# DIFFUSION TENSOR IMAGING OF THE SPINAL CORD: A REVIEW

## IMAGEM DA MEDULA ESPINAL POR TENSOR DE DIFUSÃO

## IMAGEN DE DIFUSIÓN TENSORA DE LA MÉDULA ESPINAL: UNA REVISIÓN

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## ABSTRACT

Diffusion tensor imaging (DTI) is a magnetic resonance technique capable of measuring the magnitude and direction of water molecule diffusion in various tissues. The use of DTI is being expanded to evaluate a variety of spinal cord disorders both for prognostication and to guide therapy. The purpose of this article is to review the literature on spinal cord DTI in both animal models and humans in different neurosurgical conditions. DTI of the spinal cord shows promise in traumatic spinal cord injury, cervical spondylotic myelopathy, and intramedullary tumors. However, scanning protocols and image processing need to be refined and standardized.

Keywords: Diffusion tensor imaging; Magnetic resonance spectroscopy; Spinal cord.

## RESUMO

O exame por imagem de ressonância magnética utilizando a técnica de tensores de difusão (DTI, Diffusion tensor imaging) consegue medir a magnitude e direção da difusão de moléculas de água em vários tecidos. A DTI está começando a ser usada para avaliar uma série de patologias da medula espinal, tanto para prognósticos como para orientar o tratamento. O presente artigo revisa a literatura sobre DTI da medula espinhal, em modelos animais e humanos, em diferentes condições neurocirúrgicas. A DTI da medula espinal é promissora para lesões traumáticas da medula, mielopatia espondilótica cervical e tumores intramedulares. Contudo, os protocolos de escaneamento e processamento de imagens precisam ser refinados e padronizados.

Descritores: Imagem de tensor de difusão; Espectroscopia de ressonância magnética; Medula espinal.

## RESUMEN

La técnica de imagen por difusión tensora (DTI, Diffusion tensor imaging) es una técnica de resonancia magnética que mide la magnitud y dirección de la difusión de moléculas de agua en varios tejidos. El uso de DTI se ha expandido para evaluar una variedad de disturbios de la columna vertebral tanto para pronóstico como para orientación de la terapia. La finalidad de este artículo es revisar la literatura sobre DTI de la médula espinal tanto en modelos animales como en humanos en diferentes condiciones neuroquirúrgicas. La DTI de la médula espinal se muestra promisora en las lesiones traumáticas de la médula, en la mielopatía espondilótica cervical y en los tumores intramedulares. Sin embargo, los protocolos de barrido y el procesamiento de imágenes necesitan ser refinados y estandarizados.

Descriptores: Imagen de difusión tensora; Espectroscopía de resonancia magnética; Médula espinal.

## INTRODUCTION

Diffusion tensor imaging (DTI) is a magnetic resonance technique capable of measuring the magnitude and direction of diffusion of water molecules in various tissues. DTI developed from a technique known as diffusion weighted imaging (DWI), which measures the attenuation of MR signals due to diffusion. Stejskal and Tanner[1] first reported the use of pulsed-gradient NMR to study the diffusion of water molecules. This provided the basis for all diffusion imaging technology, and DTI was formally introduced by Basser et al.[2-3]. Subsequent improvements in diffusion MR imaging as well as fiber tracking have led to the diffusion tensor tracking (DTT) technique that enables the visualization of white fiber tracts.

DTI of the brain finds application in the diagnosis of traumatic brain injury[4-6], ischemic strokes[7], and in the pre-operative planning for the treatment of brain tumors[8-9]. Tractography also enables the determination of white matter connectivity within the complex anatomy of the brain. DTI of the spinal cord in humans was initially inadequate due to the small area of the cord, cardiac and respiratory motion artifacts as well as scanning time required[10]. Improvements in scanning protocols have allowed for the use of DTI in spinal cord disease. DTI is able to detect cord damage in areas that appear normal on T2W images[11,12] and has the potential to provide noninvasive biomarkers of spinal cord pathology. Currently, the use of DTI is being expanded to evaluate a variety of spinal cord disorders both for prognostication as well as for guiding therapy.

In this paper, we review the literature on spinal cord DTI in both animal models and humans. We provide a summary of the use of spinal cord DTI in a few neurosurgical conditions. We hope that by providing a review on the current role of spinal cord DTI we may be able to better direct future efforts in this field.

### Principles of Diffusion Tensor Imaging

Diffusion MRI provides a measure of the displacement of water molecules in tissues. Displaced water molecules produce an attenuated signal during diffusion MR scanning. By its nature, the axonal architecture in CNS white matter promotes diffusion of water molecules in a direction predominantly parallel, rather than perpendicular, to axon fibers[3 13-14]. Diffusion perpendicular to the fibers seems to be limited by cell membranes more than myelin sheaths[15-16]. This direction-dependent diffusion is described as 'anisotropic' and is

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used by DTI to infer the orientation of surrounding axonal fibers and to delineate anatomical boundaries. DTI uses a tensor framework to characterize molecular motion in multiple directions in a three--dimensional space. The diffusivities along the three principle axes are defined by the eigenvectors where $\lambda 1$ (primary eigenvector) represents the direction and magnitude of the longitudinal diffusion vector, while $\lambda 2$ and $\lambda 3$ represent vectors along the minor axes. The magnitudes of these vectors are used to calculate a number of indices, of which the commonly used parameters are described below:

Fractional anisotropy (FA) = $\sqrt{}$($\lambda 1$- $\lambda 2$)$^2$ + ( $\lambda 2$- $\lambda 3$)$^2$ + ($\lambda 3$- $\lambda 1$)$^2$ / $\sqrt{}2$($\lambda 1^2$+ $\lambda 2^2$+ $\lambda 3^2$)

Longitudinal apparent diffusion coefficient (lADC) = magnitude of the primary eigenvalue ($\lambda 1$)

Transverse apparent diffusion coefficient (tADC) = average of the two minor eigenvalues ($\lambda 2$ + $\lambda 3$/2)

Mean diffusivity (MD) = average diffusivity all 3 eigenvalues ($\lambda 1$ + $\lambda 2$ + $\lambda 3$/3). This value is equivalent to the scalar ADC used in routine DWI.

Anisotropy index (AI) = tADC/lADC

FA, which ranges from 0-1, defines the degree of anisotropy and tissues with high anisotropy have a value closer to 1. While the lADC of the spinal cord represents rostro-caudal diffusivity along white matter fibers, the tADC is a measure of axial/radial diffusivity. The eigenvalues are affected by microstructural alterations that affect the diffusion of water molecules and this forms the basis for using DTI indices to identify spinal cord pathology.

### DTI studies in rat models

### DTI measurements of rat spinal cord

DTI measurements of the rat spinal cord were initially performed *ex vivo*[17-20], or *in vivo* using implantable coils[21-27]. The majority of these studies used scanners with field strengths from 4.7 T to 7 T. With improved technology, *in vivo* measurements were possible with higher field strength scanners[28,29], and without implantable coils[28-31]. The results of DTI studies on animal spinal cords indicate that DTI values clearly differentiate white (WM) and gray matter (GM)[17,26,28,32,33]. Since diffusion occurs preferentially along axonal bundles, WM is significantly more anisotropic compared to GM[16,33]. More recently, significant differences between levels (cervical, thoracic, and caudal) in lADC, tADC, MD, FA and AI have been described[28]. In particular, a lower tADC and higher lADC has been observed in WM tracts in the cervical region compared to the thoracic levels. This is probably a result of tightly packed large diameter axons in the cervical WM[34]. Also, anatomical differences account for a larger lADC and tADC in the cauda equina compared to the spinal cord WM[28]. Thus diffusion properties are not uniform throughout the length of the cord and vary according to the level being studied. These results further establish the usefulness of DTI to delineate neural structures in the spinal cord.

### DTI measurements after spinal cord injury (SCI)

One of the important applications of DTI is the evaluation of SCI in animal models. In one of the earliest studies that used a rat SCI model, Ford et al.[35] described significant decreases in lADC and increases in tADC at the level of injury as well as in areas of the cord that were apparently normal on conventional T2-weighted images. Experimental SCI leads to disruption of cell membranes and increased membrane permeability at the level of the lesion which results in increased diffusivity and lower anisotropy[21,36,37]. In hyperacute SCI (0-6 hours), diffusion measurements are able to distinguish SCI based on severity[38]. However, the unique feature of DTI is its ability to detect changes in diffusion metrics at regions remote from the lesion[21,39-41]. An overall reduction in lADC throughout the cord and a decrease in MD remote from the lesion has been described during recovery from SCI[40]. These findings are possibly related to cytotoxic edema, axonal loss or chronic atrophy[42-44]. Interestingly, the changes in DTI measures

away from the lesion are not limited to the white matter tracts only. At our center, we found that motor neurons rostral to the lesion were enlarged after SCI and this was associated with an increase in the FA of the rostral GM (unpublished data), indicating that the gray matter is also affected rostral to the lesion. Studies have shown that spinal cord gray matter is affected by ischemia due to impaired microvascular perfusion[45] and is characterized by astrogliosis during recovery[46]. Using DTI to track these remote gray matter changes will help us better understand the pathophysiology of SCI. Since there are changes in diffusivities throughout the cord after SCI, it is apparent that recovery from SCI is not limited to the epicenter alone.

Several authors have reported histological correlations to DTI changes following SCI in rat models[38,47-50]. Progressive cavitation of the cord with rostral-caudal spreading has been observed throughout the recovery period (Figure 1)[47]. Lesion growth rate, measured at about 57 micrometers/day, is consistent with axonal degeneration rates[51]. While an increase in MD after injury accurately maps the extent of degeneration, a decrease in FA is sensitive to cavity formation within the cord[47]. However, not all histological changes seem to be accurately reflected in DTI measurements[41,52,53]. DTI values have been shown to be more affected by axonal injury than demyelination[41,53], suggesting that the diverse tissue damage as a result of SCI may not be completely captured by diffusion measurements.
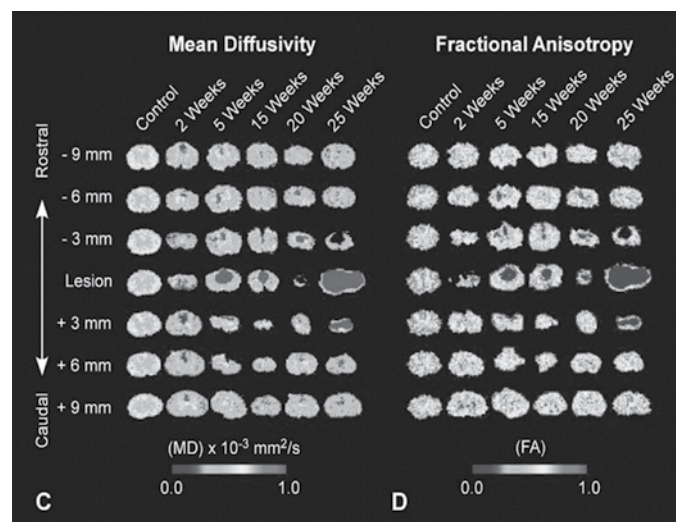


**Figure 1.** Ex vivo DTI images of axial slices of the spinal cord of example specimens at 2, 5, 15, 20 and 25 weeks post injury. DTI was useful for obtained a detailed description of the structure of the spinal cord after injury and showed the development of cavitation at the injury site. Mean diffusivity (MD) is shown on the left and fractional anisotropy (FA) is shown on the right.

### DTI and functional correlates in SCI

DTI metrics have been correlated with electophysiological measures, so as to identify which diffusion measures could act as predictors of neurological function. The use of cortical sensory evoked potentials (SEPs) to assess cord integrity in SCI models has been limited by its sensitivity to anesthetic agents[54-55] and changes in body temperature[56]. Spinal SEPs (SpSEPs) represent a reliable technique to obtain repeated recordings.[57-58] Our center established a minimally invasive method to characterize mid- to long-latency SpSEPs in a rat SCI model which correlated well with the Basso, Beattie, and Bresnahan (BBB) score[59]. Subsequently, SpSEPs were also found to be associated with changes in DTI values[60]. DTI measurements of the medial spinothalamic tracts and dorsal columns correlated with very early and early components of the SpSEPs, while diffusion measures of the lateral spinothalamic tracts were linked to the late components. In other SCI studies[21], the lADC of the rostral white matter correlated with the BBB score, while the tADC caudal to the lesion was correlated with the grid walk test[41]. Kim et al.[61] were able to predict hindlimb motor recovery using the

Basso mouse scale (BMS) by measuring the lADC of the spared ventrolateral WM at 3 hours post-SCI. Since axonal structure and integrity have been closely linked to MR diffusion measurements[34,37] the above correlations emphasize the utility of DTI to mirror both the structural and functional properties of axons.

The role of DTI in therapeutic interventions for SCI has been explored in a few studies. While DTI can accurately identify the level of white matter disruption, it can also characterize the orientation of the glial scar as well as the degree of axonal dieback and preservation, thereby providing valuable data on regenerative potential following SCI[19,20]. Additionally, the tADC and AI around the injured site have been shown to correlate with behavioral recovery in rats that were transplanted with fibroblasts following SCI[39]. In the future, it is expected that spinal cord DTI will be used to monitor transplants and other therapeutic interventions for SCI.

## DTI studies in humans

### DTI in the intact human spinal cord

DTI studies of the spinal cord in healthy subjects have established baseline values, thereby allowing us to study diseased states[62-67]. Good contrast is observed between GM and WM regions, with the highly anisotropic WM having much higher FA values than the central GM (Figure 2). While the magnitude of FA of the whole cord decreases in the rostral-caudal direction, the MD is relatively constant throughout the cord. Also, the primary eigenvalue ($\lambda_1$) is higher at the cervical levels compared to the thoracolumbar segments, probably due to the high proportion of large-diameter axons at the cervical cord[67].

DTI measurements are age-dependent, and reflect microstructural changes in the spinal cord associated with ageing[68-71]. In 25 healthy subjects studied at our center, we found that the FA across the cervical spinal cord decreased significantly after 55 years of age (accepted for publication) (Figure 3). While these results further emphasize the need to compare DTI measurements in patients with age-matched controls, they also indicate that DTI values in the elderly need to be evaluated in the light of normal age-related variations.
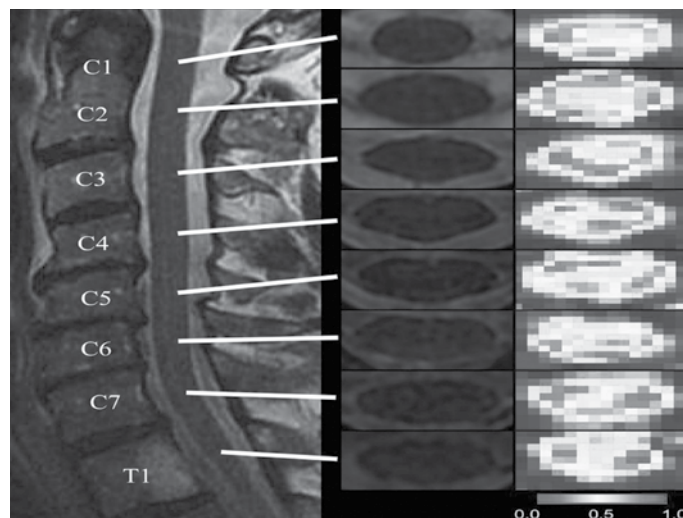


**Figure 2.** Sagittal T2W MR image (left) of the cervical spine in a normal subject with the corresponding axial T2W images at each cervical level (middle). FA maps (right) at each cervical level show better cross-sectional anatomy with lower anisotropy in the central gray matter and higher anisotropy in the white matter funiculi.

## DTI in human SCI

In acute SCI, both the FA and ADC are decreased around the injured level. Facon et al.[72] showed that although ADC decreased in the majority of SCI patients, it was not as sensitive as FA in the detection of acute SCI. The authors suggested that the use of ADC be restricted to chronic spinal cord compression. However, Shanmuganathan et al.[73] reported that ADC was the most sensitive marker
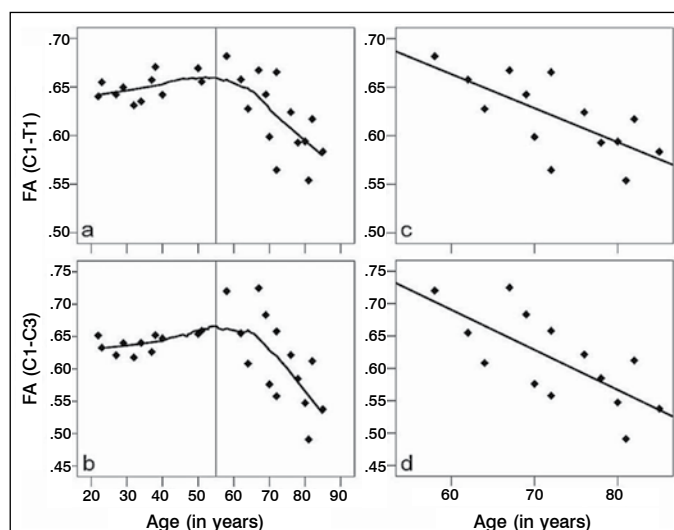


**Figure 3.** Scatter plots showing the relationship between FA and age. a-b: Lowess curves drawn on scatter plots for healthy subjects (n=25) showing a sharp decrease in FA after the age of 55 (solid line); c-d: Linear regression lines for entire cervical spinal cord (R2= 0.5, p=0.004) and upper cervical cord (R2= 0.52, p=0.003) showing FA as a function of age in subjects > 55 years (n=14).

of acute cervical cord injury and found it to be uniformly decreased in patients with cervical spine trauma. Acute SCI is characterized by edema, hemorrhage and inflammation that usually subside in 72 hours[74]. Neural injury is characterized by axonal injury, demyelination and the disruption of cellular membranes. The FA and lADC are decreased by the interruption of longitudinal white fibers, while intracellular and intercellular edema contribute to increased tADC. The FA, MD and tADC are derived parameters that are dependent on the relative changes of the individual eigenvalues. Choosing a DTI parameter that best characterizes SCI remains a challenge and authors have suggested that the individual eigenvalues are more useful than anisotropy measures in representing microstructural changes[17]. At our center, we have found that FA decreased and AI increased both at the level of injury as well as at caudal levels in patients (n=6) > 48 hours after acute SCI (unpublished data). Additionally, we have shown that axial FA maps and tractography are sensitive to asymmetric cord damage in acute SCI and can supplement conventional MR imaging in this setting[75]. The prognostic value of DTI indices in acute SCI is still unclear. In one study, higher ADC values at the injured site were associated with better postoperative neurosurgical cervical spine scale (NCSS) scores but not Frankel scale measures[76]. Another report showed that the MD, lADC and tADC were correlated with the ASIA motor score only in patients with non-hemorrhagic contusions[77]. The ASIA score is a reliable measure of spinal cord injury and is useful in tracking neurological recovery[78]. However, the correlation between DTI parameters with other outcome scales such as the functional independence measure (FIM), Walking index for spinal cord injury (WISCI), 6-minute walk test (6MWT), spinal cord injury measure (SCIM) and the modified Barthel Index (mBI)[79-80] have not been explored. There is a need to use a standardized functional outcome score in order to define the prognostic value of DTI indices. Moreover, if diffusion metrics of individual white matter tracts or funiculi within the spinal cord are measured, it becomes essential to use scales that measure both sensory and motor function.

Chronic SCI is associated with a number of microstructural neural changes including demyelination[81,82], remyelination[83,84], axonal loss[83] and atrophy[85] that affect the diffusion of water molecules. MD, tADC, and lADC have been shown to be significantly greater in injured patients compared to corresponding levels in neurologically intact controls. The FA value at the site of the lesion is greatly reduced and appears to depend on both the level of injury and the completeness of the injury[86]. Chang et al.[87] showed that FA values

and connection rates of fiber tracking correlated with motor score in patients with chronic cervical cord injury. In chronic SCI, markers of neuronal damage are important to rehabilitation and therapeutic interventions. Both cellular and electrophysiological approaches to stimulate neural regeneration in SCI patients rely on accurate delineation of the lesion. It is possible to use the FA values to locate the epicenter of the lesion, thus enabling the targeted transplantation of stem cells or drugs. While the rostral extent of the lesion can be obtained readily by clinical examination[88], the caudal boundary is more difficult to discern. DTI offers additional information on the viability of spinal cord tissue below the clinical lesion level and this is particularly important when considering interventions that target the spinal cord below the level of the lesion[89]. Additionally, mapping the lesion using DTI could be useful in newer therapeutic modalities that implant biopolymers as scaffolds for neural regeneration[90].

## DTI applications in cervical spondylotic myelopathy (CSM)

CSM is the most common spinal disorder in patients over the age of 55 years[91]. The complex pathophysiology of CSM includes mechanical spinal cord compression due to disc protrusion, osteophytes or ossified posterior longitudinal ligament as well as secondary cord ischemia[92,93]. In an effort to study CSM in animal models, a variety of methods to induce chronic cord compression have been used[94-97]. The use of DTI in animal models of CSM has been described only in a few studies, showing low FA and lADC values and increased tADC measures at the compressed level[97,98]. However, chronic compression in rat models is often induced with a dorsal or dorso-lateral approach, which does not replicate the predominantly ventral compression seen in patients. Also, CSM in humans is affected by multi-directional neck motion that cannot be adequately reproduced in animal models. Thus the use of DTI to study CSM in animals is limited, primarily due to a lack of an appropriate model.

Reis et al.[62] reported that diffusion MRI was able to detect cord changes in patients with narrow cervical canals, in spite of normal T1W and T2W images. Other authors have corroborated these findings suggesting that DTI is more sensitive to identify cord damage than regular T2W images of the cervical spine in patients with CSM[11,99-101]. Across studies, FA has been shown to be lower at the affected level in patients compared to corresponding levels in controls. MD values, however, are not uniformly sensitive to white matter changes due to chronic spinal cord compression. Mild neural damage in CSM is characterized by edema, demyelination, gliosis and nerve loss. Subsequently, necrosis and myelomalacia occur signifying permanent cord damage[102]. DTI indices in CSM patients appear to depend on the degree of cord damage. However, DTI measurements do not have consistent correlations with clinical scores of patients with CSM[101,103-105]. Recently, authors have shown that symptomatic CSM patients have lower FA values and higher ADC measures at the compressed level, as compared to asymptomatic patients[106]. It therefore appears that DTI has a role to play in the preoperative planning of CSM patients, but the use of DTI to decide on surgical intervention or monitor recovery is yet to be investigated in detail.

## DTI in spinal cord tumors

DTT has been used to describe the orientation and location of white matter fibers around brain tumors[107-109]. Recent studies have employed tractography in spinal cord astrocytomas and ependymo-

mas[110,111]. Tumor mass is characterized by a decrease in FA and increase in ADC. The use of fiber tracking to delineate displaced white matter tracts seems to be particularly useful in solid tumors. In cystic tumors and tumors with considerable vasogenic edema, the increased diffusion of water molecular leads to erroneous fiber tracking. As such, a recent study found DTT to have a sensitivity of 87.5% and a specificity of 100% for predicting tumor resectability preoperatively[112]. The authors of this study also classified tumors into 3 types based on the number of fibers coursing through the tumor. Type 1 tumors, which had no fibers within the tumor, were deemed resectable while type 3 tumors that had fibers completely encased by the tumor were considered unresectable. Type 2 tumors had variable number of fibers within the tumor substance and resectability was based on the proportion of fibers within the tumor volume. However, this study did not correlate functional outcomes with the type of tumor and this relationship needs to be explored. Overall, the use of tractography shows much promise in the surgical planning of spinal cord tumors, as it has in brain tumor resection.

DTI has been used in a variety of other spinal cord disorders including multiple sclerosis[113-115], syringomyelia[116,117], and myelitis[118]. Although, many of these studies are able to characterize DTI parameters in diseased states, the routine use of DTI in the clinical setting is yet to be realized

## Limitations of DTI

Spinal cord DTI in humans still has a number of limitations. Adequate spatial resolution remains a problem and it is difficult to visualize the individual funiculi on diffusion-weighted images, particularly in the lower thoracic cord[67]. DTI of these segments is affected more by artifacts arising from cardiac and respiratory motion as well as CSF pulsation[119]. The use of faster imaging techniques such as parallel imaging, single shot echo-planar imaging as well as the use of cardiac pulse-gating have helped to reduce these artifacts. However, scan acquisition time is still a limitation for patients with acute SCI since these patients cannot withstand even 30 minutes of additional scanning time in the MRI suite. The signal to noise ratio in human SCI is sub-optimal in most studies and can lead to overestimation of anisotropy measures, particularly in low-anisotropic tissues such as the central gray matter[120]. The use of 3T MR scanners does improve the SNR[121], but is still not used universally. The use of DTI postoperatively is hampered significantly by the use of spinal instrumentation, which creates numerous artifacts and this issue is currently unresolved. Additionally, standardized software to process tensor images is essential to make this a feasible option for routine clinical use.

## FINAL CONSIDERATIONS

DTI has given us a unique insight into the pathophysiology and microstructural alterations associated with spinal cord disorders. While initial studies in rat models have primed this modality for human research, more data is required on the accuracy and reliability of DTI indices in defining cord pathology. DTI of the spinal cord does show promise in certain neurosurgical conditions such as traumatic SCI, CSM and intramedullary tumors. However, scanning protocols and image processing need to be refined and standardized. Once these challenges are overcome, we can expect the use of DTI in mainstream clinical practice, both to prognosticate as well as monitor patients with spinal cord disease.

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