



Review Article

## Diffusion tensor imaging of the spinal cord status post trauma

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### ABSTRACT

**Background:** Since its development in 1994, diffusion tensor imaging (DTI) has been successfully used to assess structural and functional changes to neurological tissue within the central nervous system. Namely, DTI is a noninvasive magnetic resonance imaging (MRI)-based technique that uses anisotropic diffusion to visualize and estimate the organization of white matter in neuronal tissue. It has been used to study various spinal pathologies including neoplastic diseases, degenerative myelopathy, demyelinating diseases, and infections involving the spinal cord. However, due to technical uncertainties and experimental limitations, DTI has rarely been clinically applied to assess trauma-related spinal pathologies.

**Methods:** An extensive review of the published literature on DTI was performed utilizing PubMed, OVID Medline, and EMBASE journals. Terms used for the search included DTI and spine trauma.

**Results:** The search yielded full text English language-related articles regarding DTI's application, limitations, and functional outcomes secondary to spinal trauma.

**Conclusion:** DTI relies on anisotropy in CNS tissues to determine the spatial orientation of surrounding axon tracts and define anatomical boundaries. Diffusion along three principle axes is used to calculate the following four DTI indices; fractional anisotropy, apparent diffusion coefficient (ADC), longitudinal ADC, and transverse ADC. Using DTI as a diagnostic tool status, post spine trauma has proven useful in examining the morphological and physiological extent of spinal lesions beyond conventional MRI. Experimental studies are now utilizing DTI to analyze the severity of spinal cord trauma during the hyperacute phase and may potentially be used to providing additional diagnostic information for improved treatment efficiency (e.g., as shown during the stem cell therapy trials).

**Keywords:** Diffusion tensor imaging, Neuroradiology, Neurotrauma, Spinal cord, Trauma

### INTRODUCTION

Traumatic spinal cord injury (SCI) can disrupt axonal connectivity.<sup>[16]</sup> Inhibitory molecules that obstruct the reestablishment of synaptic connections and hinder axonal regrowth remain barriers

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to complete functional and neuronal recovery.<sup>[16]</sup> While conventional magnetic resonance provides an overview of the whole spinal cord, it does not document individual damaged spinal cord components. Rather, diffusion tensor imaging (DTI) is a noninvasive magnetic resonance imaging (MRI)-based technique that delineates the soft-tissue microstructure of the cord by enabling the visualization and quantification of white matter fiber tracts.<sup>[24]</sup> DTI used the magnetic field to induce water molecule movement and subsequently quantifies the directional uniformity and orientation of the diffusion of water molecules.<sup>[24]</sup> With intact nerve fibers, molecular movement is hindered; this generates a diffusion pattern.<sup>[24]</sup> Data obtained from the pattern can be used to calculate/measure the presence of various abnormalities including; edema, chronic and acute compression, ischemia, abnormal neurologic function, and axon degeneration.<sup>[24]</sup>

DTI has become increasingly incorporated into routine clinical protocols for assessing abnormalities of the brain, while protocols for clinical application to spinal cord pathology are limited. Nevertheless, various animal-based experimental studies found correlations between diffusion tensor measures after SCI and locomotor outcomes, injury severity, white matter tract disruption, and glial scar orientation.<sup>[17,18,25,33]</sup> These data suggest that quantitative DTI of axonal integrity may be a potential biomarker for prognostic and therapeutic evaluation status posttraumatic SCI.<sup>[16]</sup> Here, we provide a contemporary review of the clinical application and utility of DTI in the evaluation of the spinal cord trauma.

## TECHNOLOGY

The technology of DTI is an elegant collaboration between MRI sequences, with software that utilize the diffusion of water to generate contrast in neural tract images. This technology is derived from diffusion-weighted imaging (DWI), an MRI variant that measures signal strength based on the mean displacement of water in tissues. Today, DTI is now considered more advantageous than DWI because it can also quantify the direction of diffusion.<sup>[19]</sup> Using DTI, images can be modeled based on anisotropy and orientation to visualize microstructures within tissues, such as axonal density, myelination, or fiber direction.<sup>[2]</sup> DTI uses parameters such as apparent diffusion coefficient (ADC, the magnitude of diffusion), fractional anisotropy (FA, the fraction of anisotropic diffusion), radial diffusivity (RD) (transverse axis diffusion rate), and axial diffusivity (main axis diffusion rate) to act as quantitative biomarkers within these tissues DTI FA maps use color to show anisotropy in different axes with red for the left-right axis, blue for the inferior-superior axis, and green for the anterior-posterior axis.<sup>[29,35]</sup> Furthermore, the introduction of DTI technology meant the rotational invariance of water diffusion could be measured to allow for further visualization.

## PRINCIPLES

Diffusion MRI relies on the intrinsic properties of highly structured tissues, specifically neurons and white matter tracts in the central nervous system. In these tissues, diffusion of water molecules occurs preferentially along one direction.<sup>[3]</sup> The morphology of axons promotes diffusion of water molecules in a direction that is parallel to the axon fibers, instead of perpendicular.<sup>[3,4]</sup> The term “anisotropy” is used to describe direction-dependent diffusion and is the central principle of DTI. DTI relies on anisotropy in CNS tissues to determine the spatial orientation of surrounding axon tracts and define anatomical boundaries.<sup>[44]</sup> DTI employs a tensor framework (i.e., 3×3 matrix) to describe the molecular motion of water in three dimensions.<sup>[44]</sup> Diffusion along three principle axes is used to calculate DTI indices. These indices include FA, ADC, longitudinal apparent diffusion coefficient (lADC), and transverse apparent diffusion coefficient (tADC).

FA is a scalar number between 0 and 1 that indicates the degree of anisotropy of molecular water diffusion along and across the axon. Injuries to the spinal cord result in disruption of longitudinally arranged axons, and therefore, DTI will reveal a FA value less than 1.<sup>[14]</sup> ADC is a measure of the rate of random water diffusion without reference to a particular direction. ADC, also referred to as mean diffusivity (MD), is the average molecular water diffusion across all three principal axes.<sup>[14,44]</sup> The lADC mathematically represents the rostro-caudal or axial diffusion of water molecules along white matter tracts.<sup>[36,44]</sup> While the value of lADC is often decreased in SCI, the value for tADC is often increased by demyelination and injury.<sup>[36,37]</sup> tADC measures radial or perpendicular diffusion of water molecules.<sup>[1,37]</sup> DTI indices are highly sensitive to the microenvironment of the central nervous system and therefore provide valuable data for identifying spinal cord pathologies posttrauma.

### Advantages

DTI has many advantages to its use in the clinical setting when examining and diagnosing SCIs compared to plain MRI. Bihan *et al.* reported that DTI as a quantitative method reflects the properties of tissues while being able to be compared between patients or be compared overtime without a need for standardization.<sup>[22]</sup> Soares *et al.* detailed that DTI allows for the visualization of abnormalities in spinal cord tracts.<sup>[35]</sup> They also show how variables in DTI can relate to microstructures leading to diagnosis of myelination levels and axonal injury. Kamble *et al.* similarly revealed that DTI can show this diffuse axonal injury as previously mentioned, in addition to demyelination, even when traditional CT and MRI show normal anatomy.<sup>[15]</sup> Because DTI can show microstructures and their boundaries, Patel *et al.* and Loy

*et al.* reported that DTI is useful in the classification of SCI severity.<sup>[25,30]</sup>

Further, Patel *et al.* continued to discuss that DTI is more sensitive to SCI severity classification than other imaging modalities.<sup>[30]</sup> In another study done by Chang *et al.*, they utilized quantified analyses of DTI, using fiber tractography (FT), and were better able to correlate findings with neurological impairments when compared to routine MRI.<sup>[6]</sup> On a temporal scale, Patel *et al.* demonstrated DTI measurements showing stable predictions of SCI severity in the subacute time period (>6 h from onset), and Kim *et al.* push that boundary further in their study detailing accurate assessments of white matter integrity 3 h post-SCI.<sup>[17,30]</sup>

All in all, DTI is both a sensitive and specific test for SCI within the white matter.<sup>[25]</sup> By accurately assessing SCI severity earlier on in its time course, earlier diagnoses and treatment plans can be formulated. All of this combined allow for improved monitoring and long-term prognosis.<sup>[17]</sup> Both Kamble *et al.* and Patel *et al.* also noted how SCI assessed with DTI is a better long-term predictor of motor function recovery and does so with greater accuracy than routine MRI.<sup>[15,30]</sup> Of course, DTI would not be without its disadvantages, but, because there are multiple imaging modalities within DTI, some of the disadvantages can be mitigated.

### Disadvantages

DTI appearance is based on the premise that the direction of the fastest diffusion indicates the direction of the fibers as reported by Bihan *et al.*<sup>[22]</sup> This becomes further complicated when artifacts are introduced into the read out. This leads to errors in diffusion orientation and thus fiber orientation reconstruction is skewed.<sup>[35]</sup> DTI hardware maintains the ability to remove interfering artifacts, yet this needs to be done with specific, unique parameters, and algorithms that are not standard across all hardware as Soares *et al.* report.<sup>[35]</sup> Bihan *et al.* also noted that the diffusion measurement relies on an ADC that is unique to separate compartments of tissue being studied.<sup>[22]</sup> Between extracellular versus intracellular, ideally these subcompartments, would need to be separated and analyzed individually by DTI.

DTI is a difficult technique to analyze and implement on the spinal cord. The artifacts created by the imaging overlay the smaller size of the cord, as well, the physiologic motion created by the heart and lungs distort the image further.<sup>[40]</sup> By limiting the time required to take the image, physiological motion can be reduced to minimal interference. Single shot echo planar imaging is one such modality that can reduce these motion artifacts and distortions to make the image easier to interpret.<sup>[39,40]</sup> Beyond this, DTI has its limitations in image and spatial resolution as reported by Tsuchiya

*et al.*<sup>[40]</sup> Kim *et al.* also stated that due to the low image resolution, analyzing the spinal cord for injured tissue adds layers of difficulty.<sup>[17]</sup> Due to the anatomy being obscured and smaller than when utilizing DTI on the brain, SCI assessment is more difficult. In total, DTI is prone to artifacts and image quality issues necessitating complex algorithms be implemented.<sup>[39]</sup> Together the advantages and disadvantages make DTI a complex imaging technique to use correctly, however, very sensitive and specific when assessing SCI.

## TRIALS AND OUTCOMES

Due to limitations in finding randomized control trials and studies about DTI application secondary to spinal trauma, multiple case reports and clinical studies have investigated the posttraumatic use of DTI on the spinal cord. Studies of DTI of the spinal cord status posttrauma characterize spinal lesions and associated findings using different DTI parameters. The four major DTI parameters investigated in these studies were FA, MD, ADC, and RD. FA is the most frequently referenced DTI metric. Early studies of DTI parameters found that FA was the most sensitive parameter in detecting spinal cord abnormalities [Table 1].<sup>[11]</sup> Several studies found that FA values were decreased in patients with SCI compared to healthy subjects.<sup>[8,9,20,31]</sup> FA values appear to be dependent on the level and overall completeness of the lesion. Decreased FA values have been found to be associated with a variety of morphological and physiological conditions that were not found with conventional MRI.<sup>[12,23]</sup> FA has also been shown to be decreased in the corticospinal tracts (CSTs) throughout the spinal cord and brain in patients with SCI.<sup>[12,13]</sup> In patients with asymmetrical lesions, FA values had significant changes at the level of the lesion, showed unilateral damage to the cord morphology, and exhibited asymmetry between the left and right CSTs indicative of the laterality in neurological symptoms.<sup>[26,32,43]</sup> Finally, FA values have been

**Table 1:** Major findings from clinical studies and case reports regarding the usage of DTI of the spinal cord status posttrauma.

### Major findings of trials using DTI on spinal cord posttrauma

1. FA is the most sensitive parameter in detecting spinal cord abnormalities
2. MD, ADC, and RD parameter values were significantly higher in SCI patients. FA values found to be lower in SCI patients
3. DTI can be used to identify displacement and deformation of white matter tracts caused by lesions of the spinal cord
4. DTI parameters reveal structural abnormalities in areas of reduced gray matter volume in patients with SCI
5. DTI parameters may be useful in suggesting Wallerian Degeneration
6. DTI measurements are practical to measure SCI in the pediatric population
7. DTI is a clinically suitable method for future clinical studies

shown to correlate with clinical findings.<sup>[5,8,12,20,28,42]</sup> A second DTI parameter that is commonly mentioned in the literature is MD. MD values are significantly increased at the level of injury and significantly decreased rostral to the level of injury.<sup>[8,9]</sup> MD is significantly increased in the cranial CST in patients with SCI. Increased MD values have been correlated clinically with ISNCSCI examination findings.<sup>[28]</sup> Another common DTI parameter that is mentioned throughout the literature is ADC. ADC was investigated among other DTI parameters and found to be the most sensitive marker in patients with cervical SCI.<sup>[34]</sup> ADC was presented significantly higher in patients with SCI.<sup>[20]</sup> Increased ADC values at the injury site were correlated with better postoperative Neurosurgical Cervical Spine Scale scores.<sup>[10]</sup> In patients with asymmetrical lesions, ADC values showed significant changes at the level of the lesion.<sup>[32]</sup> The final DTI parameter that is discussed in the literature is RD. RD values in SCI subjects were significantly higher than in healthy subjects.<sup>[20]</sup> RD values were positively correlated with the degree of central canal stenosis.<sup>[23]</sup>

Available literature suggests that DTI has a variety of clinical applications. DTI parameters may be useful in detecting Wallerian degeneration (WD).<sup>[13,15]</sup> DTI can be used to identify displacement, deformation, and overall changes of spinal and cerebral white matter tracts caused by lesions of the spinal cord.<sup>[21,41]</sup> DTI parameters reveal structural abnormalities in patients with SCI and pathologies that are not detectable with conventional MRI.<sup>[20,45]</sup> DTI findings also correlate with clinical findings.<sup>[6,21]</sup> Of note, DTI parameters reflect severity of SCI and correlate well with ASIA motor scores in patients with nonhemorrhagic SCI but do not correlate with ASIA motor scores in patients with hemorrhagic SCI.<sup>[7]</sup> As previously stated, DTI can be used in patients with asymmetric spinal lesions to depict damage and display anatomical asymmetry within the cord that correlates to clinical neurological deficits.<sup>[32,43]</sup> DTI measurements have also been shown to be of practical use in the pediatric SCI population.<sup>[28]</sup> DTI has been investigated in correlation with electrophysiological techniques. It was shown that decreased DTI values correlated with both the clinical completeness of SCI and with SSEP amplitudes.<sup>[31]</sup> Moving forward, machine learning may prove useful in the advancement of DTI as a diagnostic tool. Machine learning utilizing FA values from DTI has shown potential as an aid in the diagnosis of SCI.<sup>[38]</sup> Clinical methods involving DTI as part of a multiparametric assessment of the spinal cord have also been proposed for future clinical studies.<sup>[27]</sup>

Using DTI as a diagnostic tool has shown great promise. Several clinical studies have been conducted with findings that support its use in the clinical setting. Multiple DTI parameters have proven useful in examining the morphological and physiological extent of spinal lesions

beyond conventional MRI capabilities. DTI parameters have also been shown to correlate with clinical findings. A review of available literature reveals an absence of more recent clinical studies and a lack of randomized clinical control trials further investigating DTI in spine trauma. Larger trials are necessary to further evaluate DTI of the spinal cord posttrauma before mainstream clinical use.

## FUTURE CONSIDERATIONS

The future usage of DTI technology in analyzing posttraumatic spinal pathologies is being further trialed for clinical significance. Experimental studies are now utilizing DTI to analyze the severity of spinal cord trauma during the hyperacute phase (first 6 h posttrauma).<sup>[25]</sup> DTI has undergone trials with animal models to evaluate white matter damage during the hyperacute phase, after MR sequences were found to show limited value in predicting the overall functional integrity of the spine posttrauma. The biomarkers derived from these DTI reports have appeared to be reliable predictors of posttraumatic neurological outcomes and are being assessed further before incorporation into conventional clinical practice.<sup>[25]</sup> Furthermore, DTI is being studied to evaluate the effects of stem cell implantation into the spinal cord.<sup>[15]</sup> Recently, stem cell therapy is being trialed with DTI with the hope of achieving axonal regeneration and recovery following long-term injury.<sup>[15]</sup> With recent studies showing that the expression of axon inhibitory proteins creates an environment favorable for axonal regeneration, DTI could be a biomarker for therapy success by noninvasively identifying axonal regeneration after stem cell implantation.<sup>[15]</sup> Through the works of these trials, further applications for DTI can be identified to improve treatment efficiency. With the continuation of these pending trials, management techniques of posttrauma spinal pathologies may be further implemented for SCI patients of the future.

## CONCLUSION

Studies are needed to better characterize variations in DTI parameters in various tissue pathologies such as scar formation due to astrocyte aggregation, cerebrospinal fluid infiltration, demyelination, hemorrhage, and edema.<sup>[46,47]</sup> The combination of DTI and FT also holds promise as a system to guide repair and removal of specific fiber tracts post-SCI.<sup>[47]</sup> In addition, if DTI is to be used in a clinical setting, future studies will need to establish standard, time-specific changes in DTI metrics. At present, there are no existing or pending randomized control trials for DTI in SCI.

In conclusion, the usage of DTI to detect and evaluate spinal pathologies related to trauma has shown great promise as a conventional diagnostic technique and will continue to develop as a neuropathological biomarker.



## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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## Conflicts of interest

There are no conflicts of interest.

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