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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 indices 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 non-invasive 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 indices are visualized in regions of the cord, which appear normal on conventional MRI 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; spinal cord; spinal cord injury; fractional anisotropy

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, which measures the attenuation of MR signals due to diffusion, and was initially used for brain imaging.[1] DTI was formally introduced by Basser et al[2], and subsequent improvements in this technique have led to the development of DTI as a tool to delineate white matter tracts in the brain.

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DTI of the spinal cord in humans was initially inadequate due to the small area of the cord, susceptibility artifacts, as well as cardiac and respiratory motion artifacts.[3, 4] Improvements in scanning protocols have allowed for useable 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 T2W images.[5, 6] Spinal cord DTI, therefore, represents an important advancement in the field of neuroimaging, and its use is being expanded 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 for the clinical use of spinal cord DTI in a few neurosurgical conditions. We hope that by providing a review on the current status 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 the white matter of the central nervous system promotes diffusion of water molecules in a direction predominantly parallel, rather than perpendicular, to axon fibers.[2, 7, 8] Diffusion perpendicular to the fibers seems to be limited by cell membranes more than myelin sheaths.[9, 10] This direction-dependent diffusion, described as ‘anisotropy’, is 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 used to calculate DTI indices. The commonly used indices for spinal cord DTI include fractional anisotropy (FA), apparent diffusion co-efficient (ADC), longitudinal apparent diffusion co-efficient (lADC), and transverse apparent diffusion co-efficient (tADC). Investigators determine specific regions of interest on axial or sagittal diffusion images, and DTI indices 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 due to disruption of longitudinally aligned axons, and exhibit a decrease in FA. The ADC or mean diffusivity (MD) is the mathematical average of the diffusivities in the three principal axes, and its value may increase or decrease based on the histopathological progression of the lesion. The lADC represents rostro-caudal diffusivity along white matter fibers, and is often decreased in the presence of axonal injury.[11] tADC measures radial diffusivity and is characteristically increased in the presence of demyelination.[11, 12] Overall, DTI indices 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 either *ex vivo*,[13–15] or *in vivo* using implantable coils.[16, 17] 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,[18, 19] and without implantable coils.[18, 19] Studies with animal spinal cords indicate that DTI values clearly differentiate white (WM) and gray matter (GM) (Figure 1).[13, 17, 18, 20] Since diffusion occurs preferentially along axonal bundles, WM is significantly more anisotropic as compared to GM.[10, 20] Significant differences in DTI indices are described between spinal levels (cervical, thoracic, and caudal) in rat studies.[18] This is probably a result of microstructural variations in the gray and white matter along the spinal cord.[21] 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.

DTI measurements after spinal cord injury (SCI)

One of the important applications of DTI is the evaluation of SCI in animal models. DTI demonstrates a significant decrease in anisotropy and increase in radial diffusivity at the level of injury[16, 22, 23] as well as in areas of the cord that are apparently normal on conventional T2-weighted images.[24] In hyperacute SCI (0–6 hours), diffusion measurements are able to distinguish SCI based on severity.[25] However, the unique feature of DTI is its ability to detect changes in diffusion metrics at regions rostral and caudal to the lesion.[16, 26–28] A decrease in diffusivity remote from the lesion is observed during recovery from SCI (Figure 2).[27] These findings are possibly related to cytotoxic edema, axonal loss or chronic atrophy.[29–31] Interestingly, changes in DTI indices away from the lesion correlate with the 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 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 due to impaired microvascular perfusion[32] and is characterized by astrogliosis during recovery.[33] Using DTI to track these remote 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 microstructural recovery from SCI is not limited to the epicenter alone.

Several animal studies show correlations between DTI indices and histological changes during recovery from SCI.[25, 34–37] The hyperacute phase following 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.[34, 38] Identifying specific changes in DTI metrics to characterize particular histological events during recovery from SCI remains a challenge. While an increase in MD after injury can map the extent of degeneration, a decrease in FA is

sensitive to cavity formation within the cord.[34] DTI is also able to characterize the orientation of the glial scar as well as the degree of axonal dieback and preservation.[14, 15] Changes in DTI measurements possibly reflect a combination of histopathological changes.[28, 39, 40] DTI values have been shown to be more affected by axonal injury than demyelination,[28, 40] 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 electophysiological measures, indicating that specific diffusion measures could be used 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[41, 42] and changes in body temperature[43]. Spinal SEPs (SpSEPs) represent a reliable technique to obtain repeated recordings,[44, 45] and these correlate well with the Basso, Beattie, and Bresnahan (BBB) score.[46] DTI measurements of the medial spinothalamic tracts and dorsal columns correlate with very early and early components of the SpSEPs, while diffusion measures of the lateral spinothalamic tracts are linked to the late components (Figure 3).[47] Other studies show that the lADC of the rostral white matter correlates with the BBB score,[16] while the radial diffusivity caudal to the lesion correlates with the grid walk test.[28] The lADC of the spared ventrolateral white matter can also predict hindlimb motor recovery using the Basso mouse scale.[48] Since axonal structure and integrity are closely linked to MR diffusion measurements[21, 23] the above correlations emphasize the utility of DTI to measure both the structural and functional properties of axons.

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 following SCI.[26] At our center, we find significantly increased diffusivity rostral to the injury site in rat SCI models following stem cell transplants, as compared to rats that received placebo. 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

Spinal cord DTI studies in healthy human subjects show feasibility and reliability of this procedure.[49–54] 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). While the magnitude of FA of the whole cord decreases in the rostral-caudal direction, the MD is relatively constant throughout the cord. DTI indices are age-dependent, and reflect microstructural changes in the spinal cord associated with ageing.[55–59] These results show that DTI is sensitive to degenerative changes within the spinal cord that are not visualized on conventional MRI. Moreover, they also emphasize the need to compare DTI measurements in patients with age-matched controls.

DTI in human SCI

In acute human SCI, DTI shows a reduction in diffusivity, particularly FA and lADC, around the injury site.[60, 61] Choosing a DTI parameter that best characterizes SCI remains a challenge and authors suggest that diffusivity along the individual axes are more useful than DTI indices in representing microstructural changes.[13] 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,[61, 62] 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 MR imaging in this setting.[63, 64]

The prognostic value of DTI indices in acute SCI is still unclear. Higher ADC values at the injured site is shown to be associated with better postoperative neurosurgical cervical spine scale (NCSS) scores but not Frankel scale measures.[65] Another report shows that the DTI indices are correlated with the ASIA motor score in patients with non-hemorrhagic contusions.[62] Correlations between DTI parameters and other outcome scales such as the functional independence measure (FIM), walking index for spinal cord injury (WISCI), and spinal cord injury measure (SCIM) 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 diffusivities of individual white matter tracts within the spinal cord are measured, it becomes essential to correlate the diffusion indices to scales that measure sensory and motor function separately. Chronic SCI is associated with a number of microstructural neural changes including demyelination,[66, 67] remyelination,[68, 69] axonal loss[68] and atrophy[70] 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.[71] FA values and connection rates of fiber tracking have also been shown to correlate with motor score in patients with chronic cervical cord injury.[72] Similar to acute SCI, diffusivity within the high cervical spinal cord, rostral to the chronic injury site, is significantly altered.[71, 73, 74] Importantly, rostral DTI indices correlate with functional measures in this group of patients,[73, 74] thereby demonstrating that these indices may be non-invasive imaging biomarker for spinal cord injury. Additionally, spinal cord DTI indices rostral to the injury site correlate with DTI indices within cranial white matter tracts, and could be utilized as a marker of neural reorganization and plasticity.[74] Since 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 (CSM)

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.[75, 76] Histopathological changes within the cervical cord in CSM include cavitation, demyelination and regions of cord infarction.[77] Diffusion MRI is able to detect cord changes in patients with narrow cervical canals, in spite of normal T1W and T2W images.[5, 49, 78–80] Across studies, FA is shown to be lower at the affected level in patients

compared to corresponding levels in controls. DTI indices in CSM patients appear to depend on the degree of cord damage. Symptomatic CSM patients have lower FA values and higher ADC measures at the compressed level, as compared to asymptomatic patients with radiological features of cord compression.[81] However, DTI measurements do not have consistent correlations with clinical scores of patients with CSM.[80, 82–84] 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 for spinal cord tumors

Diffusion tensor tractography is presently used to describe the orientation and location of white matter fibers around brain tumors.[85–87] Recent studies have employed tractography for intradural spinal cord tumors.[88, 89] 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 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.[90] Measurement of diffusion indices within spinal cord tumors suggests that higher tumor mass is characterized by a decrease in FA and increase in ADC. However, studies have yet to evaluate the utility of DTI indices as predictors of tumor histology. In this regard, DTI indices may be able to differentiate spinal cord lesions on conventional MR images, and provide surgeons with an idea as to 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,[91, 92] syringomyelia,[93, 94], and transverse myelitis.[95] 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.[54] DTI of these segments is affected more by artifacts arising from cardiac and respiratory motion as well as CSF pulsation.[96] 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 often cannot withstand additional scanning time in the MRI suite. Also, the signal to noise ratio is not uniform throughout the cervical spinal cord and is significantly decreased in caudal segments.[59, 97] A low signal to noise ratio can lead to overestimation of anisotropy measures, particularly in low-anisotropic tissues such as the central gray matter.[98] The use of 3T MR scanners does improve the SNR,[99] but is 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 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 are 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 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 as well as monitor patients with spinal cord disease.

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Abbreviations

DTI	diffusion tensor imaging
FA	fractional anisotropy
ADC	apparent diffusion co-efficient
lADC	longitudinal apparent diffusion co-efficient
tADC	transverse apparent diffusion co-efficient

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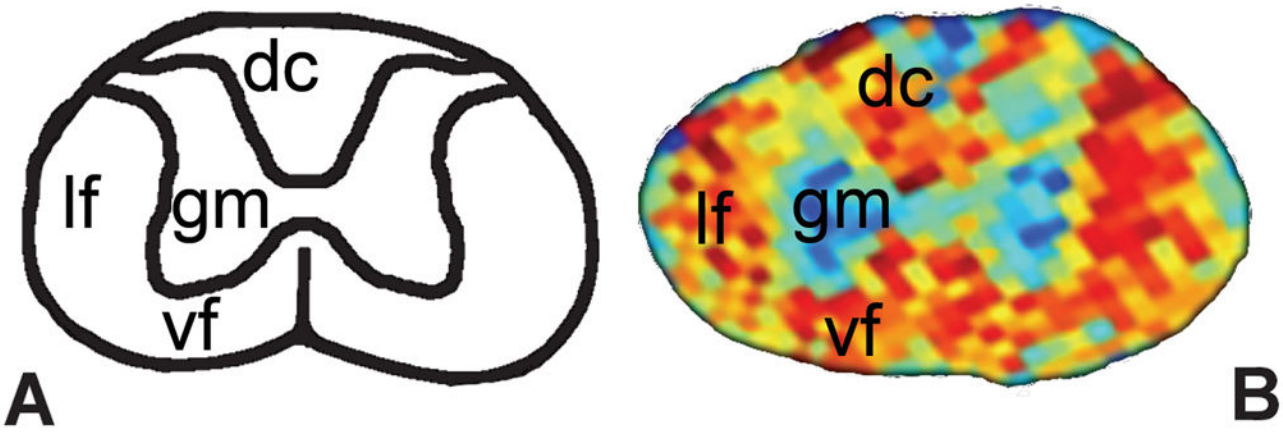

Figure 1.

A: Schematic diagram of a cross-section of a rat cervical spinal cord showing location of white matter funiculi and gray matter; **B:** Corresponding structure is shown on an axial FA map of the *ex vivo* rat cervical spinal cord obtained with a 9.4 T MR scanner. (vf- ventral funiculus, lf- lateral funiculus, dc- dorsal columns, gm- gray matter)

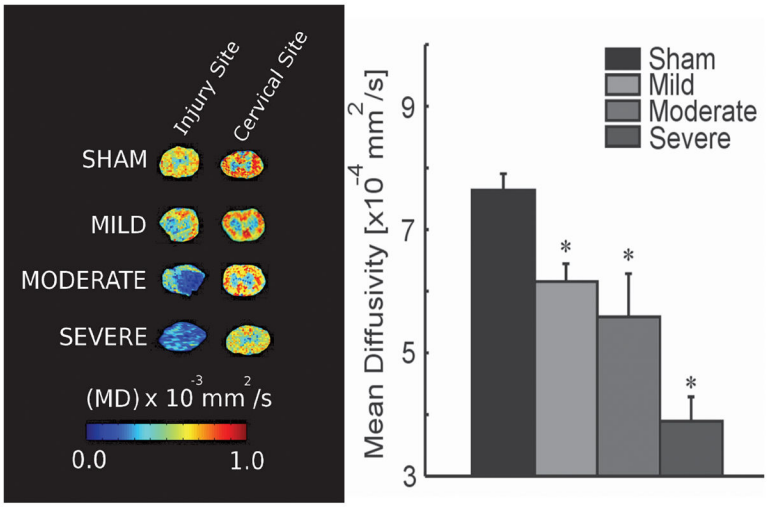

Figure 2.

Axial DTI 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 SCI of varying severity. Fractional anisotropy (FA) 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 of the cervical spinal cord sections. * $P<0.05$

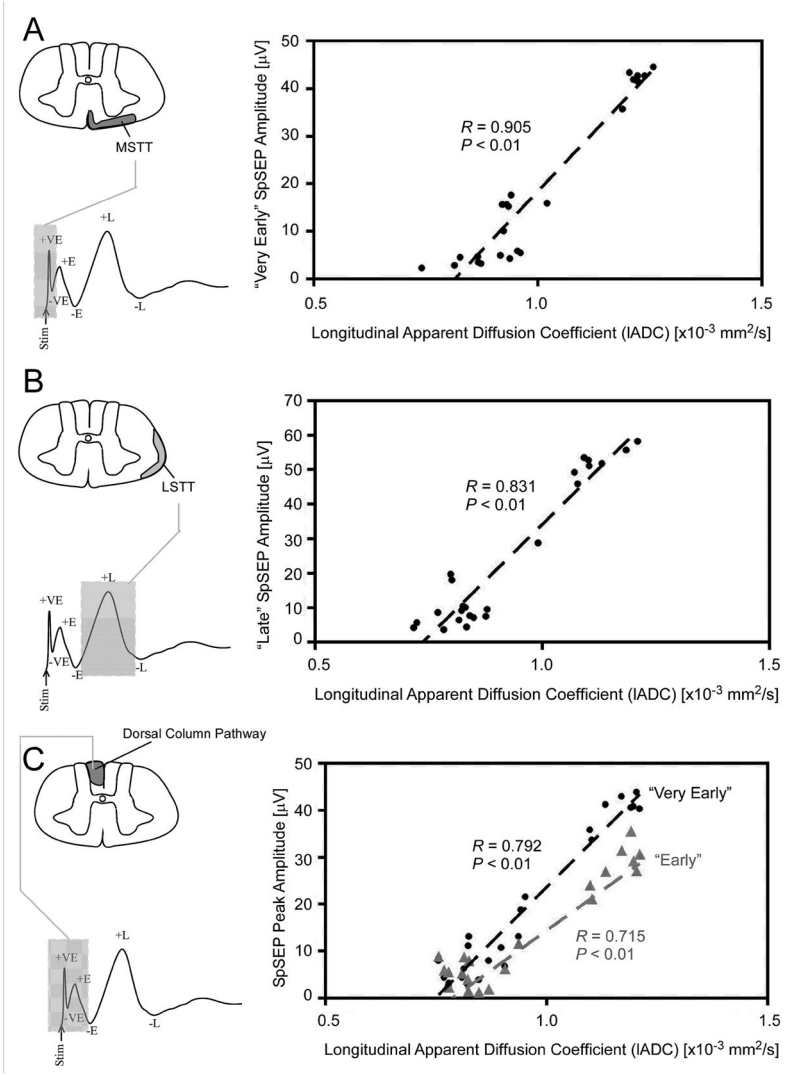

Figure 3.

Scatter plots showing correlations between spinal sensory evoked potentials (SpSEPs) amplitude and longitudinal apparent diffusion co-efficient (lADC) of the spinal cord rostral to the injury site in a rat SCI model. Significant correlations were observed for the medial (A) and lateral (B) spinothalamic tracts as well as the dorsal columns (C). MSTT- medial spinothalamic tract, LSTT- lateral spinothalamic tract.

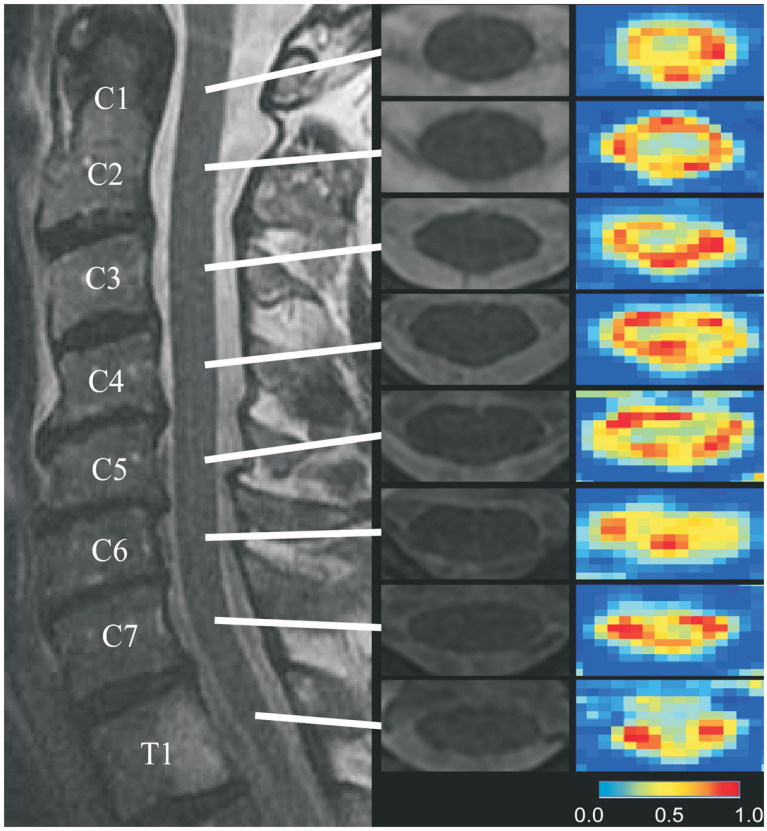

Figure 4.

Axial fractional anisotropy (FA) maps and T2-weighted images at individual levels of the cervical spinal cord in a healthy subject. Images were obtained using a standard 1.5 T clinical MR scanner. FA maps show higher anisotropy in the white matter funiculi and lower anisotropy in the central gray matter. (from [59], published with permission from Journal of Magnetic Resonance Imaging, John Wiley & Sons Inc.)