 (0.033)	0.809 (0.037)	-5.43	<.0001	1.104
Left anterior limb	0.825 (0.022)	0.801 (0.031)	-3.71	.0004	0.813
Right posterior limb	0.848 (0.031)	0.805 (0.039)	-5.01	<.0001	1.045
Left posterior limb	0.843 (0.037)	0.811 (0.047)	-3.13	.003	0.715

* SD = standard deviation; OI = orthopedic injury; TBI = traumatic brain injury.

Effect sizes are reported for Cohen's *d*, where $d \geq .80$ indicates a large effect size; $0.50-0.79$ indicates a moderate effect size.^{30,31}

Table 4
Descriptive statistics for Flanker task RT and percentage errors for groups*

Measures	Group	Mean	Median	SD	Range
Baseline RT	OI	787.60	766.94	210.52	509.68–1230.40
	TBI	750.68	760.72	214.24	498.13–1533.35
Interference RT	OI	876.94	854.17	213.87	580.28–1277.76
	TBI	860.84	858.82	210.10	540.64–1438.33
No-go % error	OI	0.084	0.063	0.103	0.000–0.406
	TBI	0.121	0.094	0.121	0.000–0.563

* SD = Standard Deviation; RT = reaction time; OI = orthopedic injury; TBI = traumatic brain injury.