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Advanced Diffusion-Weighted Magnetic Resonance Imaging Techniques of the Human Spinal Cord

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Abstract

Unlike those of the brain, advances in diffusion-weighted imaging (DWI) of the human spinal cord have been challenged by the more complicated and inhomogeneous anatomy of the spine, the differences in magnetic susceptibility between adjacent air and fluid-filled structures and the surrounding soft tissues, and the inherent limitations of the initially used echo-planar imaging techniques used to image the spine. Interval advances in DWI techniques for imaging the human spinal cord, with the specific aims of improving the diagnostic quality of the images, and the simultaneous reduction in unwanted artifacts have resulted in higher-quality images that are now able to more accurately portray the complicated underlying anatomy and depict pathologic abnormality with improved sensitivity and specificity. Diffusion tensor imaging (DTI) has benefited from the advances in DWI techniques, as DWI images form the foundation for all tractography and DTI. This review provides a synopsis of the many recent advances in DWI of the human spinal cord, as well as some of the more common clinical uses for these techniques, including DTI and tractography.

Keywords

diffusion-weighted imaging; spinal cord

Diffusion-weighted imaging (DWI) plays a unique role among current imaging techniques because it provides physiologic information about the imaged tissue,¹ is relatively reliable and reproducible as an imaging technique, is rapidly acquired, and is widely available. It has been successfully implemented to routinely image the brain^{2,3} and, more recently, to image components of the musculoskeletal system³ and the abdomen.⁴ Today, DWI of the brain has become commonplace, such that it is now considered a key sequence in neuroimaging, and considered by many to be essential in the proper evaluation of most pathologic conditions. Diffusion-weighted imaging of the brain has a relatively long history of the successful application of varying underlying techniques used to extract mean diffusivity (MD) of water on a voxel-by-voxel basis. Because of the relative uniformity of the calvarium and

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underlying brain tissue as well as the lack of a large lipid pool, many of the initial issues related to field inhomogeneity have now been overcome, albeit after some initial technical difficulty in devising appropriate sequence modifications.

Diffusion-weighted magnetic resonance imaging (MRI) is currently used to infer information regarding the microscopic behavior of water molecules, in both the intracellular and extracellular compartments. The diffusive motion is based on the random, omnidirectional movement of free water molecules, both within and between tissues, resulting from the coupled thermal energy of these molecules, according to Fick law, also known as Brownian motion. In biological tissues, the free diffusion of water molecules in any given direction is hindered by cellular membranes, organelles, and tissue planes.^{5,6} Other factors, such as cellular membrane permeability, relative size of free and bound water pools, interaction and size of the macromolecule, as well as tissue viscosity, and temperature play a role. Magnetic resonance imaging can be adopted to measure this biophysical phenomenon, by application of pulsed diffusion-encoding gradients, usually used in conjunction with a spin echo echo-planar imaging (EPI) sequence. This method is easily applied in the clinical context secondary to the rapid required imaging time, the facility of postimaging computation and generation of the diffusion maps, and the physical properties of water in biological systems. Finally, DWI is relatively unique as an imaging sequence because it provides essential information regarding the physiologic status of the imaged tissue.

The pathologic mechanism of acute infarct—thought to give rise to the observed DWI signal hyperintensity (and corresponding decreased signal on apparent diffusion coefficient [ADC] maps)—is that of cellular swelling that results from failure of the cell membrane energy-dependent sodium-potassium pumps—a well-documented observation in the process of cell death. Early in the ischemic cascade, cytotoxic edema is observed, as extracellular water is osmotically driven into the intra-cellular space. The intracellular compartment, bounded by cell membranes, organelles, and a protein-rich environment, results in greater restriction of free water movement relative to the extra-cellular space, from which the net flux of free water came. In addition, the diffusive motion of water protons in the extracellular spaces becomes more restricted due to the cell swelling. The net increase in restricted water movement within the intra-cellular space and the net decrease in free water movement within the extracellular space result in an overall decrease in the net diffusibility of protons in the affected region and are depicted by appropriate signal hyperintensities on DW sequences within minutes after ischemia onset and at a time when it is occult to other imaging sequences/modalities. This may be confounded by possible increased viscosity of the intracellular water molecules.

As is true of the brain, DWI of the spinal cord holds great promise in its ability to potentially aid in the diagnosis and understanding of many pathologic conditions resulting from injury to both the gray matter and white matter tracts. However, despite the great advances in DWI of the brain, musculoskeletal system, and other body structures, DWI of the human spinal cord has been more challenging.^{7–11} Successful implementation of human spinal cord imaging has lagged behind that of the brain, as it has proven to be more challenging to image using similar MR techniques for a number of reasons. Do note that EPI has also been

the method of choice for spinal DWI and thus perhaps the most obvious of these reasons is the more extreme field inhomogeneity of the regions surrounding the spinal column and cord.^{9,12} There are considerably challenging regions that emanate from the differences in magnetic susceptibility between air and tissue, such as at the cervicothoracic junction, for example. Moreover, the vertebrae surrounding the imaged spinal cord are inhomogeneous in bone density, depending on the specific location circumferentially about the cord, including the vertebral bodies, pedicles, laminae, and spinous processes, as well as along the craniocaudal axis, with interspersed alternating vertebrae and intervertebral disks. This results in off-resonance-related artifacts and limits the readout duration.¹³ (For EPI, these distortions are usually seen specifically along the chosen phase-encoding direction and thus may vary depending on the scan plane).

This is confounded by the small nature of the structures comprising this area of interest and the relative proximity of each structure to their surroundings, notably the spinal cord itself, which is approximately 1 cm in diameter on average, necessitating high spatial resolution. Furthermore, there is the issue of bone–cerebrospinal fluid (CSF) and air–bone interfaces in the thoracic region, given the proximity of the pulmonary parenchyma. The partial volume averaging between CSF and surrounding lipids further confounds the inaccurate depiction of normal anatomy and pathologic processes about the cord. Whenever there is narrowing of the spinal canal, either through disk herniation, spondylolysis, or trauma or in the presence of blood product, interpretation of these single-shot EPI (ss-EPI)–based DWI can be challenging because of the aforementioned sensitivity to inhomogeneous magnetic susceptibility.

Finally, the bulk physiologic motion about the cord, due to CSF pulsation, cardiac or respiratory motion or due to swallowing, results in nonlinear phase errors and shifts/dispersions of k -space if the said motion occurs during the application of diffusion-encoding gradients.¹⁴ Because these phase effects are different for each shot, images or even parts of k -space cannot easily be combined. Phase errors can result in ghosting artifacts in multishot DW images and an erroneous estimation of ADC values, which differ for each repetition time (TR). These difficulties result in artifact-laden, low-signal images of the spinal cord, which are often suboptimal for diagnostic evaluation. Some mitigation can be achieved with cardiac gating (usually through finger pulse oximeter), but even with this measure in place, pulsatile cord motion or small patient motion alone can lead to significant artifacts.

The driving force to improve spinal cord imaging is that, as is true of the brain, DWI of the spine can potentially be used in the workup and evaluation of acute infarct and ischemia,^{15–18} infection, myelopathy,^{19,20} inflammatory and demyelinating processes such as multiple sclerosis (MS) and neuromyelitis optica,^{21–24} as well as trauma^{25–28} and tumors. Recent advances in imaging, software, and coil design have allowed for development of pulse sequences that are designed to specifically remedy some of the inherent difficulties in imaging the spine, although each has its own advantages and limitations. This review will focus on a few of the more novel techniques for imaging the spinal column and cord and describe possible uses for DWI in the differential diagnosis of spinal cord pathology. It should be noted that, although there is currently greater attention paid to the clinical use of diffusion tensor techniques (DTI), it is diffusion-weighted imaging that forms the backbone

of all DTI work and is of tantamount importance in generating more robust and reliable DTI data. With the ever-increasing numbers of diffusion-encoding directions as called-for by some of the more advanced variants of DTI, acquiring diffusion-weighted images rapidly has become of significant importance.

TECHNIQUES

Single-Shot EPI

The most commonly used technique used for DWI remains ss-EPI.²⁹ Although the ss-EPI method results in a relatively long readout (several tens of milliseconds, during which the entire image is formed), with associated T2* decay and subsequent (at times significant) blurring in the phase-encoding direction (illustrated in Fig. 1), magnitude images do not suffer from ghosting artifact because the whole of k -space is acquired after a single excitation pulse. Higher resolution may be obtained using this technique by acquiring a longer echo train, but the associated more pronounced T2*-blurring is usually prohibitive. Even more so, with ss-EPI, the bandwidth along the phase-encoding direction is extremely low and is the primary reason for image distortion in regions of inhomogeneous magnetic susceptibility, sensitivity to eddy currents, and considerable water-fat shift (usually taken care of by water-only excitation or lipid suppression).¹³

One solution to the problem of magnetic field inhomogeneity about the spine lies in shortening the readout duration, which reduces off-resonance-related artifacts. Significant phase evolution due to spins being at off-resonance from eddy currents, B_0 inhomogeneities, chemical shift, and susceptibility gradients can be mediated by faster traversal through k -space. Here, focus should be given primarily to the dimension that is the slowest because it usually determines the artifacts. The use of fat suppression techniques or an initial spectral-spatial radiofrequency (RF) pulse can reduce the water-fat chemical shift artifact associated with the ss-EPI sequence. Parallel imaging, which is increasingly used for routine imaging of the brain and intracranial structures, provides the added benefit of distortion reduction in EPI sequences. Spine coils afford the highest acceleration along the craniocaudal direction. If an anterior chest/abdominal set of coils is available, at least a 2-fold acceleration along the anterior-posterior direction is possible. With larger matrix coils that have more than 1 (the standard for the old spine arrays) in the left-right dimension, accelerations along the left-right direction also become feasible. Sadly, successful implementation and application of parallel imaging in imaging the spine is limited primarily because of the current geometric arrangements of spine array coils, which is often in conflict with the preferred anterior-posterior direction of phase encoding for spine imaging.

Reduced Field-of-View ss-EPI Technique

Several methods have been developed in an attempt to mitigate the commonly associated problems of imaging the human spinal cord presented above. Recent developments in imaging have resulted in the use of a reduced field-of-view (FOV) technique with imaging performed in the sagittal plane (although imaging in the axial plane is also possible). Such a technique is better suited to the long and narrow anatomy of the spine and the small cross-sectional size.^{30–32} This method reduces off-resonance-induced artifacts while allowing use

of a ss-EPI method. More specifically, the use of a 2-dimensional spatially selective echo-planar RF excitation pulse followed by a 180-degree refocusing RF pulse is used to select a rectangular FOV, decreasing the readout duration by reducing the phase-encode direction within the excited FOV. The key idea with reduced FOV is similar to parallel imaging. By restricting the FOV that is imaged (either by a spatially limiting RF excitation scheme or retrospective unaliasing), fewer phase-encoding steps are needed, which, in turn, leads to a more rapid traversal from one end of the k -space to the other. Thus, the reduced FOV method enables higher resolution for a fixed readout length and allows for contiguous multislice imaging without the need for interslice gaps.³⁰ With the restricted FOV implementation presented by Saritas et al, there is the added bonus of simultaneous suppression of signal from fat. The method suggested by Saritas et al excites only the volume of interest, thus obviating the need for outer volume suppression pulses, as in Wilm et al.³¹ Finally, in the case of the reduced FOV DWI technique, the signal-to-noise ratio is not dependent on the number of slices obtained, as is the case using multiple 1-dimensional excitation pulses.³² However, the SNR is only the square root (rFOV) of that of the full FOV because fewer k -space lines are measured.

Recent clinical research using the previously mentioned reduced FOV ss-EPI method has shown that it is feasible to use in a clinical population, results in improvement in image quality and other radiological metrics, and is preferred over the traditional ss-EPI technique by expert readers.³³ An example of the rFOV DWI technique is provided in Figure 2, illustrating its use in the context of possible cord infarct. One of the advantages in using this technique is the apparent lack of required additional cardiac gating for routine rFOV DWI (unpublished data) as is commonly true of other sequences. However, it is less clear whether this freedom from obligate cardiac gating will hold true for advanced diffusion tensor imaging (DTI). Without the use of cardiac gating, the overall acquisition of DWI data is relatively random within the RR interval. Some experts' experience suggest that phase errors are relatively benign within diastole but can be profound within systole. The larger phase errors, which lead to significant blurring and shift of the k -space data, might not be recoverable and correctable from navigator data and nonlinear phase correction methods, respectively. Approaches that assess the quality of diffusion-weighted data in real time and initiate reacquisition might be a good alternative, at the cost of moderately increased scan time.

The ZOOM-EPI Technique

Using the rFOV technique, higher resolution is achieved by reducing the FOV and using a small k -space matrix size.³⁴ When using the previously mentioned rFOV DWI technique, there is a potential risk of introducing aliasing (or wrap around) artifacts that can arise from signals outside the prescribed FOV, notably in the phase-encoding direction.³⁵ One proposed solution to this problem is achieved with the use of zonally magnified, oblique, multislice (ZOOM) EPI,³⁶ which was first introduced in 2002 with a focus on optic nerve imaging. Subsequent work using this sequence demonstrated its successful implementation in imaging the spinal cord of healthy volunteers to generate diffusion tensor images³⁰ including rotationally invariant diffusion parameters such as MD and fractional anisotropy (FA). It should be noted that the main limitation of the initial proposed sequence was the

impossibility of acquiring contiguous slices secondary to a then obligate necessity for a 2-slice-thickness interslice gap. This necessity imposed less-than-desirable restrictions on imaging a structure as small as the human spinal cord. Do note that with an interleaved slice acquisition, odd and even slices are half a TR apart. For short TR sequences, this may still not be enough to allow for the previously excited spins to fully relax before re-excitation.

More recent developments using this sequence have allowed for contiguous slices and is aptly named CO-ZOOM-EPI (contiguous-slice ZOOM EPI).³⁵ The CO-ZOOM sequence selectively excites and refocuses only a narrow FOV while simultaneously suppressing the signal arising from outside the desired FOV. In contrast to the reduced FOV technique, the CO-ZOOM-EPI sequence uses a slice-selective 90-degree pulse followed by a dual-spin echo refocusing pulse consisting of two 180 degrees that are slice selective in the phase-encoding direction.³⁵ This results in excitation and refocusing of only a narrow cross section of the volume to be imaged, such that the out-of-phase spins within the refocusing slice undergo two 180-degree pulses to restore magnetization and minimize saturation of spins.³⁵ The multislice version of this method uses multiple regularly spaced 180-degree pulse repeats to achieve a steady state in which each slice is equally saturated. For imaging the spinal cord, it is interesting to note that use of cardiac triggering is of importance when using this technique, which is not necessary for the reduced FOV ss-EPI technique described previously.

A current example of the ZOOM-EPI technique obtained at 1.5 T, without intervening slice gap, is provided in Figure 3. Seven contiguous sagittal slices were acquired with the following imaging parameters: FOV, 18×4.5 cm; matrix size, 192×48 ; TR, 3 seconds; slice thickness, 3 mm; zoom-angle θ , 10 degrees; TE/TR, 73 milliseconds/3 seconds; partial Fourier encoding, 5; $b = 0$; isotropically distributed DW directions with $b = 500 \text{ mm}^2/\text{s}$; and scan time, 2 minutes.³⁷

One limitation of the restricted FOV RF pulse used in the original method of Saritas et al³⁴ is the maximum number of slices that can be encoded without conflicts with the replicas of the 2D RF pulse. Finsterbusch³⁸ recently proposed a solution to this problem by adding a ZOOM variant to the restricted FOV RF pulse approach, which makes the replicas fall outside the restricted FOV and thus allow more slices to be encoded.

Combined ZOOM and Readout-Segmented EPI Trajectory

The ZOOM technique discussed above uses a tilted refocusing pulse. The use of the readout-segmented (RS) EPI technique has been shown to reduce geometric distortion by covering k -space with a series of consecutive segments or “blinds.”³⁹ Because these 2 techniques have individual benefits in reducing geometric distortion, it would be advantageous to possibly combine them. Recent developments have allowed for a combined ZOOM and RS-EPI technique that demonstrates promising further reduction in geometric distortion than either method is capable of achieving alone. An example of this integrated approach is presented in Figure 4,⁴⁰ using b -values of 0 and $500 \text{ mm}^2/\text{s}$. Further research is necessary to demonstrate the clinical application of this technique in imaging the human spine in pathologic states, but initial work demonstrates this is feasible clinically.

Reduced FOV With Twice-Refocused Diffusion EPI

Diffusion-weighted image acquisition using a reduced FOV approach is one method of reducing geometric distortion by acquiring fewer phase-encoding lines, as described previously. One of the potential challenges with this technique is the presence of unwanted aliasing that can occur from signal outside the desired imaging plane that is warped into the anatomy of interest. One method of aliasing reduction relies on excitation of only the area of interest using a 2-dimensional spectral-spatial excitation pulse.³⁴ Although this greatly reduces the geometric distortion encountered by the traditional ss-EPI technique, this technique is slightly compromised by the number of slices that can be used and has been criticized for its associated lengthy preparation periods. The initial ZOOM-EPI technique, described previously, offers certain benefits but is compromised by the requirement of large interslice gaps.

One proposed recent approach at ameliorating these challenges is similar to the ZOOM-EPI technique, with the 180-degree pulses tilted by 90 degrees, allowing for a sharp selected band profile.⁴¹ Initial work using this single-shot twice-refocused DTI technique has been performed on healthy volunteers using an 8-channel spine coil at 1.5 T with the following parameters: 3 $b = 0$ -mm²/s images, 60 isotropically distributed DW directions with $b = 500$ mm²/s, collected on 7 slices with 4-mm slice thickness and no interslice gap, TR/TE of 3000/72 milliseconds, for a total scan time of 3 minutes 12 seconds. Figure 5 provides an illustration of the DWI and color FA maps that are possible with this technique, which assigns phase encoding in the A/P direction.

The pulse sequence uses an initial 90-degree spectral-spatial excitation pulse in the z -axis, with the 180-degree refocusing pulses applied in the y -axis. The resulting region of refocusing (ie, where spin echoes are formed) is at the intersection of the 2 rectangular slabs, which forms the rFOV area. The second 180-degree pulse applied here ensures that inverted spins outside the desired slice are nearly immediately reset. Here, the dual 180-degree approach to minimize eddy current distortions in DW EPI can be conveniently used to undo any spin inversion created by first 180-degree pulse outside the selected slice and thus minimize the effect it has on SNR and contrast. Although initial results are promising, as with the above-mentioned technique, further research is needed to demonstrate the feasibility and applicability of this technique in the clinical setting.

Line Scan Diffusion Imaging

Line scan diffusion imaging (LSDI) has been previously described^{42–44} and although is not a particularly recent development, provides reproducible diffusion imaging of the spinal cord using a spin echo technique. It is relatively insensitive to magnetic field inhomogeneities, bulk motion, and Eddy currents, and hence, is not uncommonly used in research and clinical applications. It relies on sequential columnar single-shot acquisitions and can provide a rectangular FOV for spinal cord imaging, encoding in 6 axes in less than 30 seconds at 1.5 T. As with fast spin echo techniques, LSDI suffers from lower spatial resolution and signal-to-noise ratio and a relatively prolonged acquisition time.

Interleaved Echo Planar DWI

Interleaved EPI is another DWI method of imaging the spine that relies on a phase-navigated multishot spin echo–interleaved DWI technique, which acquires the k -space in multiple interleaves (or lines).¹⁰ This method allows for increased velocity traversal through k -space (in the phase-encoding direction) leading to a marked reduction in EPI-specific artifacts when compared with the ss-EPI technique.^{10,45} As a result of improvements in acquisition time, via more rapid traversal through k -space, there is a reduction in the probability of motion-related artifacts. This technique also offers a modest reduction in echo train length and susceptibility. However, the overall scan time is longer than that of ss-EPI and some of the more recent techniques described previously are currently preferred.

BLADE (PROPELLER) DWI

BLADE or PROPELLER approaches are particularly promising. Here, k -space is acquired in small blade-shaped segments that are rotated about the origin of k -space with each excitation. Because the origin of k -space is acquired with each shot, there is a centrally overlapping region, which provides low-resolution information that can be shared between shots, allowing one to perform nonlinear phase correction between shots and thus affords improved spatial resolution. Another benefit of the PROPELLER technique is that each blade is, in itself, still Cartesian, which renders many image reconstruction steps (eg, phase correction, distortion correction) much simpler than when dealing with arbitrary trajectories (such as spirals). Only at the very end of image acquisition must one combine all the blade data into a single k -space data set, which can be done via gridding. The PROPELLER readout can be a FSE train,⁴⁶ a combined gradient echo/spin echo train (turboprop),⁴⁷ or a short-axis EPI train.⁴⁸ Long-axis EPI is also possible but is less advantageous because of very high distortion levels, which, for PROPELLER, would lead to prohibitive blurring. A potential benefit of PROPELLER over conventional 2D encoded imaging is the lack of Gibbs ringing artifact, which can be particularly bothersome in spinal cord imaging where the transition between bright CSF (on $b = 0$) to spinal cord often mimics possible pathologic disease such as central cord edema and syringomyelia.

DIAGNOSTIC APPLICATIONS

It has been established that diffusion anisotropy exists within the white matter of the human spinal cord.⁴⁹ ADC measurements in the spinal cord are comparable to those of the human brain, although they seem to differ in value when measured parallel versus perpendicular to the white matter fiber tracks⁴⁹ such that the latter measurements can purportedly be twice as large when measured in the former direction (using multishot, navigator-corrected, spin echo EPI pulse sequence). These findings have been demonstrated in several studies and confirmed in children as well.⁴³

Spinal Cord Infarct and Ischemia

Although relatively uncommon, the acute presentation of spinal cord ischemia and/or infarct can have devastating consequences, with often an apoplectic onset evolving over minutes. Despite the low incidence rate, the diagnosis of cord infarction and differentiation from other cord pathologies is often challenging, having a reliable diffusion-weighted sequence

that yields high-quality diagnostic images is crucial, and should be included in all spine imaging protocols. Patients often present with acute onset of pain, paraparesis or paraplegia, paresthesia, and possible urinary and bowel dysfunction.⁵⁰ The associated prognosis is poor, with reported short-term mortality rate up to 20% to 25% during the first month after the onset of symptoms,⁵¹ usually related to neuronal cell death and permanent loss of neurological function, including permanent paralysis in up to 33% of cases. Common causes of cord infarct include various pathologies that involve the aorta and/or arterial intervening feeder vessels that supply the cord. The most common location of infarct involves the anterior two thirds (or central “watershed” region) of the cord, which is supplied by the anterior spinal artery.⁵²

Atherosclerosis, aortic dissection, cardioembolism, and vascular surgery have been reported as common causes of spinal cord infarct, although the most common etiology remains “unknown.”⁵³ Although uncommon, spinal venous pathology may also produce spinal infarction. Within this context, arteritis of various causes including diabetes mellitus, systemic lupus erythematosus, granulomatous arteritis and syphilis have been implicated.⁵⁴ Rarer causes include epidural anesthesia, decompression sickness, emboli from iatrogenic procedures including surgery (especially sympathectomy), prolonged systemic hypotension, and vascular steal in the presence of an arteriovenous malformation.⁵⁵ Common imaging findings on conventional MR sequences are relatively nonspecific in the setting of acute onset of symptoms and can include focal cord edema/enlargement and central cord T2 hyperintensity, although the latter finding is routinely identified in fewer than 45% of patients later diagnosed with acute spinal cord infarct.⁵⁴ Although T2-weighted images have demonstrated spinal cord hyperintensity at or beyond 12 hours after onset of patient symptoms,⁵⁶ DWI has been reported to show signal alteration at up to 3 hours after patient symptom onset, with associated hypointensity seen on derived ADC map images. Because the maximum *b*-value used in most spinal cord studies (usually between 500 and 600 mm²/s) is significantly lower, an even higher sensitivity to stroke could be anticipated if *b*-values in the range typical for brain studies were to be used (usually 1000 mm²/s). Subsequent pseudonormalization of ADC values on follow-up MR examination (usually documented 1 week after symptom onset, with some degree of persistent DWI hyperintensity) has been demonstrated. Because of the implications for earlier clinical intervention and possible change in patient outcome, it is desirable to obtain more sensitive imaging techniques able to detect spinal cord infarcts within an earlier time window.

Multiple small studies have been performed in patients with acute spinal cord syndrome, in which patients were imaged with MRI and demonstrated diffusion signal abnormality within the cord (up to 6 patients per study to date) demonstrating the commonly associated findings of true diffusion restriction (DWI hyperintensity with associated hypointensity on ADC map images).^{15,16,19,55} These findings have been summarized by Thurnher and Bammer¹⁷ in 2006, documenting the feasibility of DWI in the context of acute cord-related symptoms. When present in the proper clinical setting, the findings present on DWI sequences described previously enabled the confident diagnosis of acute cord infarct in these cases. In the hyperacute or acute setting, DWI hyperintensity and associated low signal on ADC maps is seen, with or without accompanying T2 hyperintensity; these findings are representative

of similar findings in acute cerebral ischemia. Figure 2 provides an illustration of findings related to acute cord infarct in a patient with known chronic Type B aortic dissection with development of acute onset of symptoms.

Although these results are promising, the small number of patients presented in each study makes statistical evaluation difficult. Marcel et al⁵⁷ recently presented prospective findings in 33 patients who presented with spinal cord syndrome (with noncompressive myelopathies), in which the authors demonstrate statistically significant differences in measured ADC values in patients with spinal cord infarct versus those with inflammatory myelopathies and in normal controls. They report mean ADC values of 0.71 to 0.96 in the spinal cord injury (SCI) group (6 patients, imaged 1–8 days after onset of symptoms) and 1.06 to 1.85 in the inflammatory disease group (including MS and parainfectious myelopathies), with $P < 0.0005$. These are consistent with previously reported values, although further investigation is needed to adequately document the sensitivity and specificity of DWI in the evaluation of spinal cord infarction. With the advent of more advanced imaging techniques, it is becoming increasingly feasible to image patients with diffusion-weighted sequences in the acute setting, which offers hope in possible earlier therapeutic intervention. Diffusion-weighted imaging may play a more central role in the evaluation of acute spinal cord syndrome in the immediate future.

Inflammatory Conditions

Inflammatory conditions encompass a broad range of categories and, individually, are beyond the scope of this review. Perhaps the best-documented disease within this category is MS. However, MS has historically been an elusive disease to understand and treat, in part secondary to its many variants and poorly understood etiology. There is suggestion that SCI may play a large role in the disability of patients with MS.^{58–60} Yet, although lesion detection has been possible with conventional MRI techniques, the correlation between conventional MR measures and patient disability has been suboptimal. More quantitative MR approaches have been investigated including the use of diffusion-weighted and diffusion tensor techniques.

Multiple sclerosis is a chronic demyelinating disease of the central nervous system, characterized by both neurodegenerative and inflammatory processes. Inflammation and demyelination can lead to permanent neuronal loss and/or remyelination, leading to subcategorization of the disease including aptly named variants including relapsing-remitting and primary-progressive MS. Magnetic resonance imaging is increasingly used in the diagnosis and management of patients with MS, in which spinal cord involvement is relatively common. Multiple sclerosis plaques may be identified as hyperintense, often wedge-shaped lesions in the lateral and posterior columns on T2-weighted sequences.⁶⁰ On T1-weighted images, lesions may be isointense or hypointense, the latter often referred to as “black holes.” However, the presence of detectable lesions is a poor marker for clinical disability.

Previous studies have documented increased ADC values within the cord in patients with MR-detectable macroscopic lesions, with values ranging from 1.06 to $1.82 \times 10^{-3} \text{ mm}^2/\text{s}$ in 1 group, using an ss-EPI technique.⁵⁷ The mean (SD) ADC values in this study were 1.36

$(0.19) \times 10^{-3} \text{ mm}^2/\text{s}$ for patients with MS versus $0.93 (0.07) \times 10^{-3} \text{ mm}^2/\text{s}$ for healthy controls, which was statistically significant ($P < 0.0005$). A conventional cardiac-gated navigation diffusion-sensitized spin echo sequence was used by another group and resulted in increased diffusivity rates with mean ADC values of $1.18 (0.12)$ versus $0.91 (0.05) \times 10^{-3} \text{ mm}^2/\text{s}$ for healthy controls.⁶¹ This latter study did not find statistically significant differences in diffusion anisotropy, although a mean difference was present.

It has been postulated that a decrease in diffusion anisotropy associated with MS may in part be related to white matter axon and myelin loss and thereby represents a component of atrophy.⁶² The presence of possible active perilesional inflammatory changes and associated edema with expansion of the extracellular space may also contribute to decreased anisotropy, which has been previously documented in the brain.⁶³ However, it has been shown that axonal damage within the spinal cord of MS patients occurs largely independent of macroscopic T2 lesions.^{62,64,65} Postmortem studies have demonstrated that axonal injury and demyelination occur not only within but also outside T2 hyperintense spinal cord lesions.

Recent studies have lead to a greater understanding that diffusion anisotropy and atrophy in the setting of MS may not only be limited to the macroscopic lesions identified on conventional MR sequences. However, this observation also seems to be somewhat dependent on the subtype of MS afflicting a given patient. It has been shown that cervical cord damage outside macroscopic lesions is limited in patients with benign MS (BMS), for example, although cervical cord MD in these patients is still statistically greater than that of healthy normal controls as measured with DTI.⁶² Patients with BMS were found to have lower cord FA and lower sectional cord area (SCA) when compared with normal controls. In this latter study, imaging parameters in patients with secondary progressive MS deviated even further from those of normal controls and patients with BMS, such that patients with secondary progressive MS demonstrated the greatest cervical cord MD and, simultaneously, the least average cord FA and SCA, when compared among these 3 groups. These authors report that multivariate regression analysis identified SCA and average cord FA (as well as brain T2 lesion volume) as independent parameters influencing the expanded disability status scale (EDSS) in these patients ($P < 0.0001$).

More recently, a multicenter study using a semiautomated method for cervical cord segmentation was used to investigate the correlation between cord atrophy and clinical disability in patients with MS at 3 European centers.⁶⁶ The authors report that cervical SCA was correlated with EDSS scores ($P < 0.0001$) and was able to distinguish various MS subtypes and provided a useful marker for characterization of the clinical heterogeneity observed in patients with MS.

The previously mentioned findings are in accord with those of previously reported postmortem MRI observations that focal high T2 signal lesions represent demyelinated plaques, whereas other less well-defined areas of mild focal T2 signal abnormality represent partial demyelination⁶⁰ but may play an important role in assessing patient disability. This observation is further substantiated by postmortem findings of MS cord lesions imaged at 7 T, subsequently correlated with quantitative measurements of myelin content and axonal

density, in which a strong correlation was observed with these parameters when compared with magnetization transfer ratio (MTR), diffusion anisotropy, proton density, and prolongation of T1.⁶⁷ In this postmortem study, less significant correlation with T2 and ADC values was observed. Nonetheless, the strong correlation with diffusion anisotropy supports the future continued investigation of MS with use of DTI.

Mean diffusivity and FA histogram analysis have been previously shown to correlate with cord tissue damage and clinical disability in large cohorts of MS patients.⁶⁸ This latter study demonstrated that average cervical cord FA was significantly lower in patients with MS when compared with healthy controls and that good correlation exists between average FA and MD compared with degree of disability. Another study published by this same group demonstrated overall reduction in average cord FA with increased cord MD in patients with primary progressive MS compared with normal controls.⁶⁹ The authors conclude that DTI can provide an accurate assessment of cervical cord damage in MS and contributes to the possible explanation of the heterogeneous clinical manifestation of MS.

Animal studies performed at 8.4 T using high *b*-value *q*-space diffusion MR spectroscopy and MRI at different diffusion times suggest that the lack of myelin in myelin-deficient rat spinal cords significantly affects the diffusion characteristics and diffusion anisotropy of water in white matter in a diffusion time-dependent manner, when compared with healthy normal control rats.⁷⁰ The authors conclude that different diffusion protocols may result in different sensitivities to various pathologies and that anisotropy is diffusion time dependent and model system dependent. With this caveat in mind, the authors suggest that only apparent anisotropy is constant between imaging protocols and that reported results of diffusion anisotropy be taken with caution.

The role of DWI and DTI in the context of MS is evolving. It seems clear that diffusion imaging of MS plaques and that of the “normal-appearing white matter” of MS patients reveal abnormalities and signal alteration that are otherwise missed by more conventional imaging techniques. Studies have suggested that ADC values are likely elevated in the setting of acute plaques, possibly associated with perilesional edema. At the same time, FA and MD changes are identified with DTI that correlate well with clinical markers of disability such as EDSS scores. Further studies are needed with continued improvements in DWI techniques, which provide the backbone for ADC map generation as well as the framework for diffusion tensor experiments.

Traumatic Spinal Cord Injury

Traumatic injury to the spinal cord can result in significant impairment of motor, sensory, and autonomic function and is the subject of intense research because of its devastating consequences. The estimated annual incidence of traumatic SCI is 11,000 new cases or 40 cases per million people (ranging from 28 to 55 per million people). Most cases of traumatic SCI occur in young patients with an average age of 31.7 years in the United States, with the highest frequency noted in the 15- to 25-year-old range. These most commonly affect young adult males, who are at higher risk for violent crashes, falls, motor vehicle collisions (reportedly up to 48% of traumatic SCI), and injury from recreational and combat activities.

These injuries result in permanent paralysis in approximately 10,000 individuals, with initial injury resulting in only a fraction of the functional permanent deficits that ultimately result.

Five classic syndromes of incomplete SCI have been described in the acute phase, including: complete spinal cord transection syndrome, central cord syndrome, anterior cord syndrome, Brown-Sequard syndrome, and cauda equina and conus medullaris syndromes. Each of these can be associated with subsequent functional loss in the subacute setting secondary to delayed or “secondary” injury, which is thought to be immune mediated and may increase traumatic lesion size and perilesional edema and can result in degeneration of additional surrounding fiber tracts.⁷¹

Conventional MRI detection and quantification of functional axon integrity within the white matter tracts of injured spinal cords often capture only a fraction of the injury that is present at the time of imaging. Both DWI and DTI have demonstrated some promise in more adequately characterizing the extent of this injury. The primary goals of imaging are to monitor the efficacy of administered neuroprotective therapeutic agents and to evaluate the pathophysiologic status of the spinal cord shortly after the time of initial injury and subsequently beyond initiation of clinical intervention.

The previously described limitations of spinal cord imaging, including physiologic motion, susceptibility artifacts, and small cord size, present particular challenges to imaging the cord in the setting of acute traumatic injury in which the presence of associated edema and blood products further degrade image quality. Having high-quality baseline imaging techniques becomes tantamount under these conditions. The use of high-resolution self-navigated, interleaved, variable-density spiral acquisition DTI, originally described in 2004,⁷² was more recently used at 3.0 T to image the spinal cord of cats after traumatic SCI.⁷³ The latter authors demonstrated the feasibility of DTI using this technique on a clinical 3-T MR system and confirmed previous reports that diffusion FA is lower in injured spinal tissue, compared with normal spinal tissue. Given the somewhat greater sensitivity of self-navigated, interleaved, variable-density spiral to blurring and geometric distortions, especially with potential blood products and bony fragments in the vicinity of the lesion, some of the methods described in the previously mentioned section might even further enhance the diagnostic capability of DWI in traumatic spines.

A seminal study demonstrating the imaging detection of changes related to the use of neuroprotective agents was performed in a rat model in which injured rat spinal cords were imaged with DWI.⁷⁴ Contusively injured rats treated with neuroprotective agents (T-cell central nervous system-specific self-antigen myelin basic protein) were compared with untreated injured control rats. The authors demonstrated that the mean anisotropy ratio and ADC values in postmortem specimen cords increased gradually from the specific site of prior injury. Interestingly, the mean anisotropy ratio and ADC map values at the site of injury were significantly higher in the spinal cords of treated animals than in those of controls ($P = 0.047$ and $P = 0.028$, respectively).

More recent preliminary published research in children has demonstrated good reproducibility of DTI techniques using an ss-EPI DWI sequence at 1.5 T.⁷⁵ Reduced FA

values and increased MD were identified in 5 children with SCI when compared with 5 controls, with good clinical correlation with the *International Standards for Neurological and Functional Classification of Spinal Cord Injury*. A second, more recent publication combines the use of high-angular resolution DWI, MT, and atrophy measurements to evaluate the cervical spinal cord in 14 patients with SCI compared with age-matched controls.⁷⁶ The authors report statistically significant differences between SCI patients and controls in the normal-appearing white matter tracts for FA, axial diffusivity, radial diffusivity, MTR, and cord area, which were well correlated with clinical disability. The authors conclude that DTI, MTR, and atrophy measures can predict impairment in SCI.

An illustration of the possible use of DTI in the setting of patients with chronic SCI is illustrated in Figure 6. This patient was imaged with a reduced FOV ss-EPI DTI technique and associated tractography, demonstrating that, despite the large area of gliosis about the cord at the site of injury, there is suggestion that some fiber tracts course through the lesion and may represent incomplete old white matter tract injury and/or a component of some possible fiber regrowth.

Although the previously mentioned uses of DWI and DTI are more common, there are times when the additional information provided by the DWI sequence may be of value by the increase in diagnostic confidence in rendering a final diagnosis. Figure 7 provides an example of a patient who had previously undergone a blood patch for a cerebrospinal fluid leak but continued to experience worsening back pain after the procedure, although the pain had stabilized during the 3 weeks before being imaged. In this case, having a diagnostic quality image greatly aids in rendering the final diagnosis.

Multiple studies have demonstrated that DWI and DTI are sensitive for the detection and evaluation of SCI and acute spinal trauma. Animal research suggests that neuroprotective modulation and possible neuronal regeneration may be detected with the use of these more advanced imaging techniques. Although the presence of acute blood products and trauma-related edema further compromise evaluation of the spinal cord in the setting of acute trauma, the use of advanced DWI techniques will likely aid in improved detection of SCI and related abnormalities.

Tumor and Fiber Tract Mapping

The presence of spinal tumors, whether encapsulated or infiltrative, provides challenges in treatment options and possible surgical resection. The most commonly encountered spinal cord tumors are categorized as astrocytomas, which are infiltrative and generally eccentric in location, or ependymomas, which arise from the ependymal cells of the central canal and are thus primarily central in location. The advent of DTI has provided added insight into the microscopic and macroscopic behavior of a variety of in vivo tumors and allowed for better presurgical characterization of these tumors. Advanced DWI and DTI techniques have allowed for better delineation of these tumors and improve characterization of tumor tissue. For example, highly cellular tumors such as high-grade astrocytomas are usually T2 hypointense and can now be further characterized by associated relative low ADC values. Ependymomas, on the other hand, are usually less cellular and would be expected to demonstrate relatively high ADC values.

Diffusion tensor images allow for added elucidation of lesion integrity with better delineation of white matter spinal tracts and possibly aid in surgical navigation. Older DTI techniques were more subject to the geometric distortion related to the slow phase-encoding bandwidth or traditional EPI sequences. Recently acquired images illustrating current techniques and application of DTI and tractography to tumor mapping and surgical planning are illustrated in Figure 3.³⁷

The positive predictive value of preoperative DTI acquisition was recently demonstrated in 14 patients with intramedullary tumors of the spinal cord. In this retrospective study by Setzer et al,⁷⁷ routine MRI with additional DTI was performed preoperatively in 14 patients on a 3-T system, in which spinal cord lesions were rated as resectable or nonresectable. Lesions were classified depending on the course of the surrounding fiber tracts, which (1) did not pass through the lesion, (2) demonstrated some fibers that passed through the lesion, or (3) demonstrated tumor that completely encased the fiber tracts. In the 13 patients who underwent surgery for tumor resection, only one tumor was incorrectly classified in this study.

The possibility of obtaining DTI within the neurosurgical suites has garnered much attention. A recent study using integrated high-field intraoperative MRI and a neuronavigation system examined the use of intraoperative tractography in 28 patients with tumors located around the corticospinal tract (CST).⁷⁸ The authors found that intraoperative tractography demonstrated the precise location of the CST more accurately than did preoperative tractography and concluded that, when used in conjunction with motor-evoked potentials, can enhance the quality of glioma surgical resection in the motor eloquent areas. Although this represents only a single-institution cohort, with focus on intracranial tumors, these results suggest that there will likely be similar benefit in use of advanced DTI techniques in the operative suites when applied to spinal cord surgery.

In contrast to brain studies, DTI of the spinal cord is still challenged by low SNR, which, in turn, can challenge the veracity of tractography results because the eigenvector orientations will also fluctuate considerably if SNR is low. Therefore, the diligent neuroradiologist has to keep an eye on the SNR levels and has to entertain a healthy skepticism about tractography results if she/he looks at raw diffusion-weighted images or FA and color FA maps that appear to be corrupted by noise.

CONCLUSIONS

Both DWI and DTI techniques hold great promise in their ability to quantify and better characterize the microscopic behavior of intracellular and extracellular water molecules and their interaction with the immediate surrounding structures, based on Brownian motion and other thermodynamic qualities. Although DTI is only as good as the source DWI from which it is derived, the prospect for improvement in better defining pathologic states and the degree of surrounding involvement continues to evolve with development of more advanced, novel approaches in spinal cord diffusion imaging. Although some of the newer approaches to spinal cord DWI deal with only 1 conundrum, a few incorporate the benefits of more than one technique, at times combining them. Whereas the utility of some of these

techniques must still be further explored, the possibility for significant improvement in data acquisition remains and warrants further investigation.

This review incorporates only a short list of the possible applications of DWI and DTI that are currently being investigated, clinically. The number of novel applications is rapidly increasing, with an almost equal pace of innovative techniques that are being developed to overcome shortcomings in current imaging strategies. The use of advanced postprocessing techniques including high-angular resolution DWI and q -space imaging will likely play a critical role in deciding the future reliability of tractography, especially in the application of fiber crossing, which remains a challenge for current techniques in imaging. That said, the added number of extra diffusion-encoding directions and the added imaging time need to be carefully considered when assigning protocols using these advanced variants of DWI. The more routine clinical use of 3-T scanners and the increasing research attention paid to 7-T systems will greatly improve our understanding of the applicability of diffusion imaging in the near future and further define the use of this powerful technology.

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FIGURE 1.

Contiguous sagittal diffusion weighted images of a 46-year-old woman who presented with left-sided weakness, obtained at the same imaging session, using a standard ss-EPI sequence at 1.5 T with a 96×96 -mm matrix size (A) and then with a 196×196 -mm matrix size (B). A focal disk-osteophyte complex is identified at the C4/5 level, posteriorly (red arrow in A and B) in the setting of additional multifocal disk-osteophyte complexes. A large degree of susceptibility artifact and distortion in the phase-encoding direction (horizontal orientation) render both images suboptimal for diagnostic interpretation and make artifact difficult to distinguish from true pathology. The higher matrix size in B is associated with even greater distortion in the phase-encoding direction.

FIGURE 2.

Thoracic MR images of a 57-year-old man with history of a known type B aortic dissection, and more recent history of acute-onset paraparesis and chest pain radiating to the back that began early in the morning. A long, contiguous area of intramedullary T2 hyperintensity is identified within the thoracic spinal cord (white arrows), extending from T5 vertebrae (labeled) to the T9 level, as seen in sagittal T2 FSE (A) and sagittal STIR (B) images. The central location of this focal signal abnormality is confirmed with 3 axial images (C) obtained through the area of interest. Sagittal reduced FOV diffusion-weighted image (D) and associated sagittal ADC map (E) obtained at 1.5 T with 196×48 -mm matrix size, demonstrate corresponding diffusion restriction (black arrows) and confirm the acute nature of this segmental cord infarct. The normal cord signal is depicted by the blue arrow, located more superiorly in D and E.

FIGURE 3.

A 5-year-old boy with expansile, intramedullary mass of the upper thoracic cord, located posterior to the T1–T3 vertebral bodies, imaged at 1.5 T. The mass is hyperintense to the cord substance on sagittal T2 FSE (A) and isointense on sagittal T1 pregadolinium image (B). Patchy, mild heterogeneous enhancement is noted within the lesion on the midsagittal IDEAL T1 postgadolinium image (C). Diffusion-weighted images (D) were obtained in the sagittal plane using the ZOOM-EPI technique with an acquired matrix of 192×48 mm. Derived ADC map (E) highlights the presence of elevated ADC values noted centrally within the lesion. Derived fractional anisotropy (F) and principal eigenvector field segmentation map (G) confirm the intramedullary location of this lesion and suggest that traversing white matter tracts are splayed circumferentially about the lesion (blue arrows in F and G). This latter observation is further supported by tractography findings (H). Subsequent surgical resection confirmed the diagnosis of a grade 2 diffuse astrocytoma according to the World Health Organization by the institutional neuropathologist. Images courtesy of Drs Holdsworth, O'Halloran, Aksoy, and Yeom, Stanford University. Figure 3 can be viewed online in color at www.topicsinmri.com.

FIGURE 4.

Comparison between the $b = 0 \text{ mm}^2/\text{s}$ images of a thoracic spine using full FOV EPI ($30 \times 30 \text{ cm}$, matrix size = 200×200), ZOOM-EPI and ZOOM-RS-EPI ($30 \times 10 \text{ cm}$, matrix size = 200×60 [square pixels]). For ZOOM-RS-EPI, the isotropic DWI ($isoDWI$, $b = 500 \text{ mm}^2/\text{s}$), FA , and first eigenvector (color map) are also shown. Note that there is less “disk bulging” into the spinal canal and less blurring on the ZOOM-RS-EPI scans than on the ZOOM-EPI scans. Images courtesy Drs Holdsworth, O’Halloran, Aksoy, and Yeom, Stanford University. Figure 4 can be viewed online in color at www.topicsinmri.com.

FIGURE 5.

Single-shot twice-refocused reduced FOV midsagittal image of the cervical spine in a healthy volunteer. Please see text for imaging parameters. Images courtesy Drs Holdsworth, O'Halloran, Aksoy, and Yeom, Stanford University. Figure 5 can be viewed online in color at www.topicsinmri.com.

FIGURE 6.

A 61-year-old man with prior C6/C7 traumatic injury due to motor vehicle collision several years prior. Diffusion tensor images and tractography obtained at 3 T using a reduced FOV ss-EPI technique. Scan parameters: resolution, $0.94 \times 0.94 \times 3 \text{ mm}^3$; FOV, $18 \times 4.5 \text{ cm}^2$; number of slices, 8; scan time, 12 minutes; number of excitations, 16; $b = 500 \text{ mm}^2/\text{s}$ imaged in 12 directions; T2 weighted, 2. Image courtesy of E. Saritas and G. Zaharchuk.⁷⁹ Figure 6 can be viewed online in color at www.topicsinmri.com.

FIGURE 7.

Multifocal, lobulated mass-like subdural collections located dorsal to the thecal sac as demonstrated in sagittal T1 FSE pregadolinium image (A), sagittal postgadolinium T1-weighted image with fat suppression (B), sagittal STIR (C), and sagittal reduced FOV diffusion-weighted image (D). These collections are T1 hyperintense, T2 isointense to hypointense, and contain no fat, as demonstrated in B. Taken in the context of the diffusion signal abnormality, findings are most consistent with subacute hemorrhagic products. Follow-up imaging demonstrated decrease in size and continued evolution of blood products in the subdural space, confirming the diagnosis.