Review Article

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The role of diffusion tensor imaging in spinal pathology: A review

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Abstract:

Diffusion tensor imaging (DTI) allows for noninvasive, *in vivo* visualization of white matter fiber tracts in the central nervous system by measuring the diffusion of water molecules. It provides both quantitative and qualitative (i.e., tractography) means to describe a region-of-interest. While protocols for the use of DTI are better established in the brain, the efficacy and potential applications of DTI in spinal cord pathology are less understood. In this review, we examine the current literature regarding the use of DTI in the spinal cord pathology, and in particular its diagnostic and prognostic value in traumatic injury, spinal tumors, cervical myelopathies, amyotrophic lateral sclerosis, and multiple sclerosis. Although structural magnetic resonance imaging (MRI) has long been the gold standard for noninvasive imaging of soft tissues, DTI provides additional tissue characteristics not found in the conventional MRI. We place emphasis on the unique characteristics of DTI, its potential value as an adjunct imaging modality, and its impact on clinical practice.

Key Words:

Diffusion tensor imaging, magnetic resonance imaging, myelopathy, spinal cord, spinal pathology, trauma, tumor

Key Message:

The current literature regarding the use of diffusion tensor imaging in the noninvasive, *in vivo* visualization of white matter fiber tracts of the spinal cord by measuring the diffusion of water molecules is illustrated. Its role in spinal cord pathology, and in particular, its diagnostic and prognostic value in traumatic injury, spinal tumors, cervical myelopathies, amyotrophic lateral sclerosis, and multiple sclerosis is reviewed.

Diffusion tensor imaging (DTI) enables noninvasive investigation of the neural architecture. While structural magnetic resonance imaging (MRI) has long been considered the gold standard for imaging soft tissue in the clinical setting, DTI can provide additional insights into tissue characteristics by utilizing the diffusion of water molecules to act as a probe for assessing tissue microstructure.[1-3] In brief, a magnetic field is used to induce movement of water molecules, and the presence of intact nerve fibers and their constituents (i.e., cell membranes, myelin, and other macromolecules) hinders this movement. Analysis of these diffusion patterns provides several unique insights with multiple applications throughout the nervous system. In the brain, DTI has been used to better characterize schizophrenia, dementia, and affective disorders;[4-6] to evaluate the extent of traumatic injury[7] and ischemic infarcts; and to preserve white matter pathways during tumor resections.[8-10] Meanwhile, the role of DTI in spinal pathologies is rapidly evolving and is currently the focus of intensive research both in laboratory and in translational settings. In this review, we focus on the translational use of DTI in spinal pathologies, specifically with respect to spinal cord trauma, tumors, cervical myelopathy, amyotrophic lateral sclerosis, and multiple sclerosis.

Diffusion Tensor Imaging

DTI aggregates and superimposes signals from many water molecules in tissues to create a simple model of diffusion, whereby an elliptic (anisotropic) shape indicates strongly directional diffusion and a spherical (isotropic) shape indicates less directionality. Fibrous white matter displays a highly anisotropic diffusion pattern running parallel to the direction of axons.[11] From the data provided by DTI, several measures can be calculated, whose physical meanings and clinical interpretations are summarized in Table 1. The apparent diffusion coefficient (ADC) quantifies the

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magnitude of diffusion, with higher values indicating less restriction and thus fewer intact fibers.[12] Similarly, fractional anisotropy (FA) describes the diffusion pattern, with 'zero' meaning completely isotropic and 'one' meaning strongly anisotropic. Recently, a large systematic review investigating the use of various microstructural imaging techniques in the spinal cord – including DTI, magnetization transfer, myelin water fraction, MR spectroscopy, and functional MRI – concluded that the FA value obtained from DTI displayed the strongest empirical evidence of clinical utility.[13] Additionally, tracing these diffusion patterns (termed tractography) can guide the preoperative planning to spare white matter tracts during tumor resections.[14-16] Additionally, all of these analyses can also provide indices which estimate myelination status and tissue health,[7,17] allowing for greater diagnostic and prognostic accuracy.

Several challenges remain for the use of DTI in the spine. Spatial resolution may be coarse and individual funiculi can be difficult to distinguish.[18] Figure 1 shows an axial view of a b-zero weighted image of the cervical spine at the C5 level with typical noise and artifact. Notably, optimizing signal-to-noise ratio is challenging owing to the small volume of cord tissue[19] and non-uniform signal strength.[20,21] This signal heterogeneity increases the likelihood that FA is overestimated at lower FA values.[22] Some imaging artifacts are uniquely problematic in the spine, such as significant contributions from bone and lipid.[19] Additionally, dynamic artifacts such as cardiac and respiratory motion, and cerebrospinal fluid pulsations may also cause distortion,[19,23] but these can be mitigated by faster imaging techniques and cardiac pulse gating.[24] Figure 2 shows the axial anatomy of the cervical region with calculated FA map and labeled tracts.

Spinal Cord Injury

Noninvasive imaging is critically important for the clinical management of SCI. Clinical information, such as the level of injury, motor and sensory scores, and impairment assessments, remain a cornerstone for determining prognosis and guiding the therapeutic course for patients. However, these data can be subjective, which necessitates objective imaging modalities such as DTI to provide insight into axonal integrity and to visualize the full extent of fiber disruption within and adjacent to the injury site.[25-29] Table 2 provides an overview of human studies investigating DTI in SCI.

The injury site consistently demonstrates a lower FA value compared to the noninjured controls.[29-33] This focal reduction of FA appears dependent upon the completeness of injury, which suggests a potential role for DTI in detecting objective morphological changes during the progression between acute and chronic stages of SCI,[34-36] as well as throughout the recovery process.[31,36,37] At the injury epicenter, a longitudinal analysis of FA changes can successfully track the progression of postinjury axonal degeneration, which may augment outcome measures for predicting locomotor recovery.[36,38,39]

FA, axial diffusivity (AD), and severity in SCI have been correlated with several clinical assessment metrics including the American Spinal Injury Association motor score.[32,37] The severity of injury in these studies was confirmed histologically

Table 1: Physical measurement and clinical interpretation of quantitative indices

DTI metric	Physical measurement	Clinical interpretation
Apparent diffusion coefficient (ADC)/Mean diffusivity (MD)	Average magnitude of water diffusion in all directions	Increased: Vasogenic edema Chronic compression Decreased: Ischemia Acute compression
Axial diffusivity (AD)	Magnitude of ADC parallel to white matter orientation	*High in normal white matter* Decreased: Decreased neurologic function
Radial diffusivity (RD)	Magnitude of ADC perpendicular to white matter orientation	*Low in normal white matter* Increased: Axon degeneration Demyelination Decreased: Acute compression
Fractional anisotropy (FA)	Degree of orientation-dependent variation in ADC	Increased: Acute compression Decreased: Chronic compression

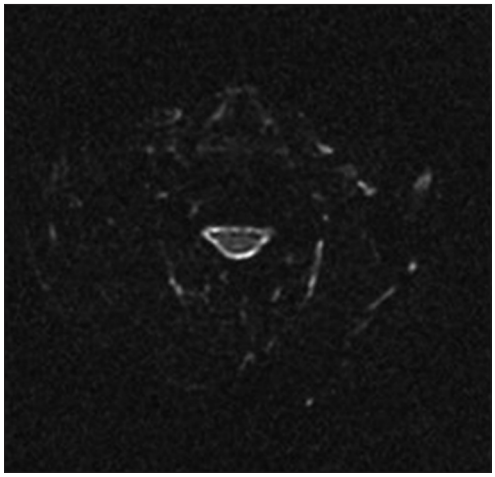

Figure 1: An axial, whole-cord b-zero weighted diffusion image taken at C5 showing typical noise and artifacts

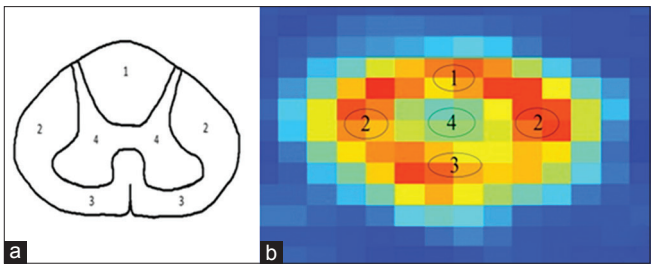

Figure 2: (a) shows a cross-section of the cervical spinal cord with the gray and white matter tracts. (b) shows the calculated fractional anisotropy of these tracts. Blue regions indicate cerebrospinal fluid

Table 2: Human studies investigating DTI in spinal cord injury

Author (year)	Study design	Subjects (number)	Key results (*P*)
Ellingson *et al*. (2008)	Prospective, cohort	SCI (10) vs ctrl (13)	↓ FA at lesion (<0.001)
			↓ MD throughout cord (<0.05)
			FA correlated with completeness of injury
Shanmuganathan *et al*. (2008)	Retrospective, cross-sectional	SCI (20) vs ctrl (8)	↓ FA (<0.0001) at lesion
			↓ADC at lesion (<0.031) and throughout cord (<0.0001)
Chang *et al*. (2010)	Prospective, cohort	SCI (10) vs ctrl (10)	↓ FA at lesion (<0.001)
			FA and FT correlated with ISCSCI functional scores
Rajasekaran *et al*. (2010)	Case report	BSS (1)	↓ FA at hemisection lesion
Cheran *et al*. (2011)	Prospective, cohort	SCI (25) vs ctrl (11)	↓ FA at (<0.001) and caudal to lesion (<0.05)
			↓ MD and↑AD throughout cord (<0.001)
Cohen-Adad *et al*. (2011)		SCI (14) vs ctrl (14)	↓ FA (<0.0001), ↓ AD (<0.05), and↓RD (<0.05) at lesion
			FA and RD correlated with AIS (<0.01)
Endo *et al*. (2011)	Prospective, longitudinal	SCI (16)	ADC correlated with postoperative recovery (=0.02)
Kamble *et al*. (2011)	Prospective, cohort	SCI (18) vs ctrl (11)	↓ FA rostral and caudal to lesion (=0.001)
Freund *et al*. (2012)		SCI (9) vs ctrl (10)	↓ FA at lesion (<0.05)
			FA correlated with ULM scores (=0.03)
Petersen *et al*. (2012)		SCI (19) vs ctrl (28)	↓ FA in whole-cord, LCST, and PC (<0.005)
			FA correlated with AIS (=0.001), SSEP (<0.001)
Koskinen *et al*. (2013)		SCI (28) vs ctrl (40)	↓ FA (<0.001), ↑ MD (<0.001) and↑RD (<0.001) at lesion
			FA correlated with ASIA score (<0.001)
Vedantam *et al*. (2012)	Case report	BSS (2)	↓ FA at hemisection lesion
Mulcahey *et al*. (2013)	Prospective, cohort	SCI (10) vs ctrl (15)	↓ FA at lesion (<0.003)
Vedantam *et al*. (2015)	Retrospective, cross-sectional	SCI (12) vs ctrl (12)	↓ FA in whole-cord (<0.01) and LCST (=0.04)
			FA correlated with AIS (=0.01), ULM score (=0.01)

ASIA = American Spinal Injury; AIS = Association Impairment Score; BSS = Brown-Sequard syndrome; ctrl = Control; FT = Fiber tractography; ISCSCI = International Standards for the Neurological Classification of Spinal Cord Injury; LCST = Lateral corticospinal tract; PC = Posterior column; SSEP = Spinal somatosensory evoked potential; ULM = Upper limb motor C score; FA: Fractional anisotropy; MD: Mean diffusivity; RD: Radial diffusivity; AD: Axial diffusivity

in the hyper-acute injury setting as early as 6 hours after the initial injury.[36,40] This result has been corroborated in multiple mouse models where comparison of DTI indices to spinal cord histopathology and to locomotor recovery demonstrate AD to be an accurate predictor of the degree of intact white matter and recovery of locomotion.[41] Additionally, elevated ADC values at the injury site have predicted improved postoperative outcomes according to the Neurosurgical Cervical Spine Scale.[42] Thus, both FA and ADC are sensitive markers of injury, with ADC showing the greatest sensitivity.[43] Quantification of intact fiber numbers in the spinal cord has proven as an effective means for determining the extent of white matter tract damage, while the effect appears more sensitive for motor rather than sensory levels.[30] Additionally, both axial FA mapping and tractography techniques have been used to detect asymmetric cord damage in acute injury.[44,45]

Unlike in acute injury, chronic injury is characterized by increased ADC, while still displaying a decreased FA.[31] As in acute injury, alterations in several DTI indices have been observed in areas of spinal cord distant from the injury epicenter.[27,46] These measures, including AD, have demonstrated correlation with functional data in chronic SCI patients,[27,30] suggesting that these data are potential noninvasive injury indicators in the chronic injury setting as well.[24] A unique feature of DTI is that it also detects significant changes in regions of the spinal cord rostral and caudal to the site of injury.[29,47,48]

Significant differences in FA and mean diffusivity (MD) between injury severity groups were also detectable in brain corticospinal tracts, the internal capsule, and pyramidal regions of the brainstem, and these differences in the brain were correlated with the extent of intact postinjury motor function.[49] DTI measurements have been corroborated by electrophysiological data as well, suggesting them to be a feasible indicator of neurological function. DTI from the medial spinothalamic tracts and dorsal columns are associated with early spinal somatosensory evoked potential (SEP) changes, while measurements from the lateral spinothalamic tracts are associated with late SEP changes.[50] In addition, the ADC of rostral white matter tracts correlates with locomotor recovery,[47]while the ADC of noninjured ventrolateral white matter tracts predicts motor recovery.[41]

Spinal Tumors

As is the case for brain tumors, the spatial and morphological relationship between spinal cord tumors and adjacent white matter tracts is closely related to predicting operative success, and thus significantly impacts patient management and prognosis. In the spinal cord, DTI tractography is able to visualize white matter fiber displacement in the presence of spinal cord lesions.[51-53] Table 3 provides an overview of human studies evaluating DTI in spinal tumors.

In a glioma-grafted rat model, imaging was able to separate tumor from host white and gray matter and also corresponded

Table 3: Human studies investigating DTI in spinal tumors

Author (year)	Study design	Subjects (number)	Key results (*P*)
Ducreux *et al.* (2006)	Prospective, cohort	Astrocytoma (5) vs ctrl (10)	↓ FA at lesion FT defined tumor borders
Setzer *et al.* (2010)	Prospective, longitudinal	ISCN (14)	FT predicted lesion resectability (<0.003)
Choudhri *et al.* (2014)	Retrospective, cross-sectional	ISCN (10)	FT predicted lesion resectability
Liu *et al.* (2014)	Prospective, cohort	ISCN (12) vs TLL (13)	↓ FA and ↑ ADC at ISCN lesion vs TLL (<0.05)

ctrl = Control; FT = Fiber tractography; ISCN = Intramedullary spinal cord neoplasm; TLL = Tumor-like lesion; SA = Spinal astrocytoma; ADC = Apparent diffusion coefficient

with conventional histopathology.[54] Surgical outcomes have demonstrated the predictive value of tractography in determining the resectability of intramedullary spinal cord tumors preoperatively in adults, with a significant concordance between DTI-based predictions and actual surgical evaluation.[55] This result is reproducible for intramedullary neoplasms in the pediatric patient population as well, where DTI positively identified fiber splaying and displacement associated with resectable tumor margins.[56]

Conventional MRI is often unable to sufficiently differentiate between ependymomas and astrocytomas in the spinal cord. DTI tractography, however, is able to delineate the fiber displacement associated with ependymomas versus the fiber infiltration associated with astrocytomas.[57,58] Additionally, delineating intramedullary tumors from nonneoplastic, tumor-like lesions (TLL) is a dilemma while using the conventional MRI. By using DTI, these tumors can be distinguished based on a decreased FA and an increased ADC in tumors from TLL.[59] Diffusion indices of cord tumors suggest that both increased FA and ADC are present in tumors of greater mass,[55] although these indices have yet to be related to tumor histology. While tractography has demonstrated the ability to visualize white matter fibers in relation to solid tumors, it has a greater difficulty with cystic tumors where significant vasogenic edema impairs the accurate measurement of water diffusion.[24]

Cervical Spondylotic Myelopathy

Conventional MRI remains the gold standard imaging modality for evaluating cord compression in CSM. However, it has several shortcomings including an inability to consistently characterize the extent of neuronal injury or functional status in patients,[60,61] or to offer prognostic value for recovery following surgical decompression.[62] The spinal cord often appears normal on MRI at the early stages of CSM,[63] which may delay intervention and subsequent recovery.[60] Here, DTI represents a promising solution to overcome the limitations imposed by the the conventional MRI, when performed alone. Table 4 provides an overview of human studies evaluating DTI in CSM.

Numerous studies have reported a decreased FA and an increased ADC in CSM,[64-71] with FA changes showing especially strong effect size at the upper cervical levels.[64,68] While these changes are most prominent at the maximum compression level (MCL),[72] the authors have also successfully identified the segmental level of dysfunction in single- and multi-level compression,[73] even against the normal changes in FA and ADC that occur with age.[67] Notably, DTI indices are detectable before the appearance of T2-weighted hyperintensity on MRI,[65] with FA changes becoming detectable earliest[74] and prior to the onset of symptoms.[75] These findings have been compared with functional electrophysiological data and abnormal sensory evoked potentials (SEPs), and were found to correspond with a decrease in FA cephalad to the MCL.[76]

Several other indices have also been investigated to detect cord compression in CSM. MD has been observed to be significantly increased at the MCL,[77,78] and displays promising sensitivity and specificity (100% and 75%, respectively).[77] Additionally, an increase in root mean square displacement and a decrease in mean diffusional kurtosis are able to identify and estimate cord compression at an early clinical stage and generally exhibit greater change from baseline than increases in ADC or decreases in FA.[79] DTI may be able to describe CSM pathology with greater precision than structural MRI. At the MCL, decreases in FA have been successfully localized to the dorsal and lateral columns,[76,78,80] while minimal changes were noted in ventral columns.[76] MD values were not only significantly increased at the MCL, but were specifically localized to dorsal regions-of-interest.[78] Here, DTI has made it possible to demonstrate region-specific alterations in CSM.

An individual's tolerance of and response to cord compression is variable, and the interpretation of MRI findings may be unclear, owing to a poor association between the detectable degree of cord compression and symptom manifestation.[81] Decreased FA and increased ADC at the MCL were more pronounced in symptomatic versus asymptomatic patients, thus discriminating these clinical subgroups.[72,82,83] FA changes also correlate with baseline myelopathy scores, including the Japanese Orthopedic Association (JOA) and Nurick scales.[84-88] Reduced field-of-view DTI has demonstrated promisingly strong correlation with clinical severity and JOA scores as well.[89,90] Delineation among clinical subgroups may also be possible using ADC values, which appear to significantly differ between moderately versus severely affected groups, and again correlate strongly with clinical symptoms.[86] With respect to morphological evidence of cord compression severity, DTI accurately computes space-available-for-cord,[91,92] estimates white matter fiber damage,[86] identifies pathological spinal cord levels,[93] and even detects microstructural changes before significant cord compression is present.[92]

Preoperative DTI also shows promise for predicting outcomes following surgical decompression, thus aiding surgical decision-making. Tractography patterns, specifically intact versus disrupted fiber bundles, while not associated with the severity of symptoms, predict postoperative neurological

Table 4: Human studies investigating DTI in cervical spondylotic myelopathy

Author (year)	Study design	Subjects (number)	Key results (*P*)
Demir *et al.* (2003)	Prospective, cohort	CSM (36) vs ctrl (8)	↓ FA at MCL (=0.007)
			FA and MD have higher SN, but lower SP, than T2W
Mamata *et al.* (2005)		CSM (79) vs ctrl (11)	↓ FA and ↑ MD within T2W hyper-intensity (<0.05)
Budzik *et al.* (2011)		CSM (20) vs ctrl (15)	↓ FA at MCL (=0.0003)
			FA correlated with UE (<0.001) and LE (<0.001) scores
Kara *et al.* (2011)	Prospective, longitudinal	CSM (16)	↓ FA among T2W hyper-intensity negative cases (<0.001)
Lee *et al.* (2011)	Prospective, cohort	CSM (20) vs ctrl (20)	↓ FA (=0.001) and↑MD (=0.001) at MCL
Song *et al.* (2011)		CSM (53) vs ctrl (20)	↓ FA (<0.01) and↑MD (<0.01) at MCL, ↓ FA at descending cervical levels (<0.01)
Hori *et al.* (2012)	Prospective, longitudinal	CSM (50)	↓ FA (=0.006), ↓ MK (=0.002), and ↑ RMSD (=0.006) at MCL
Kerkovsky *et al.* (2012)	Prospective, cohort	CSM (50) vs ctrl (13)	↓ FA for myelopathic (=0.001) and nonmyelopathic (=0.04)
Lindberg *et al.* (2012)		CSM (15) vs ctrl (10)	↓ FA (=0.02) and ↑ RD (=0.03) at MCL
Nakamura *et al.* (2012)	Prospective, longitudinal	CSM (20)	FT ratio correlated with recovery rate (=0.0006)
Gao *et al.* (2013)		CSM (104)	FA correlated with JOA score (<0.05)
Jones *et al.* (2013)		CSM (30)	FA correlated with JOA (<0.01) and Nurick (=0.01) scores
			FA predicted postoperative NDI improvement (=0.04)
Uda *et al.* (2013)	Prospective, cohort	CSM (26) vs ctrl (30)	FA had ROC AUC=76 (SN=95%, SP=50%)
			MD had ROC AUC=0.90 (SN=100%, SP=75%)
Banaszek *et al.* (2014)		CSM (132) vs ctrl (25)	↓ FA (<0.0001) and ↑ MD (<0.01) throughout cord
Ellingson *et al.* (2014)		CSM (48) vs ctrl (9)	FA correlated with JOA (<0.0001)
Li *et al.* (2014)		CSM (14) vs ctrl (14)	FA correlated with symptomatic level
Rajasekaran *et al.* (2014)		CSM (35) vs ctrl (40)	↓ FA and ↑ MD at MCL (<0.01)
Wen *et al.* (2014)		CSM (15) vs ctrl (25)	↓ FA (<0.05) and ↑ MD (<0.05) in LCST
Wen *et al.* (2014)		CSM (45) vs ctrl (20)	↓ FA at MCL (=0.02)
			FA correlated with JOA recovery ratio (=0.03)
Ahmadli *et al.* (2015)	Prospective, longitudinal	CSM (18)	↓ FA among T2W hyper-intensity negative cases
Cui *et al.* (2015)	Prospective, cohort	CSM (23) vs ctrl (20)	↓ FA in LCST and PC (<0.001)
			↑ MD, ↑ AD, and ↑ RD throughout cord (<0.05)
Guan *et al.* (2015)	Meta-analysis	CSM (479) vs ctrl (278)	↓ FA (<0.001) and ↑ ADC (<0.001) at MCL
Maki *et al.* (2015)	Prospective, cohort	CSM (20) vs ctrl (10)	↓ FA in LCST (<0.01) and PC (=0.01)
			FA correlated with JOA in LCST and PC (=0.03)
Wang *et al.* (2015)		CSM (4) vs ctrl (5)	↓ FA (=0.05) and ↑ MD (=0.014) at MCL in LCST and PC
Chen *et al.* (2016)		CSM (10) vs ctrl (10)	↓ FA (=0.002) and ↑ ADC (<0.001) at MCL↓FA (=0.003) and↑ADC (<0.001) at lumbosacral enlargement
Murphy *et al.* (2016)		CSM (14) vs ctrl (7)	FA correlated with 9-PT and 30-MWT
Rajasekaran *et al.* (2016)	Prospective, longitudinal	CSM (35)	ADC (<0.001) correlated with postoperative recovery
Suetomi *et al.* (2016)	Retrospective, cross-sectional	CSM (10) vs ctrl (11)	FA and ADC correlated with segmental level dysfunction
Toktas *et al.* (2016)	Prospective, longitudinal	CSM (21)	↓ FA (<0.001) and ↑ FA (<0.001) in stenotic segments

30MWT = 30-meter walking time; 9-PT = 9-hole peg test; ctrl = Control; FT = Fiber tractography; LCST = Lateral corticospinal tract; LE = lower extremity; MCL = Maximum compression level, MK = Mean kurtosis; PC = Posterior column; ROC AUC = Receiver operating characteristic area under the curve; RMSD = Root mean squared displacement; SN = Sensitivity; SP = Specificity; T2W = T2-weighted MRI; UE = Upper extremity; FA = Fractional anisotropy; MD = Mean diffusivity; ADC = Apparent diffusion coefficient; JOA = Japanese Orthopedic Association; RD = Radial diffusivity

improvement.[66] Tractography can also be used to compute a fiber tract (FT) ratio, representing the proportion of intact fibers at the MCL versus the C2 level. Poor postoperative neurological recovery was expected for a preoperative FT ratio <60%, especially among patients with significant symptoms.[84,85] In contrast, no such differences in functional recovery were observed in patients with high versus low signal intensity on the preoperative MRI.[84,94] Additionally, postoperative MRI results often suggest adequate cord decompression regardless of the clinical outcome, but postoperative DTI results among these patients were more varied. Specifically, changes in postoperative ADC were observed in patients who showed neurologic recovery, but no such changes were observed in patients whose neurologic status worsened or remained unchanged after surgery.[95]

Amyotrophic Lateral Sclerosis

Therapeutics development for ALS has been hindered by a dearth of biomarkers sensitive to the spatial and temporal patterns and progression of neurodegeneration. Much research has been dedicated to investigating imaging measures in ALS brains, but fewer studies have done so in the spinal cord. Table 5 provides an overview of human studies evaluating DTI in ALS.

The most robust finding has been that FA values are significantly decreased in ALS compared to healthy controls,[96-100] which appears to be most pronounced between the C2-C5 levels.[97] In SOD-1 ALS (Cu, Zn-superoxide dismutase-1 amyotropic lateral sclerosis) model mice, this decrease in FA has been

Table 5: Human studies investigating DTI in amyotrophic lateral sclerosis (ALS)

Author (year)	Study design	Subjects (number)	Key results (*P*)
Valsasina *et al.* (2007)	Prospective, cohort	ALS (28) vs ctrl (20)	↓ FA at lesion (=0.002) correlated with ALSFRS(<0.001)
Agosta *et al.* (2009)		ALS (17) vs ctrl (20)	↓ FA (=0.01) and ↑ MD(=0.01) at lesion
Nair *et al.* (2010)		ALS (14) vs ctrl (15)	↓ FA (=0.03) and ↑ RD (=0.003) at lesion
			FA correlated with EDSS recovery (=0.02)
			FA (=0.02) and RD (=0.03) correlated with finger/foot tapping
			RD and MD correlated with ALSFRS (=0.04) and FVC (=0.01)
Cohen-Adad *et al.* (2013)		ALS (29) vs ctrl (21)	↓ FA in LCST (<0.0005)
			FA correlated with ALSFRS (=0.04) and TMS threshold (=0.02)
El Mendili *et al.* (2014)	Prospective, longitudinal	ALS (29)	FA in LCST correlated with ALSFRS (=0.001)
Wang *et al.* (2014)	Prospective, cohort	ALS (24) vs ctrl (16)	↓ FA (<0.01) and ↑ MD (<0.05) in LCST
Iglesias *et al.* (2015)		ALS (21) vs ctrl (21)	↑ MD and ↑ RD in PC (<0.05)
Budrewicz *et al.* (2016)		ALS (15) vs ctrl (15)	↓ FA in right (=0.0037) and left (=0.015) PC

ALSFRS = ALS Functional Rating Scale; ctrl = Control; EDSS = Expanded Disability Status Scale; JOA = Japanese Orthopedic Association; score, LCST = Lateral corticospinal tract; PC = Posterior column; TMS = Transcranial magnetic stimulation, motor threshold; FA = Fractional anisotropy; MD = Mean diffusivity; RD = Radial diffusivity; FVC = Forced vital capacity

localized to the ventral white matter tracts, and is more pronounced as the disease progresses.[101] Electrophysiological data also suggest an association between decreased FA values and the presence of abnormal SEP recordings, a marker of ALS disease severity.[102] The degree of FA change has been consistently correlated with disease severity, specifically in ALS Functional Rating Scale (ALSFRS-R)[99,103,104] and finger and foot tap scores.[98] The association between cord FA and ALSFRS-R scores is strong, while the association between cord FA and brain FA is only moderate.[99] Additionally, imaging results in the brain generally correlate poorly with spinal cord pathology and damage.[96] Taken together, these findings are consistent with the hypothesis that spinal cord pathology in ALS is independent of concomitant brain changes, and thus that FA values are an useful adjunct to monitor ALS progression.

Other DTI indices are significantly changed in ALS spinal cords, including decreases in ADC[100] and cross-sectional area,[96,99] and increases in MD[96] and radial diffusivity (RD),[98] with changes in RD correlating with several ALS severity markers such as forced expiratory volume, finger and foot tap scores, and ALSFRS-R scores.[98] In addition to motor fiber pathology, previously unobservable, early-stage damage to sensory fibers of the lateral and dorsal columns has been described in roughly 60% of ALS patients using DTI.[103]

Multiple Sclerosis

Table 6 provides an overview of human studies looking at MS. Numerous studies have shown a decrease in FA at spinal MS lesions.[105-110] These FA changes are notably present in white matter tracts that appear normal on conventional MRI,[105,111,112] and are less prone to underestimate the size of MS cord lesions.[113] This decreased FA has demonstrated promising functional correlates. For example, asymmetrically decreased FA predicts differences in right- versus left-sided slowing of conduction time.[114] Additionally, the magnitude of decrease in FA is greater in MS plaques than in normal appearing white matter, which is then greater than in healthy controls.[111,115] With respect to clinical correlates, a decreased FA value is associated with poorer results on the Expanded Disability Status Scale (EDSS)[107,116] and with greater severity of fatigue, which has been shown to be related to the extent of cord involvement.[117]

Other DTI metrics have also shown associations with cord changes in MS including increased MD[105,107] and RD,[108] along with decreased ADC[113] and RD.[112] Increased MD and RD values correlate with various clinical tests such as gait testing and EDSS,[118,119] with a less increased RD being associated with better clinical outcomes.[120] These indices were also able to distinguish highly versus moderately disabled subgroups of patients, further suggesting their utility as markers for MS pathogenesis.[121] These results have been corroborated in an induced dorsal column experimental autoimmune encephalomyelitis model of inflammatory demyelination, a rat model of MS,[122] where FA, AD, and RD were found to correlate with axonal degeneration at the primary lesion site and in adjacent areas of the spinal cord.[123] Notably, these changes in DTI indices along with FA changes do not demonstrate correlation with imaging results in the brain of MS patients, suggesting cord pathology to be independent of concomitant brain changes.[105,109]

DTI may also have a role to play in evaluating therapeutic options and tracking recovery for MS patients. After steroid therapy, symptoms improvement could be tracked as FA increased and RD decreased back toward baseline, and a more robust response to steroid therapy could be predicted in patients with initially greater FA and lower RD values.[113] Additionally, the extent and severity of white matter damage after nataluzimab treatment could be tracked using FA values as well.[124]

Conclusion

While the efficacy of DTI for mapping neuronal connectivity in the brain has been well characterized, the utility of DTI in the spinal cord remains an evolving and promising area of investigation. Both region-of-interest-based DTI metrics and DTI tractography have demonstrated numerous clinical applications in the setting of spinal cord pathologies, including early detection, surgical planning, outcome prediction, pathologic subgroup differentiation, and monitoring disease progression after treatment. Structural T1- and T2-weighted MRI remains the first line modality for the evaluation of spinal pathologies. A unique feature of DTI, however, appears to be the ability to detect pathological states in the spinal cord in situations where conventional MR images appear normal.

Table 6: Human studies investigating DTI in multiple sclerosis (MS)

Author (year)	Study design	Subjects (number)	Key results (*P*)
Agosta *et al*. (2005)	Prospective, cohort	PPMS (24) vs ctrl (13)	↓ FA (=0.007) and ↑ MD (=0.024) at lesion
Hesseltine *et al*. (2006)		RRMS (24) vs ctrl (24)	↓ FA in LCST (<0.0001) and PC (=0.001)
Agosta *et al*. (2007)		MS (42) vs ctrl (9)	↓ FA (=0.01) and ↑ MD (<0.001) at lesion FA correlated with EDSS (=0.001)
Ciccarelli *et al*. (2007)		MS (14) vs ctrl (13)	↓ FA in LCST (=0.02) FA correlated with 9PT (<0.05)
Ohgiya *et al*. (2007)		MS (21) vs ctrl (21)	↓ FA (<0.001) and ↑ MD (<0.05) throughout cord FA in plaques<NAWM<ctrl (<0.01)
Cruz *et al*. (2009)		RRMS (41) vs ctrl (37)	FA in plaques<NASC (<0.001) < ctrl (<0.05)
van Hecke *et al*. (2009)		MS (21) vs ctrl (21)	↓ FA at lesion (<0.01)
Benedetti *et al*. (2010)		MS (68) vs ctrl (18)	↓ FA (=0.001) and ↑ MD (<0.001) at lesion FA correlated with EDSS (=0.002)
Freund *et al*. (2010)		MS (14) vs ctrl (13)	↓ FA and ↑ RD throughout cord (<0.05) RD correlated with EDSS, 9PT, and TWT (<0.05)
Rocca *et al*. (2012)		MS (35) vs ctrl (20)	↓ FA and ↑ MD at lesion (<0.001)
Theaudin *et al*. (2012)	Prospective, longitudinal	MS (16)	FA (=0.04) and RD (=0.05) correlated with lesion size and AIS improvements
Miraldi *et al*. (2013)	Prospective, cohort	RRMS (32) vs ctrl (17)	↓ FA, ↑ MD, and ↑ RD at lesion
Oh *et al*. (2013)		MS (129) vs ctrl (14)	FA, MD, and RD correlated with EDSS (<0.05) FA and RD correlated with vibration test (<0.05) MD, AD, and RD correlated with hip flexion (<0.05)
Raz *et al*. (2013)		RRMS (19) vs ctrl (16)	↓ FA at lesion (=0.01) FA in plaques<NASC (<0.0001) MD in plaques>NASC (<0.0001) FA and MD correlated with EDSS (<0.01)
von Meyerberg *et al*. (2013)		MS (38) vs ctrl (28)	↓ FA throughout cord (<0.001) Tract-specific FA correlated with MEP (<0.01)
Toosy *et al*. (2014)		MS (1s4) vs ctrl (11)	↓ FA and ↑ RD at lesion (<0.001) FA and RD correlated with EDSS (=0.05 and=0.01, respectively) and TWT (=0.02 ad=0.05, respectively)
Hubbard *et al*. (2016)	Prospective, longitudinal	MS (69)	RD, AD, and MD correlated with gait testing (<0.05) MD correlated with 6MW and TWT (<0.05)
Wiebenga *et al*. (2016)	Prospective, cohort	RRMS, Tx nat (22) vs Tx ctrl (17) vs ctrl (12)	↓ FA with nataluzimab treatment (=0.02)

6MW = 6-minute walk; 9PT = 9-hole peg test; ASIA = American Spinal Injury Association; AIS = Impairment Score; EDSS = Expanded Disability Status Scale; ctrl = Control ; LCST = lateral corticospinal tract; MEP = Motor evoked potential; NASC = Normal-appearing spinal cord; NAWM = Normal-appearing white matter; PC = Posterior column; PPMS = Primary progressive multiple sclerosis; RRMS = Relapsing-remitting multiple sclerosis; Tx nat = Treatment with nataluzimab; Tx ctrl = Treatment with control; TWT = Timed 25-foot walk test; FA: Fractional anisotropy; MD: Mean diffusivity; RD: Radial diffusivity; RRMS: Relapsing-remitting multiple sclerosis; PPMS: Primary progressive multiple sclerosis

Taken together, the literature suggests that DTI may become a robust, routine adjunct to conventional MRI for the evaluation and management of patients suffering from spinal pathologies.

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Conflicts of interest

There are no conflicts of interest.

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