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Simulation of Changes in Diffusion Related to Different Pathologies at Cellular Level After Traumatic Brain Injury

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Abstract

Purpose—The goal of the current study was to investigate tissue pathology at the cellular level in traumatic brain injury (TBI) as revealed by Monte Carlo simulation of diffusion tensor imaging (DTI)-derived parameters and elucidate the possible sources of conflicting findings of DTI abnormalities as reported in the TBI literature.

Methods—A model with three compartments separated by permeable membranes was employed to represent the diffusion environment of water molecules in brain white matter. The dynamic diffusion process was simulated with a Monte Carlo method using adjustable parameters of intra-axonal diffusivity, axon separation, glial cell volume fraction, and myelin sheath permeability. The effects of tissue pathology on DTI parameters were investigated by adjusting the parameters of the model corresponding to different stages of brain injury.

Results—The results suggest that the model is appropriate and the DTI-derived parameters simulate the predominant cellular pathology after TBI. Our results further indicate that when edema is not prevalent, axial and radial diffusivity have better sensitivity to axonal injury and demyelination than other DTI parameters.

Conclusion—DTI is a promising biomarker to detect and stage tissue injury after TBI. The observed inconsistencies among previous studies are likely due to scanning at different stages of tissue injury after TBI.

Keywords

Monte Carlo simulation; DTI; TBI; demyelination; edema; axonal injury

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INTRODUCTION

Traumatic brain injury (TBI) commonly occurs when the brain is exposed to a strong external force (e.g., during a car accident). In the United States alone, an estimated 1.7 million people sustain a TBI annually, resulting in 52,000 deaths and 275,000 hospitalizations (1). Survivors of TBI suffer from a broad spectrum of ailments, ranging from temporal unconsciousness to permanent cognitive deficit. Even though the conventional neuroimaging methods such as CT and MR structural scans can detect many trauma-induced lesions, the correlation between imaging abnormalities and long-term outcomes remain elusive (2).

Diffusion tensor imaging (DTI) is a promising noninvasive method for identifying and characterizing brain injury. DTI reflects the extent to which the Brownian motion of water molecules is hindered by barriers at the cellular level. DTI measurements are affected by physical properties of tissues including the size and shape of cells and the space between them, as well as the permeability of cell membranes. However, conventional DTI models cannot distinguish between these properties. DTI has been used widely over the last decade to investigate pathological changes in patients with various neurological diseases. For example, in chronic neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis, reduced fractional anisotropy (FA) and reduced axial diffusivity (DA) are often correlated with the presence of axonal loss, whereas increased mean diffusivity (MD) and increased radial diffusion (DR) are often correlated with demyelination (3,4). In ailments such as TBI, the results are more variable, and three distinctive patterns of diffusion abnormalities have been reported: pattern 1, reduced FA and reduced or unchanged MD (5,6); pattern 2, elevated FA and reduced MD (7–9); and pattern 3, reduced FA and elevated MD (10,11).

A parameter that is likely related to the observed differences in the DTI metrics is the timing between TBI and MR scanning. In a controlled environment using a mouse TBI model, MacDonald et al. (12) showed that the pathology in the acute stage is dominated by pure axonal injury, which is caused by disrupted neural filaments and accumulated organelles (13–15). This can hinder water diffusion along axons. In the subacute stage, demyelination is the prominent pathological change that is expected to reduce barriers to diffusion perpendicular to the fiber direction (12,16). In addition, TBI is often associated with edema, which can further complicate the interpretation of changes in DTI parameters. There are two types of edema: cytotoxic (or cellular) edema and vasogenic edema. Cytotoxic edema, which is often observed in contusive or relative severe diffuse injury in the acute stage (17–19), is characterized by a reduction in MD because of high water content (20). However, Barzo et al. (21) demonstrated that if the injury is severe enough to increase blood–brain barrier permeability, a vasogenic edema will develop, causing MD to increase.

Although DTI metrics can reflect specific tissue pathology as described above, the coexistence of different types of tissue injury at different stages further complicates the interpretation of observed DTI metrics. In order to address these issues, advanced analytic models have been proposed. For example, the CHARMED model accounts for axon density of white matter (22), and the two-compartment Kärger model considers water exchange

(23). However, such models require well-defined tissue geometry parameters that may not exist physiologically due to the complex brain microstructure. The advantage of Monte Carlo methods is that they are not limited by the complexity of tissues, as any 2D or 3D shapes and geometry from micrographs can be adopted for the diffusion environment. While analytical models can be used to infer tissue properties from diffusion measurements, Monte Carlo simulation, as a forward model used to synthesize measurements, can bridge between the microstructural properties and DTI parameters. For example, Szafer et al. (24) and Ford and Hackney (25) used Monte Carlo simulations to study changes in diffusion in brain tissues after ischemic stroke and rat spinal cord injury, respectively. Regan and Kuchel (26) investigated the effect of packing arrangement of red blood cells on the coherence patterns in q-space plots. Hall and Alexander (27) incorporated swelling in a tissue model to explain the mechanism of ADC changes in stroke.

In the present study, we applied Monte Carlo simulations to investigate four pathological changes after TBI: axonal injury, vasogenic edema, cytotoxic edema, and demyelination. The diffusion-weighted signal in a pulsed gradient spin echo (PGSE) pulse sequence was synthesized by a Monte Carlo method where molecular diffusion was simulated in a three-dimensional tissue model consisting of axons, glial cells, and extracellular space. Diffusion parameters (i.e., fractional anisotropy, mean diffusivity, axial/radial diffusivity) were obtained from simulations of the respective pathologies under different experimental parameters (e.g., diffusion time, b value). The results of the simulation provide new insights into the relationship between altered diffusion parameters and the underlying pathology during the evolution of TBI.

METHODS

Tissue Model

In previous studies, tissue models with only intra-axonal and extra-axonal space were adopted to represent white matter (28–31). Because white matter in the central nervous system consists of both axons and glial cells (32), those models are insufficient for describing white matter pathology. Given that cytotoxic edema induces swelling in glial cells (33,34), a glial cell compartment was also included in our model.

The virtual tissue used in this study consisted of an array of every three hexagonal columns, each containing an axon, surrounding a glial cell (Fig. 1). The axon and the glial cell were modeled by a cylinder and ellipsoid, respectively. A hexagonal shape was chosen as the basic unit based on previous studies (26,28–30) which demonstrated its efficient use of space, with the maximum axonal volume fraction being 90.7% (versus 78.5% for square packing). For glial cells, cytotoxic edema causes them to swell isotropically in gray matter. However, the space in white matter is elongated along the fiber direction, which restricts the expansion of glial cells perpendicular to the fibers. Thus, unlike previous studies (35) in which a spherical model was used for glial cells, we used an ellipsoid shape in this study. Changes in the volume fraction of glial cells (which is normally about 10%–20%) (35) were modeled by adjusting the length of the ellipsoid axes. It should be emphasized that glial cells (eg, astrocytes and oligodendrocytes) in real tissue all have highly irregular shapes, and their dimensions vary greatly.

Both the column and the axon were centered on the same Cartesian origin. The lattice of columns had a periodic arrangement in the x - y plane, and the arrangement of ellipsoids was also periodic in the z direction, with the coordinates extending to infinity. Each column consisted of an intra- and extra-axonal space separated by a myelin sheath. The extra-axonal space was further divided into glial cells and the interstitial space was separated by the glial cell membrane. The diffusivities of these components were represented by the intra-axonal diffusivity (D_i), the extra-axonal diffusivity (D_e), and the glial cell diffusivity (also D_e), respectively. Both the myelin sheath and cellular membrane are permeable boundaries, but the former has a much lower permeability due to its more compact structure. In accordance with previous investigations (36), we assumed that the rate of exchange of magnetization between intra- and extra-axonal water has an inverse relationship with myelin integrity.

Movement of Molecule in Monte Carlo Simulation

The diffusion process of water molecules was discretized by separating the diffusion time into T steps. Thus, in each step $\delta t = T$, each molecule's displacement is constant in magnitude $\sqrt{6D\delta t}$ and random in orientations, where D is the local diffusivity.

When a molecule collides with a membrane, a random number was generated within [0 1] and compared with the transmission probability. The molecule only passes the membrane when the random value is smaller than the transmission probability (defined below). Otherwise, it is reflected elastically at the membrane. It was assumed that this reflection is a rigid-body collision, and that the reflected path $\vec{l}_1$ can be calculated with the original velocity $\vec{l}_0$ and a basic vector $\vec{n}$ perpendicular to the tangent plane.

$$\vec{l}_1 = \vec{l}_0 - 2(\vec{l}_0 \cdot \vec{n})\vec{n}, \quad [1]$$

Because the collision can happen multiple times, the net displacement of a particle in each step is given by:

$$\vec{l}_{net} = \vec{l}_0 + \vec{l}_1 + \dots + \vec{l}_n, \quad [2]$$

where $\vec{l}_n$ is the n th reflected path.

The transmission probability (p_t) was used to represent the chance of transmission across membranes, as described by Regan and Kuchel (37): $p_t = P/D$, where P is the permeability of the membrane. After substituting D_i and D_e into this formula, we obtain the transmission probability across the myelin sheath and glial cell membrane—that is, p_{tie} , p_{teir} and p_{tgr} respectively (24):

$$p_{tie} = 4P(6\delta t/D_i)^{1/2} \quad [3]$$

$$p_{tg}=p_{tei}=4P(6\delta t/D_e)^{1/2}. \quad [4]$$

The averaged lifetime $\hat{\tau}$, which is how long a molecule spends inside an axon before leaving, is related to the permeability (37),

$$P=\frac{d}{4\hat{\tau}}, \quad [5]$$

where d is the diameter of the axon.

In the beginning of the diffusion process, each molecule was assigned to a random starting position in the central hexagon. A periodic boundary condition was assumed (ie, if a molecule reached one side of this hexagon, it would re-enter at the opposite side of the hexagon). However, all the true positions in the diffusion process were still kept (Fig. 2a). The displacement during the diffusion time was saved for data synthesis until the end of the simulation (Fig. 2b).

Diffusion Signal Synthesis

The diffusion-weighted signal was synthesized following the time evolution of water molecules under the pulsed gradient spin echo sequence with two gradient pulses of rectangular lobes. Diffusion-weighted signal S is the sum of magnetization of all the particles (27),

$$S=\sum_{k=1}^N \exp \left(i\gamma \vec{g} \left(\int_0^\delta \vec{r}_k(t) dt - \int_0^{\Delta+\delta} \vec{r}_k(t) dt \right) - \int_0^{\Delta+\delta} 1/T_2(\vec{r}_k) dt \right), \quad [6]$$

where N is the number of particles, k is the particle index and $\vec{r}_k$ is the displacement of the k th particle. The first two terms of the exponent describes the accumulated phase generated by gradients and the last term represents the T2 decay that depends on where the molecule is located.

FA, MD, DA, and DR were calculated based on the diffusion tensor model. In order to investigate the effects of different simulation parameters on DTI metrics, three sets of simulation parameters were used. Because most clinical DWI and DTI studies have used b values less than 1500 s/mm² [with b values up to 3000 s/mm² used primarily in research (38)], we chose diffusion times of 25, 50, and 75 ms to correspond to b values of 500, 1000, and 1500 s/mm², respectively, with the duration of the gradient lobe fixed at 10 ms for most simulations (except when indicated otherwise). We believe this set of simulation parameters allows the evaluation of changes in the brain reflecting TBI observed in most clinical studies. It should be noted that when the duration of the gradient is not an integer multiple of the update time (δt), it leads to a mismatch between the gradient onset/end and the assumed

gradient pulse duration, which can cause bias to the simulation. In our study, this was avoided by recalculating the update time at the edges of the gradient pulse, so that only the displacement within the gradient pulse duration contributed to the diffusion-weighted signal according to Equation [6].

Simulations consisted of a group of 1×10^6 particles. The number of diffusion steps (T) varied from 7500 to 21,500 making the relative step length equal to 10% of the axon diameter. All the simulations were performed with MATLAB 2014a (MathWorks, Natick, Massachusetts, USA) on a Mac Pro platform (2×3.06 GHz 6-Core Intel Xeon CPU, 64GB RAM).

Simulation of TBI Pathology

We made some assumptions about the simulation parameters based on previous simulation studies and histological observations. In the central nervous system, myelinated axons have a wide range of diameters and densities, but we fixed the axonal diameter at $2 \mu\text{m}$ and the separation between axons at $3 \mu\text{m}$, which fell into the range of values from histological studies (39,40), resulting in an axon volume fraction of 40.3%. The membrane water permeability in tissue varies from 1×10^{-4} to 1×10^{-2} cm/s, and we chose 1×10^{-3} cm/s as a reasonable value for glial cell membrane (41). A diffusion coefficient of $2.0 \mu\text{m}^2/\text{ms}$ was chosen for the extra- and intra-axonal spaces, which is in the normal range for brain tissue and has also been used in other simulation studies (27). In addition, the myelin sheath was assumed to be permeable only in the demyelination experiment, because the water exchange is negligible when myelin is intact.

Only the typical pathological changes in acute and subacute stages of TBI were simulated with model parameters, since a thorough analysis of the TBI cascade involving all possible pathological stages is far more complicated and was beyond the scope of this study. Our model manipulates four independent tissue parameters to reflect TBI pathology: 1) intra-axonal diffusivity, 2) axon separation, 3) volume fraction of glial cells, and 4) myelin sheath permeability. In order to investigate the dependence of the diffusion parameters on tissue pathology, we performed four sets of experiments concerning both the severity and the stages of TBI. The workflow is illustrated in Figure 3.

After axonal injury, extensive axonal beading have been observed in a postmortem study using APP immunohistochemistry (42). This pathology indicates disrupted axonal transport and accumulated organelles in axons, which potentially reduces D_i . This is also supported by evidence from DTI studies showing reduced axial diffusivity (6,12). In our model, the effect of pure axonal injury on diffusion parameters was represented by decreasing intra-axonal diffusivity while keeping extra-axonal diffusivity invariant. An initial value of $2 \mu\text{m}^2/\text{ms}$ was assumed for the normal state. Then, reflecting axonal injury in TBI, the intra-axonal diffusivity was reduced to $1 \mu\text{m}^2/\text{ms}$ (12).

Cytotoxic and vasogenic edema are related phenomena in that they both involve a shift of water into different cellular compartments. Cytotoxic edema is characterized by an increase of intracellular sodium and water leading to cell swelling with decreased interstitial space (43). We represented this by increasing the volume fraction of glial cell in our model, which

ranged from 12% to 21%. To increase the volume of the ellipsoid representing glial cells, we fixed the short axis at 0.7 μm and increased the long axis from 0.7 μm to 1.0 μm to meet the corresponding glial cell volume fractions. Vasogenic edema is characterized by dissociated neuronal fibers with enlarged interfiber and extracellular spaces (44), which corresponded to an increased axonal separation in our model. In vasogenic edema, the separation between axons was increased from 3 μm to 3.54 μm , reducing the volume fraction of axons from 40% to 29%, similar to the value of axon and glial cell fraction used in previous studies (35,45).

Demyelination usually occurs in the subacute stage. The intact myelin sheath restricts water molecules in their respective space (intra- or extra-axonal), making the exchange across it negligible in the typical diffusion time scale. This “impermeability” relies on the lipid composition and multilamellar structure of the myelin sheath. The myelinated axons thus have lower permeability than demyelinated axons and glial cells (35,41). Based on the residence time of different cells (41), the effect of demyelination was simulated by making the intra-axonal lifetime range from infinity to 5 ms, corresponding to changes in membrane permeability from 0 to 0.015 cm/s.

Validation of Simulation with Analytical Models and Tests of Dependence on Signal-to-Noise Ratio

In order to validate the simulation, two groups of simulations were conducted, and the simulated signal arising from the intra-axonal spins was compared with an analytical model as functions of relative step length and b value, respectively. The signal attenuation model of restricted diffusion in a cylindrical axon is given by (46)

$$\ln \frac{M(\delta, \Delta, G)}{M_0} = -2\gamma^2 G^2 \sum_{m=1}^{\infty} \frac{2D\alpha_m^2 \delta - 2 + 2e^{-D\alpha_m^2 \delta} + 2e^{-D\alpha_m^2 \Delta} - e^{-D\alpha_m^2 (\Delta - \delta)} - e^{-D\alpha_m^2 (\Delta + \delta)}}{D^2 \alpha_m^2 (R^2 \alpha_m^2 - 1)},$$

[7]

where R is the radius of the cylinder, D is the diffusivity, G is the gradient amplitude, and α_m is the m th root of $J_1'(\alpha_m R) = 0$. In the first group of simulations, the signal from axons was followed with relative step length varying from 2% to 14% of the cylinder diameter, whereas the b value and diffusion time were fixed at 500 s/mm² and 25 ms, respectively. The spin number was fixed at 1×10^2 , 1×10^3 , 1×10^4 , and 1×10^5 in four sets of experiments. In the second group, the b value varied from 400 s/mm² to 1600 s/mm², whereas the relative step length was fixed as 10% of the cylinder diameter and the particle number was 1×10^5 . Three diffusion times were used (25 ms, 50 ms, and 75 ms), and the gradient amplitude varied according to the corresponding b values. Each simulation was repeated 10 times to obtain the coefficient of variation.

To investigate the effects of noise on the observed trends, different levels of noise were added to the synthesized data. The signal-to-noise ratios (SNRs), relative to signal at b=0, were 100, 56, 32, 18, and 10. Signal changes during axonal injury was simulated with a

diffusion time 50 ms and a b value 1000 s/mm². D_i was varied from 2 to 1 $\mu\text{m}^2/\text{ms}$ for the axonal compartment, whereas D_e , axon separation, and permeability were fixed.

RESULTS

Validation of Simulation with Analytical Models

The bias in the simulations was calculated as a deviation from Equation [7]. The synthesized signals of the simulation were generally coincident with the analytical model, as the bias relative to the analytical solution was close to zero with increasing step length (Fig. 4a). Furthermore, the bias decreased with the increasing number of particles. When this number reached 1×10^5 , the bias was at the magnitude of 1×10^{-5} , providing highly reliable simulations. As shown in Fig. 4b, the coefficient of variation decreased with increasing number of particles and remained stable with increasing step length. These results are consistent with a previous study by Hall and Alexander (27). Conversely, the values of bias and coefficient of variation increased as the b values increased (Fig. 4c and 4d). This effect became more obvious with shorter diffusion times, because for a smaller diffusion time at a fixed b value a larger gradient strength is required, which causes more signal decay. On the other hand, at a fixed gradient, the mean displacement barely increased with increasing diffusion time due to restriction to diffusion in axons. For the remaining simulations, a relative step length of 10% and number of particles 1×10^6 were used to provide reliable synthesized data.

Tests of Dependence on SNR

In the noise-free measurements (Fig. 5a), the data points were well convergent, almost aligned along a monotonically decreasing line from the normal condition. As the SNR was decreased from 100 to 10, more fluctuation was seen in the data points, and the trend was weakened by increasing noise (Fig. 5b–5d). At clinical achievable SNR down to 18, the expected decreasing trend of FA and MD was still observable. At an SNR of 10, the first and the last data points showed little difference in FA, while the reduction in MD still remains, suggesting the trend of FA is more easily corrupted by noise than that of MD.

Changes in DTI Parameters Reflecting Tissue Pathology Due to TBI

Changes in FA and MD representing different tissue pathology due to TBI are shown in Figure 6. The pathological evolution of tissue injury is color-coded, with blue representing the normal state and red representing the most severe pathology. Axonal injury played a dominant role in the acute stage, and the injury-induced reduction in D_i caused marked reductions in both FA and MD (Fig. 6a). This result is consistent with clinical observations and animal models of acute injury wherein DTI metrics showed reduced FA and reduced or unchanged MD (pattern 1). Vasogenic and cytotoxic edema can co-occur. Although both arise from accumulated tissue water, they have opposite effects on DTI parameters. Vasogenic edema alone could lead to a combination of reduced FA and elevated MD (Fig. 6b, pattern 3). On the contrary, cytotoxic edema is more likely to cause elevated FA and reduced MD (Fig. 6c, pattern 2). Demyelination happens more often in the subacute stage. Our simulations show that its major effect is on the reduction of FA and the elevation of MD (Fig. 6d, pattern 3).

Besides FA and MD, the DTI metrics that are most frequently reported in the literature, our simulation further investigated the contribution of axial and radial diffusivity (DA and DR, shown in Fig. 7). For example, during axonal injury (Fig. 7a) when the b value was 1000 s/mm², DA decreased (−24%) more than DR (−3%). However, vasogenic and cytotoxic edema affected DA (Fig. 7b) and DR (Fig. 7c) in opposite ways. Specifically, with vasogenic edema, both DA and DR were increased (Fig. 7b), whereas cytotoxic edema reduced both of them (Fig. 7c). Interestingly, DR seems more sensitive to both types of edema than DA (47% versus 8% and −14% versus −3%). In the case of demyelination, as shown in Figure 7d, DA changed minimally, whereas DR increased greatly (42%).

Although absolute differences in the diffusion parameters (FA, MD, DA, RA) were observed in this study with the different b values/diffusion times, the general trend remained the same. The general trend of tissue pathology on DTI-derived parameters is summarized Table 1. The maximum fractional change of each parameter is also given in the bracket, which is equal to (Diseased − Normal)/Normal × 100%. This rate provides an indication of what may be the dominant change in each pathology, and how sensitive each parameter reflects the specific pathology. For example, greatly reduced FA, MD, and DA as well as subtly reduced DR could indicate axonal injury. Increased FA and reduced MD, DR, and DA could indicate cytotoxic edema. Furthermore, among all DTI parameters, DA was most sensitive (−24%) to axonal injury and DR was most sensitive to vasogenic (47%) and cytotoxic (−14%) edema as well as demyelination (42%). These results are based on a b value of 1000 s/mm² and a diffusion time of 50 ms, but simulations with the other parameters yielded similar results (data not shown). Although it was beyond the scope of this investigation, it may be possible to optimize experimental parameters for detecting or distinguishing between specific TBI-induced pathologies.

DISCUSSION

This study used Monte Carlo simulations to investigate changes in DTI metrics that may occur at different time points after TBI. The pattern of injury investigated included axonal injury, cytotoxic and vasogenic edema, and demyelination.

In TBI, axons and small blood vessels are the most vulnerable part of the brain parenchyma to mechanical force. The pathologic findings, such as axonal swellings and petechial hemorrhages, as well as disconnections of axons, may reflect a direct injury (13,47), but these findings are rare in the mild TBI. Rather, DTI abnormalities observed in mild human TBI and animal models are likely caused by axonal microtubule destruction and disruption of axonal transport (42,48). The hypothesis in our study is that the integrity of axonal structure is the premise of normal diffusivity in the intra-axonal space. Thus, the damaged axons would lead to reduced FA and MD (pattern 1) as shown in Figure 6a. In a human study, Liu et al. (49) reported that significant decreases in MD values could be found in the presence of diffuse axonal injury well into the subacute period. This observation is also confirmed in a previous animal study by MacDonald et al. (12), who reported a reduction in FA and a slight reduction in MD during the acute phase after TBI.

The presence of cytotoxic edema and vasogenic edema in the acute stage can explain the observed pattern 2 (ie, elevated FA and reduced MD) and pattern 3 (ie, reduced FA and elevated MD), respectively. Although both types of edema can be present independently in TBI, they tend to occur in sequence, and there may be a transition between them. As has been reported in both human and rat models, a predominantly vasogenic edema forms immediately after injury, followed later by cytotoxic edema, which continues to a lesser degree into the subacute stage (20,21). Following our model, the two types of edema can have opposite effects on DTI parameters: vasogenic edema increases extra-axonal diffusivity leading to decreased FA and increased MD (pattern 3) as shown in Figure 6b; and cytotoxic edema increases extra-axonal tortuosity leading to increased FA and reduced MD (pattern 2) as shown in Figure 6c. It must be emphasized that vasogenic and cytotoxic edema could also coexist, contributing simultaneously to DTI signal and therefore cancel out the opposing effects. For example, at the very time point when the predominance in the edema turns from vasogenic to cytotoxic, the DTI parameters may show no sign of abnormalities.

Demyelination can be another factor that causes changes in DTI parameters reflected by pattern 3 in the subacute stage. In a well-established animal model, Liu et al. (50) showed that demyelination is initiated as early as several hours after TBI and peaks as early as several days after TBI, which is roughly the subacute stage. The loss of myelin sheath integrity exposes axonal membranes to extra-axonal spaces and facilitates water exchange between intra-axonal space and extra-axonal space. A large increase of membrane permeability to sodium and potassium has been observed in demyelinated rat brain fibers (51), which is likely accompanied by an increase in water permeability. As a result, diffusion is less restricted by the myelin sheath leading to smaller tortuosity perpendicular to the axons. Investigations on how demyelination affects DTI parameters have shown that DR is elevated significantly, whereas DA remains unaffected in the presence of intact axons (16,52), which is consistent with the reduced FA and elevated MD (pattern 3) in Figure 6d and elevated DR in Figure 7d. It must be emphasized that demyelination is not the only pathology in the subacute stage; for example, the axonal injury may also be present and lead to reduced FA and MD as discussed above. In fact, the evolution of MD is more complicated than FA, and as MD changes from lower than normal (acute) to above-normal (subacute), a process known as “pseudo-normalization” occurs. This is consistent with studies on mild TBI patients at later time points, which reveal decreased FA values but MD values that vary widely (10,53–55).

Similar to MD and FA, DA and DR can be used to differentiate abnormalities in TBI. Furthermore, some previous studies and our own data suggest that they are more sensitive indicators of axonal injury and demyelination. As shown in Figure 6a and Figure 7a, during axonal injury, DA has a sharper reduction than FA and MD, whereas DR is basically unchanged. In contrast, DR is more sensitive to demyelination than FA and MD, whereas DA is quite insensitive (comparing Fig. 6d and Fig. 7d). This result agrees with the mouse study by MacDonald et al. (12). However, few human TBI studies have focused on DA and DR, and results for systematic comparison and corroboration are not available.

The clinical achievable SNR that is relative to the b_0 image can range from 10 to 100 s in amplitude ratio, depending on field strength, image resolution, number of averages, and so

forth (56,57). As shown in the SNR simulations (Fig. 5), the minimum SNR to observe a FA trend is <18 (Fig. 5e) and the minimum SNR to observe a MD trend is <10 (Fig. 5f), which is achievable for most clinical measurements. Thus, our conclusions are applicable at both 1.5T and 3T.

We are not aware of any simulation studies focused on human TBI. However, Monte Carlo simulations have been used in other contexts to investigate axonal diffusivity and show excellent agreement with in vivo measurements (29,30). Monte Carlo simulation has also been used to validate the water exchange model in ischemia (58,59). In these studies, membrane permeability is used to mediate water exchange.

We used a sole physical parameter to represent each pathology. Other effects may also exist but manifest less prominently. For example, axonal injury can cause the interruption of axonal transport leading to accumulation of the transported materials. The axonal beadings or axonal swellings will occur at focal sites but there are fewer than two axonal beadings per 100 μm axonal length, which makes a negligible contribution to the axon diameter (42,48,60). On the other hand, as myelin sheath supports the normal structure of the axon, minimal water accumulates in myelinated axons. Therefore, in the acute phase of mild TBI, when the myelin is intact, cytotoxic edema should only appear in glial cells, thus the change of axon volume can be ignored.

One limitation of the present study is that we assumed constant radius and hexagonal packing of axons, even though in vivo, this long-range order and regular packing of the microstructure does not exist. Actually, the axons are arranged randomly in space and have a distribution of radii. However, many previous Monte Carlo studies have used regular packing for the tissue structure (24,26,29,30,58,61,62). Even though the structure is regular, simulation based on random motion (change of directions randomly) has resulted in useful gross effects of microstructures to the diffusion process. Fieremans et al. (28) compared the effects of different packing geometries (square, hexagonal, and random) on apparent diffusion coefficient in parallel and transverse directions. They reported that parallel ADC was independent of packing geometries but that transverse direction ADC had a lower value in regular packing (square and hexagonal) relative to random packing. If random packing had been used in our study, compared with regular packing, DR and MD values would increase, DA would be unchanged, and FA would also increase. However, the overall trend due to TBI pathology would remain.

A second limitation of the present study is that a homogenous T2 is assumed. Studies on frog sciatic nerve show that there are three T2 components from MRI signal (63): 1) a short T2 component from bonded water associated with proteins and phospholipids; 2) an intermediate T2 component to axoplasmic water, and 3) a long T2 component to extracellular water. Taking into consideration the T2 inhomogeneity, the simulation by Szafer et al. (24) shows that the diffusion-weighted signal of the compartment with short T2 will be suppressed due to the fast attenuation. For any compartment, the effect of longer T2 is equivalent to a greater volume fraction, as both increase the compartment's weighting on synthesized data. If extra-axonal T2 were assumed to be larger than intra-axonal T2, for each experiment, the change of DR and MD would be increased, as extra-axonal diffusion has a

larger weighting on them than intra-axonal diffusion, while the change of DA and FA would be reduced as they are mainly affected by intra-axonal diffusion. The inhomogeneous T2 only affects the magnitude of the change in the parameter, but not its directionality and interpretation; therefore, our results are still valid.

A third limitation of this study is that the myelin sheath is taken as part of the axonal membrane and this simplification can cause the following issues regarding the simulation of demyelination. First, histomorphometric analysis shows that myelin content makes up 30%–40% of total area in rat nerves (64) and an increase in myelin content is believed to contribute to increased diffusion anisotropy (65). As an independent component between intra- and extra-axonal space, myelin plays an important role in modulating the exchange of these two water pools. The accuracy of the diffusion simulation may be improved if myelin is taken into consideration as a separate compartment, because myelin water has a lower T2 than that in intra-/extra-axonal space. In demyelination, reduced myelin content will lead to an increase in average T2, which can in turn cause a deviation in the estimation. In our future studies, a new compartment—myelin sheath with finite thickness—will be incorporated to address the effect of myelin in greater detail.

CONCLUSIONS

This study links the pathological changes in TBI occurring at the cellular level with DTI-derived parameters. We show that the Monte Carlo simulation can provide insight into conflicting TBI DTI findings reported in the literature. We have investigated the sensitivity of DTI-derived parameters in TBI at different stages of tissue pathology. The ability to assess pathological changes associated with TBI provides a window for evaluation of severity and evolution of injury that could be used for medical intervention.

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References

1. Faul, M.; Xu, L.; Wald, M.; Coronado, VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. p. 2-70.
2. Toledo E, Lebel A, Becerra L, Minster A, Linnman C, Maleki N, Dodick DW, Borsook D. The young brain and concussion: imaging as a biomarker for diagnosis and prognosis. *Neurosci Biobehav Rev.* 2012; 36:1510–1531. [PubMed: 22476089]
3. Choi SJ, Lim KO, Monteiro I, Reisberg B. Diffusion tensor imaging of frontal white matter microstructure in early Alzheimer's disease: a preliminary study. *J Geriatr Psychiatry Neurol.* 2005; 18:12–19. [PubMed: 15681623]
4. Werring D, Clark C, Barker G, Thompson A, Miller D. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. *Neurology.* 1999; 52:1626–1626. [PubMed: 10331689]

5. Huisman TA, Schwamm LH, Schaefer PW, Koroshetz WJ, Shetty-Alva N, Ozsunar Y, Wu O, Sorensen AG. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2004; 25:370–376. [PubMed: 15037457]
6. Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2002; 23:794–802. [PubMed: 12006280]
7. Bazarian JJ, Zhong J, Blyth B, Zhu T, Kavcic V, Peterson D. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J Neurotrauma*. 2007; 24:1447–1459. [PubMed: 17892407]
8. Wilde E, McCauley S, Hunter J, Bigler E, Chu Z, Wang Z, Hanten G, Troyanskaya M, Yallampalli R, Li X. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*. 2008; 70:948–955. [PubMed: 18347317]
9. Mayer A, Ling J, Mannell M, Gasparovic C, Phillips J, Doezeema D, Reichard R, Yeo R. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology*. 2010; 74:643–650. [PubMed: 20089939]
10. Rutgers D, Fillard P, Paradot G, Tadie M, Lasjaunias P, Ducreux D. Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *AJNR Am J Neuroradiol*. 2008; 29:1730–1735. [PubMed: 18617586]
11. Miles L, Grossman RI, Johnson G, Babb JS, Diller L, Inglese M. Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury. *Brain Inj*. 2008; 22:115–122. [PubMed: 18240040]
12. MacDonald CL, Dikranian K, Bayly P, Holtzman D, Brody D. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J Neurosci*. 2007; 27:11869–11876. [PubMed: 17978027]
13. Povlishock JT. Pathobiology of traumatically induced axonal injury in animals and man. *Ann Emerg Med*. 1993; 22:980–986. [PubMed: 8503536]
14. Gorrie C, Oakes S, Duflo J, Blumbergs P, Waite PM. Axonal injury in children after motor vehicle crashes: extent, distribution, and size of axonal swellings using β -APP immunohistochemistry. *J Neurotrauma*. 2002; 19:1171–1182. [PubMed: 12427326]
15. Maxwell WL, Domleo A, McColl G, Jafari SS, Graham DI. Post-acute alterations in the axonal cytoskeleton after traumatic axonal injury. *J Neurotrauma*. 2003; 20:151–168. [PubMed: 12675969]
16. Song S-K, Yoshino J, Le TQ, Lin S-J, Sun S-W, Cross AH, Armstrong RC. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage*. 2005; 26:132–140. [PubMed: 15862213]
17. Singleton RH, Zhu J, Stone JR, Povlishock JT. Traumatically induced axotomy adjacent to the soma does not result in acute neuronal death. *J Neurosci*. 2002; 22:791–802. [PubMed: 11826109]
18. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean A. Staining of amyloid amyloid precursor protein to study axonal damage in mild head injury. *Lancet*. 1994; 344:1055–1056. [PubMed: 7523810]
19. Blumbergs PC, Scott G, Vis JM, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. *J Neurotrauma*. 1995; 12:565–572. [PubMed: 8683607]
20. Marmarou, A.; Signoretti, S.; Aygok, G.; Fatouros, P.; Portella, G. *Brain Edema*. Vol. XIII. Vienna: Springer; 2006. Traumatic brain edema in diffuse and focal injury: cellular or vasogenic?; p. 24–29.
21. Barzo, P.; Marmarou, A.; Fatouros, P.; Hayasaki, K.; Corwin, F. *Brain Edema*. Vol. X. Vienna: Springer; 1997. Biphasic pathophysiological response of vasogenic and cellular edema in traumatic brain swelling; p. 119–122.
22. Assaf Y, Basser PJ. Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. *Neuroimage*. 2005; 27:48–58. [PubMed: 15979342]
23. Kärger J. Principles and applications of self-diffusion measurements by nuclear magnetic resonance. *Adv Magn Reson*. 1988; 12:1–89.

24. Szafer A, Zhong J, Gore JC. Theoretical model for water diffusion in tissues. *Magn Reson Med*. 1995; 33:697–712. [PubMed: 7596275]
25. Ford JC, Hackney DB. Numerical model for calculation of apparent diffusion coefficients (ADC) in permeable cylinders—comparison with measured ADC in spinal cord white matter. *Magn Reson Med*. 1997; 37:387–394. [PubMed: 9055229]
26. Regan DG, Kuchel PW. Simulations of NMR-detected diffusion in suspensions of red cells: the “signatures” in q-space plots of various lattice arrangements. *Eur Biophys J*. 2003; 31:563–574. [PubMed: 12582816]
27. Hall MG, Alexander DC. Convergence and parameter choice for Monte-Carlo simulations of diffusion MRI. *IEEE Trans Med Imaging*. 2009; 28:1354–1364. [PubMed: 19273001]
28. Fieremans E, De Deene Y, Delpitte S, Özdemir MS, D’Asseler Y, Vlassenbroeck J, Deblaere K, Achten E, Lemahieu I. Simulation and experimental verification of the diffusion in an anisotropic fiber phantom. *J Magn Reson*. 2008; 190:189–199. [PubMed: 18023218]
29. Budde MD, Frank JA. Neurite beading is sufficient to decrease the apparent diffusion coefficient after ischemic stroke. *Proc Natl Acad Sci U S A*. 2010; 107:14472–14477. [PubMed: 20660718]
30. Nilsson M, Lätt J, Ståhlberg F, Westen D, Hagglätt H. The importance of axonal undulation in diffusion MR measurements: a Monte Carlo simulation study. *NMR Biomed*. 2012; 25:795–805. [PubMed: 22020832]
31. Nilsson M, Lätt J, Nordh E, Wirestam R, Ståhlberg F, Brockstedt S. On the effects of a varied diffusion time in vivo: is the diffusion in white matter restricted? *Magn Reson Imaging*. 2009; 27:176–187. [PubMed: 18657924]
32. Edgar JM, Griffiths IR. Chapter 7 – White Matter Structure: A Microscopist’s View. *Diffusion Mri*. 2014:127–153.
33. Ishiguri, H.; Kuchiwaki, H.; Misu, N.; Takada, S.; Inao, S.; Itoh, J.; Ikeda, A.; Kageyama, N. *Brain Edema*. Berlin Heidelberg: Springer; 1985. Thermal analysis of edema fluid and electron microscopic studies in 6-ANA brain edema; p. 20-31.
34. Hossmann, K-A. *Brain Edema*. Berlin Heidelberg: Springer; 1985. The pathophysiology of ischemic brain swelling; p. 367-384.
35. Stanisiz GJ, Wright GA, Henkelman RM, Szafer A. An analytical model of restricted diffusion in bovine optic nerve. *Magn Reson Med*. 1997; 37:103–111. [PubMed: 8978638]
36. Harkins KD, Dula AN, Does MD. Effect of intercompartmental water exchange on the apparent myelin water fraction in multiexponential T2 measurements of rat spinal cord. *Magn Reson Med*. 2012; 67:793–800. [PubMed: 21713984]
37. Regan DG, Kuchel PW. Mean residence time of molecules diffusing in a cell bounded by a semi-permeable membrane: Monte Carlo simulations and an expression relating membrane transition probability to permeability. *Eur Biophys J*. 2000; 29:221–227. [PubMed: 10968214]
38. Hulkower M, Poliak D, Rosenbaum S, Zimmerman M, Lipton M. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *AJNR Am J Neuroradiol*. 2013; 34:2064–2074. [PubMed: 23306011]
39. Graf von Keyserlingk D, Schramm U. Diameter of axons and thickness of myelin sheaths of the pyramidal tract fibres in the adult human medullary pyramid. *Anat Anz*. 1984; 157:97–111. [PubMed: 6507887]
40. Sargon MF, Çelik HH, Aksit MD, Karaagaoglu E. Quantitative analysis of myelinated axons of corpus callosum in the human brain. *Int J Neurosci*. 2007; 117:749–755. [PubMed: 17454242]
41. Quirk JD, Bretthorst GL, Duong TQ, Snyder AZ, Springer CS, Ackerman JJ, Neil JJ. Equilibrium water exchange between the intra- and extracellular spaces of mammalian brain. *Magn Reson Med*. 2003; 50:493–499. [PubMed: 12939756]
42. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013; 246:35–43. [PubMed: 22285252]
43. Spatz, M. *Brain Edema*. Vol. XIV. Vienna: Springer; 2010. Past and recent BBB studies with particular emphasis on changes in ischemic brain edema; p. 21-27.
44. Zhao, F.; Kuroiwa, T.; Miyasakai, N.; Tanabe, F.; Nagaoka, T.; Akimoto, H.; Ohno, K.; Tamura, A. *Brain Edema*. Vol. XIII. Vienna: Springer; 2006. Diffusion tensor feature in vasogenic brain edema in cats; p. 168-170.

45. Assaf Y, Freidlin RZ, Rohde GK, Basser PJ. New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. *Magn Reson Med*. 2004; 52:965–978. [PubMed: 15508168]
46. Vangelder P, DesPres D, Vanzijl P, Moonen C. Evaluation of restricted diffusion in cylinders. Phosphocreatine in rabbit leg muscle. *J Magn Reson B*. 1994; 103:255–260. [PubMed: 8019777]
47. Maxwell WL, Povlishock JT, Graham DL. A mechanistic analysis of nondisruptive axonal injury: a review. *J Neurotraum*. 1997; 14:419–440.
48. Kilinc D, Gallo G, Barbee KA. Mechanically-induced membrane poration causes axonal beading and localized cytoskeletal damage. *Exp Neurol*. 2008; 212:422–430. [PubMed: 18572167]
49. Liu AY, Maldjian JA, Bagley LJ, Sinson GP, Grossman RI. Traumatic brain injury: diffusion-weighted MR imaging findings. *AJNR Am J Neuroradiol*. 1999; 20:1636–1641. [PubMed: 10543633]
50. Liu MC, Akle V, Zheng W, Kitlen J, O'Steen B, Lerner SF, Dave JR, Tortella FC, Hayes RL, Wang KK. Extensive degradation of myelin basic protein isoforms by calpain following traumatic brain injury. *J Neurochem*. 2006; 98:700–712. [PubMed: 16893416]
51. Brismar T. Specific permeability properties of demyelinated rat nerve fibres. *Acta Physiol Scand*. 1981; 113:167–176. [PubMed: 7315447]
52. Song S-K, Sun S-W, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*. 2002; 17:1429–1436. [PubMed: 12414282]
53. Salmond C, Menon D, Chatfield D, Williams G, Pena A, Sahakian B, Pickard J. Diffusion tensor imaging in chronic head injury survivors: correlations with learning and memory indices. *Neuroimage*. 2006; 29:117–124. [PubMed: 16084738]
54. Rutgers D, Toulgoat F, Cazejust J, Fillard P, Lasjaunias P, Ducreux D. White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2008; 29:514–519. [PubMed: 18039754]
55. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*. 2007; 130:2508–2519. [PubMed: 17872928]
56. Landman BA, Farrell JA, Huang H, Prince JL, Mori S. Diffusion tensor imaging at low SNR: nonmonotonic behaviors of tensor contrasts. *Magn Reson Imaging*. 2008; 26:790–800. [PubMed: 18499378]
57. Farrell JA, Landman BA, Jones CK, Smith SA, Prince JL, van Zijl P, Mori S. Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T. *J Magn Reson Imaging*. 2007; 26:756–767. [PubMed: 17729339]
58. Lätt J, Nilsson M, van Westen D, Wirestam R, Ståhlberg F, Brockstedt S. Diffusion-weighted MRI measurements on stroke patients reveal water-exchange mechanisms in sub-acute ischaemic lesions. *NMR Biomed*. 2009; 22:619–628. [PubMed: 19306340]
59. Fieremans E, Novikov DS, Jensen JH, Helpert JA. Monte Carlo study of a two-compartment exchange model of diffusion. *NMR Biomed*. 2010; 23:711–724. [PubMed: 20882537]
60. Stone JR, Singleton RH, Povlishock JT. Intra-axonal neurofilament compaction does not evoke local axonal swelling in all traumatically injured axons. *Exp Neurol*. 2001; 172:320–331. [PubMed: 11716556]
61. Nilsson M, Alerstam E, Wirestam R, Brockstedt S, Lätt J. Evaluating the accuracy and precision of a two-compartment Kärger model using Monte Carlo simulations. *J Magn Reson*. 2010; 206:59–67. [PubMed: 20594881]
62. Ölviczky BP, Verkman A. Monte Carlo analysis of obstructed diffusion in three dimensions: application to molecular diffusion in organelles. *Biophys J*. 1998; 74:2722–2730. [PubMed: 9591696]
63. Peled S, Cory DG, Raymond SA, Kirschner DA, Jolesz FA. Water diffusion, T2, and compartmentation in frog sciatic nerve. *Magn Reson Med*. 1999; 42:911–918. [PubMed: 10542350]

64. Webb S, Munro CA, Midha R, Stanisz GJ. Is multicomponent T2 a good measure of myelin content in peripheral nerve? *Magn Reson Med*. 2003; 49:638–645. [PubMed: 12652534]
65. Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR Biomed*. 2002; 15:435–455. [PubMed: 12489094]

FIG. 1.

General tissue model. An axon is contained in a hexagon column and is surrounded by a permeable membrane. The axon is represented by a cylinder along the z direction. The diffusion coefficients in intra- and extra-axonal space are D_i and D_e respectively.

FIG. 2.

Mapping of molecule coordinates. **(a)** After each step, all molecules are relocated into the central column. **(b)** Actual mapping of final coordinates of molecules.

FIG. 3. Schematic of workflow. Simulation of DTI parameters is associated with tissue pathology. Axonal injury takes effect by reducing diffusivity in axons directly, whereas vasogenic edema, cytotoxic edema, and demyelination affect DTI parameters via tortuosity. The simulations are validated with clinical and animal model observations.

FIG. 4.

Effects of number of particles, relative step length, diffusion time, and b value on biases and coefficient of variation of synthesized signal. The bias is the deviation of the synthesized data from Equation 7. (a, b) The bias and coefficient of variation are shown as functions of relative step length. The b value and diffusion time are 500 s/mm^2 and 25 ms, respectively. (c, d) The bias and coefficient of variation are shown as functions of b value. The number of particles and relative step length are 1×10^5 and 10%, respectively.

FIG. 5.

FA and MD changes in axonal compartment with different noise level. The pathological evolution of tissue injury is color-coded, with blue representing the normal state and red representing the most severe pathology. (a) Noise-free signal. (b–f) Signal of SNR are equal to 100, 56, 32, 18 and 10.

FIG. 6.

FA and MD changes at different stages of tissue pathology. The tissue pathology evolution is color-coded, where blue and the surrounding region indicates the normal condition and red indicates the most severe pathology. Note that different scales are used for each subplot. **(a)** Axonal injury leads to pattern 1 of the DTI parameter changes of reduced FA and reduced MD. **(b)** Vasogenic edema leads to pattern 3 of the DTI parameter changes of reduced FA and elevated MD. **(c)** Cytotoxic edema leads to pattern 2 of the DTI parameter changes of elevated FA and reduced MD. **(d)** Demyelination leads to pattern 3 of the DTI parameter changes of reduced FA and elevated MD.

FIG. 7.

DA and DR changes at different stages of tissue pathology. The tissue pathology evolution is color-coded, where blue and the surrounding region indicates the normal condition and red indicates the most severe pathology. Note that different scales are used for each subplot. **(a)** Axial diffusivity is greatly reduced while radial diffusivity is relatively insensitive to axonal injury. **(b)** Both axial and radial diffusivities are elevated in vasogenic edema and the trend in increased diffusivity is greater for radial diffusivity than axial diffusivity. **(c)** Both axial and radial diffusivities are reduced in cytotoxic edema and the trend of radial diffusivity reduction is greater than in axial diffusivity. **(d)** Radial diffusivity is greatly elevated, whereas axial diffusivity is relatively insensitive to demyelination.

Table 1

Effects of Different Pathologies on DTI Parameters

Pathology	FA	MD	DR	DA
Axonal injury	↓(-17%)	↓(-16%)	↓(-3%)	↓(-24%)
Vasogenic edema	↓(-22%)	↑(23%)	↑(47%)	↑(8%)
Cytotoxic edema	↑(8%)	↓(-7%)	↓(-14%)	↓(-3%)
Demyelination	↓(-26%)	↑(16%)	↑(42%)	≈(0%)

↓, decrease; ↑, increase. The maximum fractional change of each parameter is given in parentheses and is equal to (Diseased – Normal)/Normal × 100%. The b value and diffusion time are 1000 s/mm² and 50 ms, respectively.