A primer on diffusion tensor imaging of anatomical substructures

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In this article, the authors review the application of diffusion tensor (DT) magnetic resonance (MR) imaging to demonstrate anatomical substructures that cannot be resolved by conventional structural imaging. They review the physical basis of DT imaging and provide illustrative anatomical examples. The DT imaging technique measures the self-diffusion, or random thermal motion, of the endogenous water in nerve tissue. Because of the preferred diffusion of water molecules along the nerve fiber direction, DT imaging can measure the orientation of the neural fiber structure within each voxel of the MR image. The fiber orientation information yielded by DT imaging provides a new contrast mechanism that can be used to resolve images of anatomical substructures that cannot otherwise be visualized using conventional structural imaging. The authors illustrate how DT imaging can resolve individual pathways in the brainstem as well as individual nuclei of the thalamus and conclude by describing potential applications in neurosurgery.

KEY WORDS • diffusion tensor imaging • trigeminal nerve • brainstem • thalamus

Since the advent of DT imaging in the early 1990s,[2,20,26] the technique has generated a tremendous amount of interest in the clinical and laboratory domains. This modality measures the random thermal displacement (that is, Browian motion) of molecules in tissue, typically water molecules. Two aspects of DT imaging render the modality very powerful. First, the microscopic lengthscale of water diffusion in tissue gives DT imaging microscopic spatial sensitivity. Second, in fibrous tissues, such as cerebral white matter or organized gray matter, the diffusion is anisotropic, that is, orientation dependent. The orientation dependence of the diffusion signal enables DT imaging to measure the fiber orientation within each voxel of the image.

DIFFUSION TENSOR IMAGING

The relative contribution of the various cellular and subcellular components to diffusion anisotropy is not completely understood and represents an active area of research. Myelin is thought to be one of the most significant contributors to diffusion anisotropy because of the diffusion barrier imposed by the lipid bilayer. Myelin, however, is not an obligatory requirement for diffusion anisotropy. Beaulieu and Allen[4] showed that the trigeminal, optical, and olfactory nerves in garfish presented significant anisotropy equivalent to humans despite the nonmyelination of the olfactory nerve, suggesting that the dense packing of axons, as well as the axonal structures such as membranes, microtubules, neurofilaments, and microfilaments may contribute to the anisotropy. In addition to structural components, there are other metabolic mechanisms that may contribute to the diffusion anisotropy, including axonal transport and cytosolic streaming.[3]

For isotropic, orientation-independent diffusion, such as that occurring in cerebrospinal fluid, the diffusion can be described in terms of the apparent diffusion coefficient.

For anisotropic, orientation-dependent diffusion, however, the diffusion is described through the diffusion tensor "D." The direction of greatest diffusion is given by the principal eigenvector "e_1" of the diffusion tensor. As the direction of greatest diffusion, the principal eigenvector parallels the local fiber direction within each voxel. The principal eigenvector maps, which display the fiber orientation, can be visualized as vector-field or color-coded maps. To visualize the fiber direction map in the context of a conventional structural image, the fiber map can be registered to and superimposed on a structural image, such as a high-resolution T_1-weighted MR image. In Figure 1, a mosaic of color-coded DT image maps superimposed on the MPRAGE structural image obtained in the same patient is shown. The DT image map was registered to the MPRAGE images by using the Functional Linear Imaging Registration Tool,[17] which is distributed

Abbreviations used in this paper: DT = diffusion tensor; MPRAGE = magnetization-prepared rapid-acquisition gradient-echo; MR = magnetic resonance; MS = multiple sclerosis.

by the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain. In registering the DT image to the structural images, the tensors were also reoriented to account for the different slice orientations of the two different images. The fiber orientation information provided by color-coded DT imaging maps can be used to differentiate among nerve fiber pathways. Further, the fiber orientation maps can delineate anatomical substructures based on their distinct fiber architecture.

Although a promising neuroimaging technique, there are few caveats to consider when using this modality. In regions of intravoxel fiber crossing, the fiber vector represents a partial volume mean and therefore does not reflect the underlying fiber structure. To resolve this partial volume effect, novel approaches such as high angular resolution diffusion imaging are being developed.[13,30] Another restriction of DT imaging is sensitivity to motion, including pulsatile cardiac and respiratory motion. Additionally, echo planar imaging– based DT imaging is hindered by susceptibility distortions at the proximity of the skull base and air-filled spaces, such as in the case of the trigeminal nerve root and brainstem. Such susceptibility distortions can be eliminated using non–echo planar imaging sequences, which improve localization of the cranial nerves.[18]

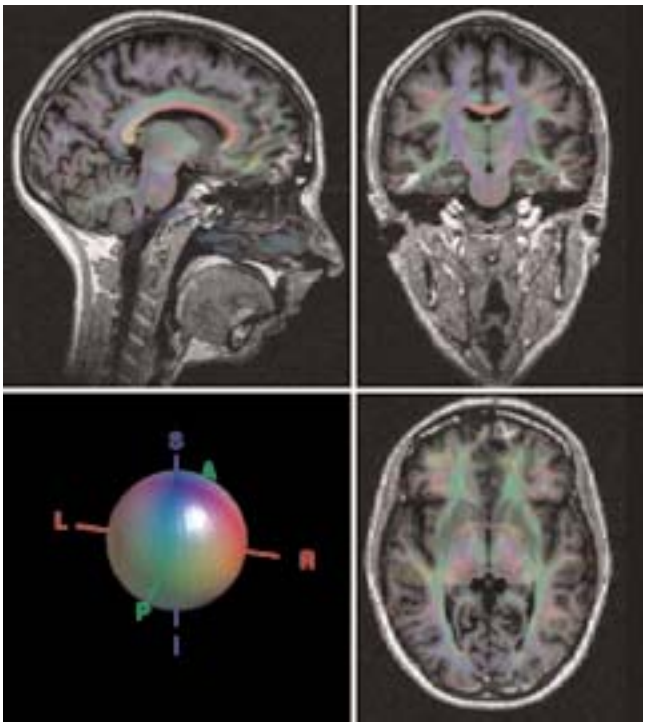

Fig. 1. Color-coded DT image map superimposed on a high-resolution anatomical image. The DT image map is rendered in the sagittal *(upper left)*, coronal *(upper right)*, and axial *(lower right)* planes. The color coding depicts the local fiber orientation (that is, the principal eigenvector of the diffusion tensor) with *red* indicating mediolateral, *green* anteroposterior, and *blue* superoinferior. The color coding is also indicated by the *red-green-blue* sphere *(lower left)*. The DT imaging data were collected with a twice-refocused balanced echo sequence (b = 700 second/mm^2, isotropic 1.8-mm resolution). The MPRAGE anatomical image was acquired using isotropic 1-mm resolution.

Anatomical Substructure in the Brainstem and Thalamus

To illustrate the ability of DT imaging to demonstrate anatomical substructure, we provide examples from the brainstem and the thalamus.

Brainstem. The brainstem contains several ascending and descending tracts between the spinal cord and the forebrain, and it relays afferent and efferent neuronal fibers through several nuclei. These nuclei also receive inputs from the cranial nerves. The trigeminal nerve can be demonstrated on DT imaging, along the projection of the nerve root from the trigeminal ganglion to the brainstem (Fig. 2). At the insertion to the brainstem, the trigeminal fibers connect to the mesencephalic, motor, main sensory, and spinal trigeminal brainstem nuclei.[9,27] Using DT imaging, Mamata and colleagues[22] were able to reveal the subsequent tracts, including the trigeminothalamic and spinothalamic tracts, conveying the sensory information to the forebrain. In another study, using three-dimensional-guided quantitative and tracking analysis, Stieltjes, et al.,[29] distinguished the corticospinal tract, the medial lemniscus, and the superior, medial, and inferior cerebellar peduncles.

Potential Applications in the Brainstem. The ability to resolve images of anatomical substructure in the brainstem with DT imaging will help localize surgical targets with respect to specific tracts or nuclei. For example, DT imaging may be able to identify the trigeminal subnucle-

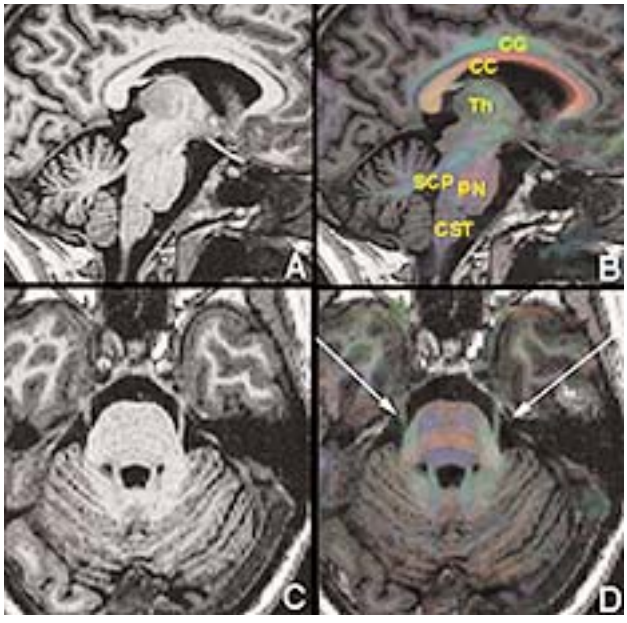

Fig. 2. Color-coded DT image map superimposed on high-resolution anatomical image. The directional color coding is the same as that in Fig. 1. A and B: A parasagittal structural image (A) and the corresponding DT image map (B) from the brainstem are shown. C and D: An axial structural image (C) and the corresponding DT image map (D) are shown for comparison. The trigeminal roots are indicated by the *white arrows*. The superior cerebellar peduncle pathways (green) can also be seen on the posterior aspect of the pons. CC = corpus callosum; CG = cingulate gyrus; CST = corticospinal tract; PN = pontine nucleus; SCP = superior cerebellar peduncle; Th = thalamus.

us caudalis, which is a target for ablation in cases of trigeminal chronic pain. In cases of trigeminal neuralgia, in which the origin is believed by some to be vascular compression of the trigeminal root at the level of the pons,[21] DT imaging may be able to depict the compression-induced fiber displacement. Evaluation of the affected tissue obtained from biopsy samples of the nerve root obtained during microvascular decompression in trigeminal neuralgia has shown different levels of axonopathies and myelin irregularities in addition to proliferation of collagen.[11] Other than vascular compression, tumors and MS lesions are known to reproduce symptoms of typical and atypical trigeminal neuralgias and dysfunctions depending on their location in the trigeminal sensory system.[1,7,24] Therefore, it is reasonable to predict that the measurement and mapping of changes in the diffusion anisotropy for different portions of the trigeminal system can supply additional information pertaining to the differential diagnosis of trigeminal neuropathies.

In diagnosing trigeminal neuralgia, it is essential to exclude a diagnosis of MS,[25] especially in young patients. The authors of some studies have shown a decrease in the diffusion anisotropy and an increase in the mean diffusivity of MS lesions of different phases, including relapsing–remitting and progressive phases.[8,12] Because active MS lesions may induce distal degenerative changes in white matter not conventionally detected on MR imaging[5] (normal-appearing white matter), DT imaging can be used to demonstrate the real extension of the axonal damage.

Thalamus. In the thalamus, pathways responsible for sensory, motor, and cognitive processing are organized into distinct nuclei. These nuclei can be differentiated based on their distinct histological features but cannot be distinguished on conventional MR images. Recently, Wiegell and colleagues[31] have shown that DT imaging can resolve individual thalamic nuclei based on their characteristic fiber orientations. Using an automated clustering algorithm, they extracted 14 hemispheric thalamic nuclei and subnuclei. The anatomical parcellation results corresponded with previous histology-based descriptions of the nuclei. Figure 3 provides a comparison of an axial structural MPRAGE image and a DT imaging image at the level of the thalamus. Whereas little discernible thalamic substructure can be seen on the MPRAGE image, the DT image reveals the nuclear organization based on fiber orientation.

Potential Applications in the Thalamus. Localization of thalamic nuclei based on fiber architecture will provide for more accurate surgery in the thalamic region. This would be especially useful for preoperative planning of ablative or electrical stimulation neurosurgeries in which different substructures are targeted, such as the ventral posterior nucleus for chronic pain disorders,[19] subthalamic nuclei for Parkinson disease[10] and epilepsy,[6] posterior hypothalamus for cluster headache,[14] and internal capsule for obsessive–compulsive disorder.[15]

Other Applications of DT Imaging in Preop Planning

The sensitivity of DT imaging to fiber orientation and density can facilitate the differential diagnosis of tumors. In particular, DT imaging has been used to quantify mass-induced fiber reorientation and/or compression.[16] Additionally, DT imaging can demonstrate compression effects due to vascular malformations. Wieshmann and colleagues[33] reported that DT images demonstrated the displacement of nearby healthy structures due to a low-grade glioma in the frontal lobe without degeneration of the fibers, which was in agreement with the clinical findings. In another report of two different cases of anaplastic astrocytoma, the DT color-coded images were used to characterize displacement and infiltration of nearby white matter.[23] In a larger study of nine patients with high-grade cerebral glioblastoma, Sinha and colleagues[28] reported that mean diffusion, but not diffusion anisotropy, was significantly helpful for the delineation of the tumor margins, its consequent edema, and the surrounding healthy white matter. The same results were achieved in patients with brain tumor after dexamethasone treatment, and a significant decrease in the mean diffusion of the tumor and edema area was also found. Although the authors of another DT imaging study identified reduced anisotropy in different brain tumors, including meningioma, hypothalamic hamartoma, and glioma compared with control individuals,[32] additional studies are needed to enhance the power of DT imaging to define precisely the boundaries between tumors and healthy tissue.

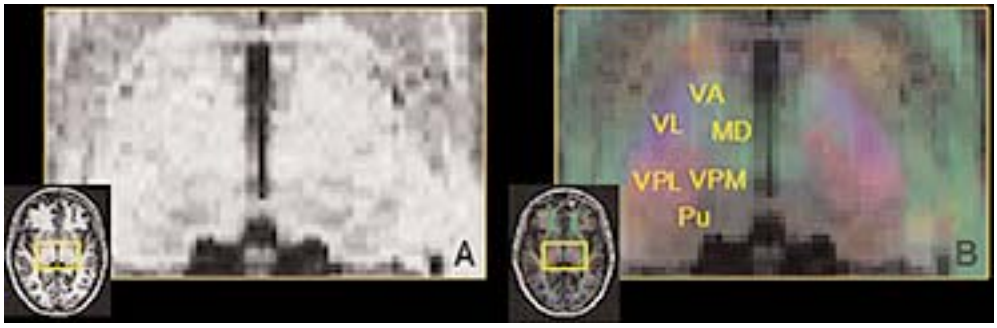

Fig. 3. An axial MPRAGE structural image (A) and the corresponding color coded DT image (B) are shown for comparison. The directional color coding is the same as that in Fig. 1. The region of interest is taken from the *yellow box* shown in the whole slice image in the lower left corner. On the MPRAGE, the thalamus appears homogeneous, whereas the DT image map demonstrates significant substructure. The thalamic nuclei have been labeled according to their anatomical position and fiber orientation. MD = mediodorsal; Pu = pulvinar; VA = ventral anterior; VL = ventrolateral; VPL = ventral posterolateral; VPM = ventral posteromedial.

CONCLUSIONS

Recent advances in DT imaging promise a revolution in MR imaging for presurgical planning. This modality will increase our capacity to identify anatomical substructures that cannot be visualized by other existing neuroimaging tools. Furthermore, as we have illustrated here, visualization of DT fiber direction maps in the context of structural images provides enhanced localization of anatomical substructures. Last, the microscopic sensitivity of DT imaging will benefit the noninvasive assessment of the microstructural aspects of brain lesions.

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