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# Diffusion Tensor Imaging of the Spinal Cord: Insights from Animal and Human Studies

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## Abstract

Diffusion tensor imaging (DTI) provides a measure of the directional diffusion of water molecules in tissues. The measurement of DTI indexes within the spinal cord provides a quantitative assessment of neural damage in various spinal cord pathologies. DTI studies in animal models of spinal cord injury indicate that DTI is a reliable imaging technique with important histological and functional correlates. These studies demonstrate that DTI is a noninvasive marker of microstructural change within the spinal cord. In human studies, spinal cord DTI shows definite changes in subjects with acute and chronic spinal cord injury, as well as cervical spondylotic myelopathy. Interestingly, changes in DTI indexes are visualized in regions of the cord, which appear normal on conventional magnetic resonance imaging and are remote from the site of cord compression. Spinal cord DTI provides data that can help us understand underlying microstructural changes within the cord and assist in prognostication and planning of therapies. In this article, we review the use of DTI to investigate spinal cord pathology in animals and humans and describe advances in this technique that establish DTI as a promising biomarker for spinal cord disorders.

## Keywords

Diffusion tensor imaging, Fractional anisotropy, Spinal cord, Spinal cord injury

Diffusion tensor imaging (DTI) is a magnetic resonance (MR) 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, which measures the attenuation of MR signals caused by diffusion, and was initially used for brain imaging. DTI was formally introduced by Basser et al,<sup>2</sup> and subsequent improvements in this technique have led to the development of DTI as a tool to delineate white matter tracts in the brain.

DTI of the spinal cord in humans was initially inadequate because of the small area of the cord, susceptibility artifacts, and cardiac and respiratory motion artifacts.<sup>3,4</sup> Improvements in scanning protocols have allowed usable diffusion images of the spinal cord. Spinal cord DTI, initially performed in animals, is now used to evaluate spinal cord disorders in humans. Investigators have shown that DTI is able to detect cord damage in regions of the cord that appear normal on T2-weighted images.<sup>5,6</sup> Spinal cord DTI therefore represents an important advancement in the field of neuroimaging, and its use is being expanded both for prognostication and for guiding therapy.

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

## PRINCIPLES OF DTI

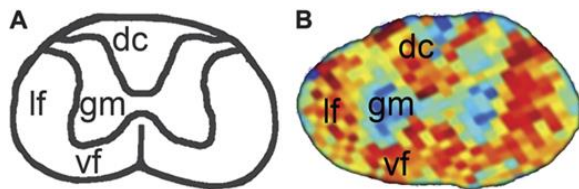
Diffusion MR imaging (MRI) provides a measure of the displacement of water molecules in tissues. Displaced water molecules produce an attenuated signal during diffusion MR scanning. By its nature, the axonal architecture in the white matter of the central nervous system promotes diffusion of water molecules in a direction predominantly parallel, rather than perpendicular, to axon fibers.<sup>2,7,8</sup> Diffusion perpendicular to the fibers seems to be limited by cell membranes more than myelin sheaths.<sup>9,10</sup> This direction-dependent diffusion, described as anisotropy, is used by DTI to infer the orientation of surrounding axonal fibers and to delineate anatomic boundaries. DTI uses a tensor framework to characterize molecular motion in multiple directions in a 3-dimensional space. The diffusivities along the 3 principal axes are used to calculate DTI indexes. The commonly used indexes for spinal cord DTI include fractional anisotropy (FA), apparent diffusion coefficient (ADC), longitudinal apparent diffusion co-efficient (IADC), and transverse ADC. Investigators determine specific regions

of interest on axial or sagittal diffusion images, and DTI indexes for these regions are calculated from individual vectors using dedicated software tools. FA, which ranges from 0 to 1, defines the degree of anisotropy, and tissues with high anisotropy such as white matter tracts have a value closer to 1. Injured spinal cords show a decrease in anisotropy resulting from disruption of longitudinally aligned axons and exhibit a decrease in FA. The ADC or mean diffusivity is the mathematical average of the diffusivities in the 3 principal axes, and its value may increase or decrease depending on the histopathological progression of the lesion. The IADC represents rostrocaudal diffusivity along white matter fibers and is often decreased in the presence of axonal injury.<sup>11</sup> Transverse ADC measures radial diffusivity and is characteristically increased in the presence of demyelination.<sup>11,12</sup> Overall, DTI indexes are affected by microstructural alterations that affect the diffusion of water molecules, and this forms the basis for using DTI indexes 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 either *ex vivo*<sup>13-15</sup> or *in vivo* with implantable coils.<sup>16-17</sup> The majority of these studies used scanners with field strengths from 4.7 to 7 T. With improved technology, *in vivo* measurements were possible with higher-field-strength scanners<sup>18-19</sup> and without implantable coils.<sup>18-19</sup> Studies with animal spinal cords indicate that DTI values clearly differentiate white and gray matter (Figure 1).<sup>13-17-18-20</sup> Because diffusion occurs preferentially along axonal bundles, white matter is significantly more anisotropic than gray matter.<sup>10-20</sup> Significant differences in DTI indexes are described between spinal levels (cervical, thoracic, and caudal) in rat studies.<sup>18</sup> This is probably a result of microstructural variations in the gray and white matter along the spinal cord.<sup>21</sup> These results indicate that 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.

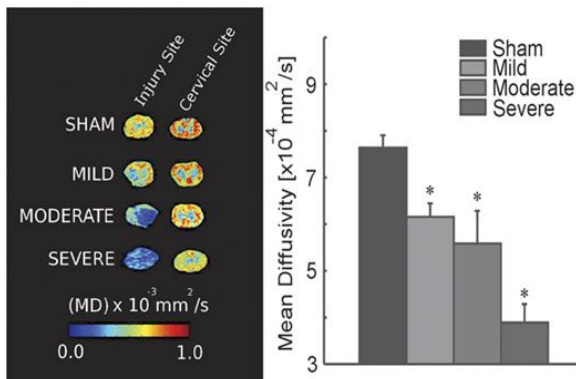


**FIGURE 1.** **A**, schematic diagram of a cross section of a rat cervical spinal cord showing the location of white matter funiculi and gray matter (gm). **B**, corresponding structure is shown on an axial fractional anisotropy map of the *ex vivo* rat cervical spinal cord obtained with a 9.4-T magnetic resonance scanner. dc, dorsal columns; lf, lateral funiculus; vf, ventral funiculus.

### DTI Measurements After Spinal Cord Injury

One of the important applications of DTI is the evaluation of spinal cord injury (SCI) in animal models. DTI demonstrates a significant decrease in anisotropy and increase in radial diffusivity at the level of injury<sup>16-22-23</sup> and in areas of the cord that are apparently normal on conventional T2-weighted images.<sup>24</sup> In hyperacute SCI (0–6 hours), diffusion measurements are able to distinguish SCI on the basis of severity.<sup>25</sup> However, the unique feature of DTI is its ability to detect changes in diffusion metrics at regions rostral and caudal to the lesion.<sup>16-26-28</sup> A decrease in diffusivity remote from the lesion is observed during recovery from SCI (Figure 2).<sup>27</sup> These findings are possibly related to cytotoxic edema, axonal loss, or chronic atrophy.<sup>29-31</sup> Interestingly, changes in DTI indexes away from the lesion correlate with injury severity, indicating that they may be used as surrogate markers of neural injury (Figure 2). Moreover, these changes are not limited to the white matter tracts only. At our center, we find that motor neurons rostral to the lesion are enlarged after SCI and that this is associated with an increase in the FA of the rostral gray matter (unpublished

data). Studies show that spinal cord gray matter is affected by ischemia as a result of impaired microvascular perfusion<sup>32</sup> and is characterized by astrogliosis during recovery.<sup>33</sup> Using DTI to track these remote changes will help us better understand the pathophysiology of SCI. Because there are changes in diffusivities throughout the cord after SCI, it is apparent that microstructural recovery from SCI is not limited to the epicenter alone.



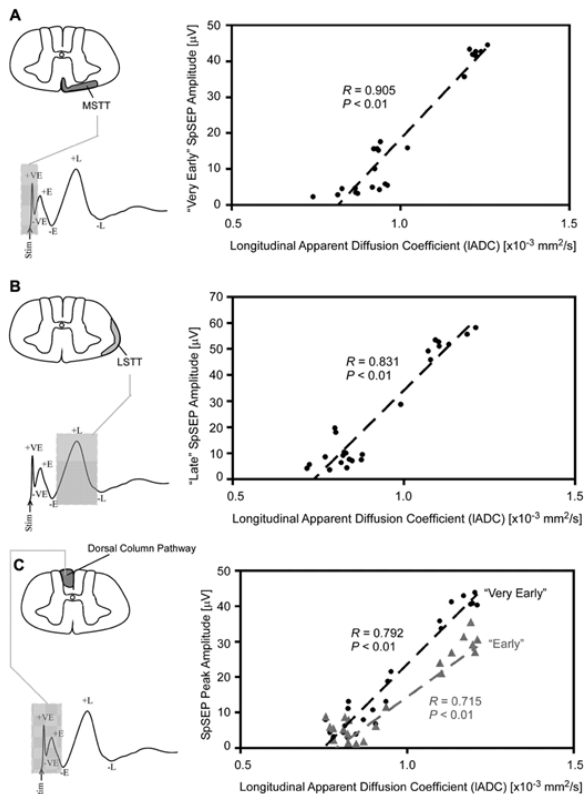
**FIGURE 2.** Axial diffusion tensor images obtained from ex vivo rat spinal cord specimens at the injury site (thoracic cord) and at a rostral site in the cervical spinal cord 10 weeks after contusive spinal cord injury of varying severity. Fractional anisotropy maps demonstrate loss of anisotropy at the injury site. Sham spinal cords showed intact cord structure with normal central gray matter morphology. Bar graph showing significant differences between severity groups in mean diffusivity (MD) of the cervical spinal cord sections. \* $P < .05$ .

Several animal studies show correlations between DTI indexes and histological changes during recovery from SCI.<sup>25,34-37</sup> The hyperacute phase after SCI is associated with edema, hemorrhage, and inflammation. Following this, there is an intermediate phase characterized by a robust glial response and revascularization process. The chronic phase of SCI shows wallerian degeneration, astroglial scar formation, and progressive cavitation of the cord with rostral-caudal spreading.<sup>34,38</sup> Identifying specific changes in DTI metrics to characterize particular histological events during recovery from SCI remains a challenge. Although an increase in mean diffusivity after injury can map the extent of degeneration, a decrease in FA is sensitive to cavity formation within the cord.<sup>34</sup> DTI is also able to characterize the orientation of the glial scar and the degree of axonal dieback and preservation.<sup>14,15</sup> Changes in DTI measurements possibly reflect a combination of histopathological changes.<sup>28,39,40</sup> DTI values have been shown to be more affected by axonal injury than demyelination,<sup>28,40</sup> suggesting that the diverse tissue damage as a result of SCI may not be completely captured by diffusion measurements.

## DTI and Functional Correlates in SCI

DTI metrics correlate with electrophysiological measures, indicating that specific diffusion measures could be used as predictors of neurological function. The use of cortical sensory evoked potentials to assess cord integrity in SCI models has been limited by its sensitivity to anesthetic agents<sup>41,42</sup> and changes in body temperature.<sup>43</sup> Spinal sensory evoked potentials represent a reliable technique to obtain repeated recordings,<sup>44,45</sup> and these correlate well with the Basso, Beattie, and Bresnahan score.<sup>46</sup> DTI measurements of the medial spinothalamic tracts and dorsal columns correlate with very early and early components of the spinal sensory evoked potentials, whereas diffusion measures of the lateral spinothalamic tracts are linked to the late components (Figure 3).<sup>47</sup> Other studies show that the IADC of the rostral white matter correlates with the Basso, Beattie, and Bresnahan score,<sup>16</sup> and the radial diffusivity caudal to the lesion correlates with the grid walk test.<sup>28</sup> The IADC of the spared ventrolateral white matter can also predict hind-limb motor recovery using the Basso mouse scale.<sup>48</sup> Because axonal structure and integrity are closely linked to MR diffusion

measurements,<sup>21-23</sup> the above correlations emphasize the utility of DTI to measure both the structural and functional properties of axons.



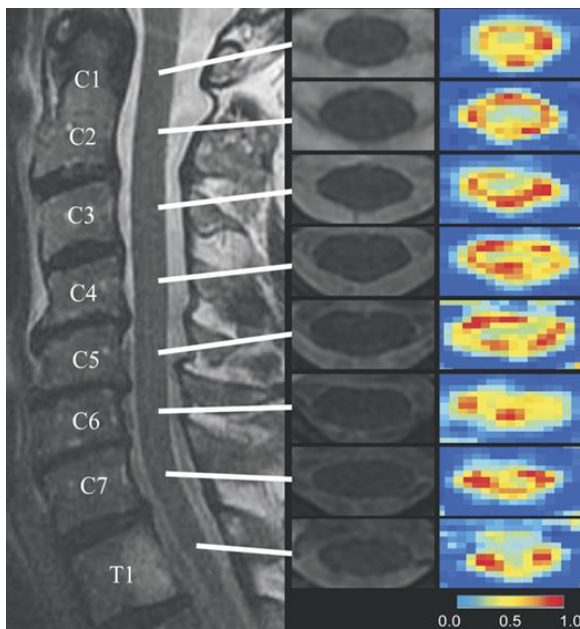
**FIGURE 3.** Scatterplots showing correlations between spinal sensory evoked potentials (SpSEPs) amplitude and longitudinal apparent diffusion coefficient (IADC) of the spinal cord rostral to the injury site in a rat spinal cord injury model. Significant correlations were observed for the medial (MSTT; **A**) and lateral (LSTT; **B**) spinothalamic tracts and the dorsal columns (**C**).

The role of DTI in therapeutic interventions for SCI is the focus of a few animal studies. The radial diffusivity around the injured site correlates with behavioral recovery in rats that are transplanted with fibroblasts after SCI.<sup>26</sup> At our center, we find significantly increased diffusivity rostral to the injury site in rat SCI models after stem cell transplantation compared with rats that received placebo. In the future, it is expected that spinal cord DTI will be used to monitor transplantations and other therapeutic interventions for SCI.

## DTI STUDIES IN HUMANS

### DTI in the Intact Human Spinal Cord

Spinal cord DTI studies in healthy human subjects show feasibility and reliability of this procedure.<sup>49-54</sup> Good contrast is observed between gray and white regions, with the highly anisotropic white matter showing much higher FA values than the central gray matter (Figure 4). Although the magnitude of FA of the whole cord decreases in the rostral-caudal direction, the mean diffusivity is relatively constant throughout the cord. DTI indexes are age dependent and reflect microstructural changes in the spinal cord associated with aging.<sup>55-59</sup> These results show that DTI is sensitive to degenerative changes within the spinal cord that are not visualized on conventional MRI. Moreover, they emphasize the need to compare DTI measurements in patients with age-matched control subjects.



**FIGURE 4.** Axial fractional anisotropy (FA) maps and T2-weighted images at individual levels of the cervical spinal cord in a healthy subject. Images were obtained with a standard 1.5-T clinical magnetic resonance scanner. FA maps show higher anisotropy in the white matter funiculi and lower anisotropy in the central gray matter. From Vedantam et al.<sup>59</sup> Reprinted with permission from the *Journal of Magnetic Resonance Imaging*. Copyright © 2013 John Wiley & Sons Inc.

## DTI in Human SCI

In acute human SCI, DTI shows a reduction in diffusivity, particularly FA and IADC, around the injury site.<sup>60-61</sup> Choosing a DTI parameter that best characterizes SCI remains a challenge, and authors suggest that diffusivity along the individual axes is more useful than DTI indexes in representing microstructural changes.<sup>13</sup> Similar to animal studies, human SCI is characterized by changes in diffusivity rostral to the injury site, in regions of the cord that appear normal on conventional MRI,<sup>61-62</sup> and possibly reflect retrograde neural injury. Axial FA maps and tractography are also sensitive to asymmetric cord damage in acute SCI and can supplement conventional MRI in this setting.<sup>63-64</sup>

The prognostic value of DTI indexes in acute SCI is still unclear. Higher ADC values at the injured site are shown to be associated with better postoperative Neurosurgical Cervical Spine Scale scores but not Frankel Scale measures.<sup>65</sup> Another report shows that the DTI indexes are correlated with the American Spinal Injury Association motor score in patients with nonhemorrhagic contusions.<sup>62</sup> Correlations between DTI parameters and other outcome scales such as the Functional Independence Measure, Walking Index for Spinal Cord Injury, and Spinal Cord Injury Measure have not been explored. There is a need to use a standardized functional outcome score to define the prognostic value of DTI indexes. Moreover, if diffusivities of individual white matter tracts within the spinal cord are measured, it becomes essential to correlate the diffusion indexes to scales that measure sensory and motor function separately.

Chronic SCI is associated with a number of microstructural neural changes, including demyelination,<sup>66-67</sup> remyelination,<sup>68-69</sup> axonal loss,<sup>68</sup> and atrophy,<sup>70</sup> that affect the diffusion of water molecules. As opposed to acute SCI, the injury site is characterized by increased diffusivity in patients with chronic SCI. FA at the injury site, however, is greatly reduced and appears to depend on both the level of injury and the completeness of the injury.<sup>71</sup> FA values and connection rates of fiber tracking have also been shown to correlate with motor score in patients with chronic cervical cord injury.<sup>72</sup> Similar to acute SCI, diffusivity within



the high cervical spinal cord, rostral to the chronic injury site, is significantly altered.<sup>71-73-74</sup> Importantly, rostral DTI indexes correlate with functional measures in this group of patients,<sup>73-74</sup> thereby demonstrating that these indexes may be noninvasive imaging biomarkers for SCI. Additionally, spinal cord DTI indexes rostral to the injury site correlate with DTI indexes within cranial white matter tracts and could be used as a marker of neural reorganization and plasticity.<sup>74</sup> Because spinal fixation hardware around the injury site creates artifacts on diffusion images, DTI of the spinal cord, rostral to the injury site, allows us to evaluate neural injury without directly imaging the injury site. This may be a useful approach for future studies that investigate longitudinal changes in diffusivity during recovery from SCI.

### DTI Applications in Cervical Spondylotic Myelopathy

The complex pathophysiology includes mechanical spinal cord compression caused by disk protrusion, osteophytes, or ossified posterior longitudinal ligament and secondary cord ischemia.<sup>75-76</sup> Histopathological changes within the cervical cord in cervical spondylotic myelopathy include cavitation, demyelination, and regions of cord infarction.<sup>77</sup> Diffusion MRI is able to detect cord changes in patients with narrow cervical canals despite normal T1- and T2-weighted images.<sup>5-49-78-80</sup> Across studies, FA is shown to be lower at the affected level in patients compared with corresponding levels in control subjects. DTI indexes in cervical spondylotic myelopathy patients appear to depend on the degree of cord damage. Symptomatic cervical spondylotic myelopathy patients have lower FA values and higher ADC measures at the compressed level compared with asymptomatic patients with radiological features of cord compression.<sup>81</sup> However, DTI measurements do not have consistent correlations with clinical scores of patients with cervical spondylotic myelopathy.<sup>80-82-84</sup> It therefore appears that DTI has a role to play in the preoperative planning of cervical spondylotic myelopathy patients, but the use of DTI to decide on surgical intervention or monitor recovery has yet to be investigated in detail.

### DTI for Spinal Cord Tumors

Diffusion tensor tractography is currently used to describe the orientation and location of white matter fibers around brain tumors.<sup>85-87</sup> Recent studies have used tractography for intradural spinal cord tumors.<sup>88-89</sup> 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 can lead to erroneous fiber tracking. A recent study showed that diffusion tensor tractography has a sensitivity of 87.5% and a specificity of 100% for predicting tumor resectability preoperatively.<sup>90</sup> Measurement of diffusion indexes within spinal cord tumors suggests that higher tumor mass is characterized by a decrease in FA and an increase in ADC. However, studies have yet to evaluate the utility of DTI indexes as predictors of tumor histology. In this regard, DTI indexes may be able to differentiate spinal cord lesions on conventional MRIs and provide surgeons with an idea about the possible pathology. Overall, the use of DTI shows much promise in planning surgical approaches for 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,<sup>91-92</sup> syringomyelia,<sup>93-94</sup> and transverse myelitis.<sup>95</sup> Although many of these studies are able to characterize DTI parameters in diseased states, the routine use of spinal cord 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.<sup>54</sup> DTI of these segments is affected more by artifacts arising from cardiac and respiratory motion and cerebrospinal fluid pulsation.<sup>96</sup> The use of faster imaging techniques such as parallel imaging and single-shot echo-planar imaging and 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 because these patients often cannot withstand additional scanning time in the MRI suite. In addition, the signal-to-noise ratio is not uniform throughout the cervical spinal cord and is significantly decreased in caudal segments.<sup>59-97</sup> A low signal-to-noise ratio can lead to overestimation of anisotropy measures, particularly in low-anisotropy tissues such as the central gray matter.<sup>98</sup> The use of 3-T MR scanners improves the signal-to-noise ratio<sup>99</sup> but they are still not used universally. The use of DTI postoperatively is hampered significantly by the use of spinal instrumentation, which creates numerous artifacts. Additionally, standardized software to process tensor images is essential to make this a feasible option for routine clinical use.

## CONCLUSION

DTI provides unique insight into the pathophysiology and microstructural alterations associated with spinal cord disorders. Although initial studies in rat models have primed this modality for human research, more data are required on the accuracy and reliability of DTI indexes in defining cord pathology. DTI of the spinal cord shows promise in certain neurosurgical conditions such as traumatic SCI, cervical spondylotic myelopathy, and spinal cord 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 and to monitor patients with spinal cord disease.

## ABBREVIATIONS

ADC apparent diffusion coefficient

DTI diffusion tensor imaging

FA fractional anisotropy

IADC longitudinal apparent diffusion coefficient

SCI spinal cord injury

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## COMMENT

In the article, we are able to see how an initially complex technique has evolved into an essential clinical tool. Indeed, the concept of diffusion-weighted imaging is far from new, but because of an inherent susceptibility to motion artifacts, it was at first almost impossible to use in the brain. However, this was overcome with the use of fast so-called echo-planar techniques that froze motion, allowing a new contrast from the brain tissue that represented molecular motion. One was thus able to measure units called the apparent diffusion coefficient and the fractional anisotropy of tissues. This was a breakthrough for cerebral ischemia but also led to the development of even fancier imaging techniques such as tractography. Although these techniques have been standard for brain imaging for quite some time, at the level of the spinal cord, it was considered for a very long time almost impossible to perform these techniques, at least in the living (there were some initial beautiful experiments with isolated cat spinal cords), and as for most modern neuroimaging techniques, spinal imaging was considered the poor cousin. Indeed, at the level of the spine, one has motion, pulsation, and susceptibility artifacts galore, and let us not forget that the areas we want to image are a fraction of that of the brain. However, with further advances in both software and hardware in magnetic resonance techniques, great progress has been made so that now these diffusion-derived techniques can be performed at the level of the spinal cord. This represents potentially an even greater breakthrough because one is able to see intramedullary changes caused by displacement of the fibers resulting from either intrinsic or extrinsic processes with a degree of contrast that was unbelievable just half a decade ago. This should allow not just the detection of the presence of intramedullary lesions but also the determination of their effect on neighboring white matter structures to preserve them during treatment, which should allow a more precise diagnosis to improve outcomes of patients with spinal diseases. One may also soon be able to use the sensitivity to motion to differentiate between different pathological entities, as one currently does in brain imaging when using diffusion-weighted imaging for brain masses.

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## CME Questions:

1. Diffusion tensor imaging relies on measuring differences in the directional diffusion of water molecules in tissues. What is this direction-dependent diffusion called?
  - A. Apparent diffusion coefficient
  - B. Anisotropy
  - C. Axial diffusivity
  - D. Mean diffusivity
  - E. Radial diffusivity
2. What are the predicted changes in fractional anisotropy (FA) and radial diffusivity (RD) following acute spinal cord injury?
  - A. FA increased, RD increased
  - B. FA increased, RD decreased
  - C. FA decreased, RD increased

- D. FA decreased, RD decreased
  - E. FA unchanged, RD decreased
3. A patient with an acute thoracic spinal cord injury undergoes decompression and instrumented stabilization. What is the best imaging modality for following the evolution of the cord injury?
- A. CT myelogram
  - B. DTI MRI at the site of injury
  - C. DTI MRI rostral to the injury
  - D. MRI with gadolinium
  - E. Functional MRI of the injured site