Diffusion tensor imaging of the spinal cord and its clinical applications

The identification of the extent of neural damage in patients with acute or chronic spinal cord injury is imperative for the accurate prediction of neurological recovery. The changes in signal intensity shown on routine MRI sequences are of limited value for predicting functional outcome. Diffusion tensor imaging (DTI) is a novel radiological imaging technique which has the potential to identify intact nerve fibre tracts, and has been used to image the brain for a variety of conditions. DTI imaging of the spinal cord is currently only a research tool, but preliminary studies have shown that it holds considerable promise in predicting the severity of spinal cord injury.

This paper briefly reviews our current knowledge of this technique.

The ability to identify the extent of neural damage after both acute and chronic spinal cord injury is essential if the degree of recovery is to be predicted.1,2 Currently this is usually assessed by magnetic resonance imaging (MRI).3 Although spinal cord oedema, haemorrhage and interstitial fibrosis will appear as changes in signal intensity on conventional MRI, these changes are of only limited value in the prediction of functional outcome.4 It is not possible to distinguish between neuronal structures and interstitial parenchymal tissues on MRI. Hence, any method that could improve our ability to evaluate the integrity of nerve fibre tracts and assess the functional status of the spinal cord would be of value.

Diffusion tensor imaging (DTI) is extensively used to image the brain and show specific nerve fibre tract bundles. It can potentially detect early damage to the myelin sheath before gross changes are obvious. However, its efficacy in imaging of the spinal cord remains largely unexplored.

Principles of MRI

The basic principles of MRI have been described by various authors.5-8 The nucleus of an atom consists of protons and neutrons, which are in constant motion. Both neutrons and protons spin about their axes. The proton has a specific mass and is positively charged. When it spins, it produces a small magnetic field which is referred to as the magnetic moment. The collective magnetic moment associated with the millions of protons in human tissue forms the basis of MRI. The magnetic moment of each proton remains too small and randomly oriented in direction to measure. When the human body is placed in a large magnetic field, free hydrogen nuclei in the tissues align themselves either parallel or antiparallel to the applied magnetic field, creating a large magnetic moment. Next, a radiofrequency (RF) pulse is applied which causes the magnetic moment to tilt away from the applied magnetic field for a brief period. Once the RF signal is removed, the protons revert to their original orientation, such that their magnetic moment is again realigned with the magnetic field. This return to equilibrium is referred to as relaxation of protons. During relaxation, the nuclei lose energy by emitting their own RF signal. This signal is measured by a RF coil placed around the patient and then reconstructed into grey-scale MRIs.

Although conventional MRI shows the detailed anatomy of the structures imaged, the functional status of these tissues cannot be determined: for example, in cervical myelopathy, even though the affected segment of the spinal cord shows changes in signal intensity, the physiological state and functional integrity of the nerve fibre tracts of the spinal cord are not shown. However, pathological conditions affect the diffusion of water in the tissues, and it is this phenomenon that is used by DTI to assess the affected tissues.

Diffusion

Water molecules in body tissue exhibit a random translational moment, termed brownian motion or diffusion, because of their inherent...
latent thermal energy. When this molecular moment is unrestricted in all directions, it is classified as isotropic (Fig. 1). However, in biological tissues such as muscle fibres and axons, this mobility is usually restricted to one particular direction by the presence of biological barriers such as cell membranes, where the diffusion is termed anisotropic. Anisotropic diffusion can thus be measured for both direction and speed, and forms the basis of DTI. In DTI, any longitudinal structure that is imaged is broken down into small three-dimensional structures called voxels. DTI is able to tract the integrity of long linear structures by calculating the direction and speed of diffusion occurring in adjacent voxels serially. Interruption or alteration of linear molecular movement (diffusion) at any particular point of the longitudinal structure can be the first sign of a physiological disturbance, which makes DTI more sensitive to early change even before gross structural changes are evident. These changes in DTI can be assessed either by ‘fibre tracking techniques’ (tractography) or by calculating DTI anisotropy indices (datametrics).

Diffusion tensor tractography
Tractography gives a visual representation and assessment of the diffusion status of the evaluated structure. Here, each voxel is compared to an ellipsoid that has three vectors, E1 being the main vector and representing the main direction in which the molecules are diffusing (Fig. 2). In DTI, the E1s of adjacent voxels are linked in sequence, which allows tracking of the longitudinal structure, for example the axons. The direction of diffusion can also be
colour-coded and traditionally, diffusion from left to right is represented by red, anteroposterior direction by green, and craniocaudal by blue. This allows for clear documentation of the nerve fibres in the brain, where they are multidirectional (Fig. 3). There is considerable literature describing the use of DTI in detecting pathological conditions of the brain, in which abnormal fibre connections and decussations of nerve fibre tracts can clearly be documented in addition to the displacement of the tracts by space-occupying lesions.\textsuperscript{11,12} For example, in patients with progressive scoliosis and a horizontal gaze palsy, DTI clearly demonstrates no crossing-over of major nerve tract fibres at the level of the pons\textsuperscript{11} (Fig. 4).
In the spine, as the fibres are mainly craniocaudal, the tracts are always represented in blue (Fig. 5). Spinal tractography can show the macroscopic orientation of fibres with dramatic representation of the disruption of tracts, which can be poorly seen on plain MRI (Fig. 6). Clinically, this information allows better delineation of damaged fibre tracts in the injured spinal cord (Fig. 7). Tractography also depicts the lack of functional continuity and disrupted physiological status of the tracts in chronic compressive myelopathies (Fig. 8).

**Diffusion anisotropy indices**

Anisotropy indices or DTI datametrics provide a quantitative perspective and a numerical value to the diffusion in any particular voxel. Among the different indices described, the most commonly used are fractional anisotropy (FA), apparent diffusion coefficient (ADC), volume ratio (VR), relative anisotropy (RA) and eigenvectors. These indices are derived from the eigenvector values. Fractional anisotropy measures the fraction of the ‘magnitude’ of total diffusion which occurs in one particular voxel that can be attributed to anisotropic diffusion. FA varies between 0 for diffusion in a perfect sphere (isotropic diffusion) and 1 for diffusion in a perfect thinnest cylinder (infinite anisotropy). Usually, in intact neurons, the FA value is closer to 1 because of the high degree of anisotropy. When there is any damage to the axonal membrane, the diffusion at that level becomes unrestricted and isotropic. The FA
value decreases at that level; the amount by which it
decreases depends on the extent of remaining anisotropic
diffusion at that level. The other important index is the
apparent diffusion coefficient (ADC). When various barri-
ers and restricting factors interfere with free diffusion, the
diffusion coefficient measured is called an apparent diffu-
sion coefficient because the measurement fails to (or can-
not) notice the interfering effects of local tissue
microstructures such as the myelin sheath, and makes the
calculation as if all the diffusion rates were solely due to
brownian motion. ADC measures the magnitude of diffu-
sion (of water molecules) within the imaged structure. A
low value for ADC indicates that the imaged structure (e.g.
nerve fibres) is organised, whereas a high value indicates
that these fibres are disorganised due to injury.

**Diffusion imaging in the brain**
The diffusion anisotropy phenomenon was first observed in
the white matter of the human brain in stroke patients.13,14
Diffusion tensor imaging of the brain is now well estab-
lished. Current methods have enabled reliable assessment
of the three-dimensional anatomy of nerve fibres in the nor-
mal brain. The changes in the organisation of fibre tracts
during normal development of the child, and any that occur
in the disease state, can also be shown by DTI. The ability of tractography techniques to visualise the nerve fibre tracts clearly have been useful in various conditions such as stroke, brain injury, demyelinating disorders and inflammatory disease, and has also been used in neurosurgical planning for the localisation of tumour and selective resection of nerve fibre tracts.

Challenges in spinal cord DTI

Theoretically, in the spinal cord the presence of organised, longitudinally placed tracts of white matter with grey matter in their centre, surrounded by cerebrospinal fluid, should allow the application of diffusion principles and thereby show the three-dimensional anatomy of the nerve fibre tracts. However, DTI of the spinal cord is more problematic. First, the spinal cord is surrounded by the bony vertebral column, which can cause magnetic susceptibility artefacts at the bone-tissue interface and result in distortion of the images. Other magnetic susceptibility artefacts, such as chemical-shift effects owing to the presence of lipids in the fatty marrow of the vertebral bodies, also affect the quality of the images. Secondly, diffusion imaging is quite sensitive to movement. Several continuous dynamic events that occur in the human body, such as carotid and aortic pulsations, cardiac activity, respiratory movements and cerebrospinal fluid (CSF) pulsations, can lead to ghosting artefacts. Swallowing and other subtle movements of the patient while the images are being acquired can also result in artefacts. Thirdly, the diffusion in CSF is less anisotropic than that in the spinal cord tracts. Hence the surrounding CSF can affect the diffusion anisotropy indices due to partial volume effects. Fourthly, the deep location of the spinal cord inside the body and the close and compact packing of millions of spinal neurons in the smaller spinal cord compared with the brain mandate the need for very high-resolution imaging. But such high-strength MRI is not applicable in practice for clinical purposes; it is also difficult to achieve adequate signal-to-noise ratio with high spatial resolution.

Consequently, these investigations are still in the preliminary stage with regards to the spinal cord. Different sequencing techniques have been tried by various research groups and achieved some degree of clinical success. Initial diffusion images of the spinal cord were obtained using a pulsed-gradient spin echo sequence. This technique had disadvantages including long scan times and the need for cardiac gating. To avoid problems such as long scan times, high signal-to-noise ratio and distortion artefacts, different techniques like interleaved echo planar imaging, fast spin echo diffusion-weighted sequences, single-shot echo planar imaging, the use of parallel imaging techniques and line scan diffusion imaging have been used by different research groups, with varying degrees of success.

Clinical applications

DTI in cervical myelopathy. DTI in the spinal cord has been shown to be capable of detecting changes in the integrity of white matter and to provide complementary or additional information to MRI in spinal diseases such as multiple sclerosis, acute and chronic injury of the spinal cord, chronic cord compression, syringomyelia and spinal cord tumours. DTI has the potential to detect more subtle changes that are not seen on conventional T2-weighted images, because FA/ADC values and fibre tracking contain more, and complementary, information about the microstructure of white and grey matter than the
conventional imaging contrasts (Fig. 9). It is therefore reasonable to use DTI as an additional imaging modality for improved detection and description of spinal cord lesions such as spondyloptic myelopathy.

In the spinal cord with a chronically poor blood supply, histopathological changes, such as gliosis, cystic degenerative change, and extracellular oedema, lead to increased mobility of water. These histological changes are believed to be similar to changes that result from vascular occlusion or venous congestion caused by compression by discs or osteophytes. In spondyloptic stenosis, these changes in blood circulation may be underlying the observed ADC and FA changes. In an unpublished study of 64 patients with cervical myelopathy in the authors’ hospital, most patients had decreased FA values and increased ADC values at the site of the lesion, which would suggest either local extracellular oedema or a decreased number of fibres with increased extracellular space, or both. It was noted that disturbances in tractography may be a better indicator of the level of maximum functional disturbance in the myelopathy of multilevel chronic spondylosis. Thus, changes in tissue water diffusion detected by DTI may prove useful in assessing the severity of long-standing ischaemia of the spinal cord, and in establishing the correct time for decompressive surgery before irreversible changes occur.

Demir et al showed that diffusion weighting increased the sensitivity of MRI for the depiction of changes in the spinal cord in patients with cervical spondyloptic myelopathy. The sensitivity of diffusion-weighted imaging (DWI) was 90% for patients in whom symptoms of myelopathy were confirmed by electrophysiological findings. Other authors have shown that is more sensitive than T2-weighted images in patients with cervical myelopathy. Using line scan diffusion tensor imaging in normal and spondyloptic patients, Shanmuganathan et al investigated DTI in patients with cervical myelopathy and concluded that DTI indices are sensitive markers of cervical cord injury, and that ADC values also showed significant changes, which suggested abnormal diffusion patterns at the site of the injury (Fig. 6). Fujiyoshi et al investigated the effective use of tractography to image both intact and surgically disrupted spinal long tracts in adult common marmosets. DTI clearly illustrated the corticospinal tract in the control animals and the severed long tracts in the injured animals. Shanmuganathan et al investigated DTI in patients with cervical cord injury and concluded that DTI indices are sensitive markers of cervical cord injury, and that ADC values showed significant changes at the level of injury. One practical limitation in patients with multiple

**DTI in spinal cord-injured patients.** The prognosis for neurological recovery of the patient with an acute spinal cord injury can be determined, to a certain extent, from their initial neurological status and MRI findings. However, the literature is ambivalent about the relationship between MRI findings and neurological recovery. With the exception of cord transection and large-segment haemorrhage, MRI does not give any particular insight into the extent and severity of neuronal injury sustained in the patient with a spinal cord injury.

Experimental studies in animals have shown that DTI can differentiate interrupted nerve fibre tracts from intact regions. In an experimental study on calf spinal cord specimens, the authors were able to show disruption of spinal cord tracts at the level of injury, whereas conventional MRI could only show changes in signal intensity. The FA and ADC values also showed significant changes, which suggested abnormal diffusion patterns at the site of the injury (Fig. 6). Fujiyoshi et al, in an animal study, reported the effective use of tractography to image both intact and surgically disrupted spinal long tracts in adult common marmosets. DTI clearly illustrated the corticospinal tract in the control animals and the severed long tracts in the injured animals. Shanmuganathan et al investigated DTI in patients with cervical cord injury and concluded that DTI indices are sensitive markers of cervical cord injury, and that ADC values showed significant changes at the level of injury. One practical limitation in patients with multiple

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**Fig. 10a** – sagittal MRI scan of a patient with burst fracture of the cervical spine and complete neurological deficit. MRI shows cord compression and intraparenchymal haemorrhage. **Fig. 10b** – DTI tractography shows complete interruption of nerve fibre tracking below the level of injury consistent with the complete neurological deficit of the patient.

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The entire sequence we use (single-shot echo planar imaging) takes between 10 and 12 minutes; the patient is asked to breathe calmly and avoid movements of the trunk and frequent swallowing. After data acquisition, further processing of DTI images is needed to create tractography images and acquire the DTI indices. There are many types of post-processing software available. We use a Magnetom Symphony (Siemens AG, Munich, Germany).
Injuries is that they tend to move while the scan is being performed, and hence data acquisition can be affected. In clinical practice, the identification of undamaged fibres in patients with a spinal cord injury may help the surgeon predict their neurological recovery (Fig. 10). Similarly, the identification of subtle cord changes due to mild compression in patients with a cervical myelopathy may, in future, indicate the need for earlier surgery. Although complete and incomplete spinal cord injuries can be differentiated using DTI tractography, the available information is currently too limited to support or refute early surgery.

After surgical decompression, a DTI scan can be performed to assess improvements in the integrity of nerve fibres. In patients who have undergone stabilisation of the spine, the presence of titanium screws posteriorly in the lateral masses or pedicles interferes with the quality of images acquired. However, adequate imaging is possible if anterior cervical plating has been performed.

Conclusions
DTI provides useful information about the direction of fibres and the diffusion anisotropy properties of neural tissue and complements the information obtained by conventional MRI. While matter fibre tracking in the brain is being used to help diagnose various clinical conditions, but its exact application in spinal imaging is largely unexplored. In future, fibre tracking and DTI indices may help the surgeon to determine their surgical approach. Correlation between quantitative diffusion measures, such as FA and ADC, and acute and chronic injuries of the spinal cord may be useful to predict outcome and monitor the response to treatment.

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References