Clinical Applications of Diffusion Tensor Imaging

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Key words
- Advanced MR imaging
- Clinical applications
- Diffusion tensor imaging, DTI

Abbreviations and Acronyms
AD: Alzheimer disease
ADC: Apparent diffusion coefficient
DAI: Diffuse axonal injury
DES: Direct cortical and subcortical electrical stimulation
DSI: Diffusion spectrum imaging
DTI: Diffusion tensor imaging
DWI: Diffusion-weighted imaging
EPI: Echo planar imaging
FA: Fractional anisotropy
HARDI: High-angular resolution diffusion-weighted imaging
HV: Hippocampal volumes
MCI: Mild cognitive impairment
MD: Mean diffusivity
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
NAWM: Normal-appearing white matter
ROI: Region of interest
TBI: Traumatic brain injury
T1WI: T1-weighted Imaging


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Advancements in diffusion-weighted imaging during the past decade have led to the use of diffusion tensor imaging to further characterize the structural integrity of neural tissue and to noninvasively trace neuronal tracts in the brain and spine. This has led to many clinical applications that have aided in surgical planning for brain and spinal cord tumors and has increased the diagnostic potential of magnetic resonance imaging in disorders such as multiple sclerosis, Alzheimer disease, and traumatic brain injury.

BASIC PRINCIPLES

Diffusion-weight imaging (DWI) relies on proton diffusion as a contrast-determining parameter in magnetic resonance imaging (MRI). In DWI, a spin-echo sequence with a pair of strong diffusion-weighted gradients is used, known as the Stejskal-Tanner pulse sequence (120). The diffusion-weighting applied is dependent on multiple factors represented by the diffusion attenuation factor or b-value. A conventional DWI sequence evaluates diffusion in all directions. In contradistinction, diffusion tensor imaging (DTI) evaluates diffusion in multiple different directions (represented by vectors with magnitude and direction) to investigate the three-dimensional microanatomical structure of brain parenchyma. Each point of the imaged tissue is mathematically represented as a multidimensional diffusion vector that is known as a diffusion tensor. In pure water or cerebrospinal fluid, the diffusion of protons is unrestricted in all directions, and therefore isotropic, often represented as a spherical tensor (Figure 1). In highly organized biological tissue, diffusion often is restricted in some directions or anisotropic. The diffusion coefficient is different when measured along different directions and may be represented by an elongated ellipsoid tensor (Figure 1). Anisotropic diffusion is seen within white matter tracts where diffusion is greater parallel to fiber tracts and lower perpendicular to fiber tracts. Basser et al. (8, 9) modeled diffusion as a three-dimensional Gaussian distribution which can be represented as a rank 2 tensor. To estimate this model a minimum of six DWI acquisitions along noncolinear gradient directions is needed; however, in clinical practice more than six directions are often acquired to improve the estimation of the diffusion tensor. The diffusion tensor can be fully characterized by calculating its "eigenvalues" (λ_1, λ_2, and λ_3), which describe the length of the three axes of the ellipsoid, and their corresponding "eigenvectors" (ϵ_1, ϵ_2, and ϵ_3), which describe the orientation of these axes in space. The eigenvectors provide information about the direction of maximum diffusion within a voxel (longitudinal eigenvector ϵ_1) and are the basis for three-dimensional fiber tracking (10, 89). From the eigenvalues, the mean diffusivity (MD), or trace of the diffusion tensor matrix, is calculated. The most commonly used measure for diffusion anisotropy is fractional anisotropy (FA), which is calculated from the eigenvalues and gives a normalized value to the tensor's degree of anisotropy (0 is completely isotropic and 1 is completely anisotropic). Diffusion tensors are commonly visualized with color encoded FA maps, which display fiber orientation with three standard colors: red (transverse), blue (craniocaudal), and green (anteroposterior).

The tensor model for diffusion is a simplified model that assumes a Gaussian distribution of proton displacement. Techniques such as high-angular resolution diffusion-weighted imaging (HARDI) (45, 46) and Q-ball imaging (128) have been used to better characterize the complex interplay of structures within a voxel such as merging or crossing fiber tracts that result in a non-Gaussian diffusion (77). Diffusion spectrum imaging (DSI) allows for even more accurate characterization of diffusion as represented by displacement probability density function. In addition to overcoming DTI associated artifacts, DSI and HARDI are capable of more precise and detailed characterization of white matter fibers that allow for advanced analysis of cerebral white matter and computation of structural networks. Although DSI is a valuable technique in MR connectomics research, it is not currently in clinical use as it requires high-performance hardware and very long acquisition times (52). Hardware and time limitations have

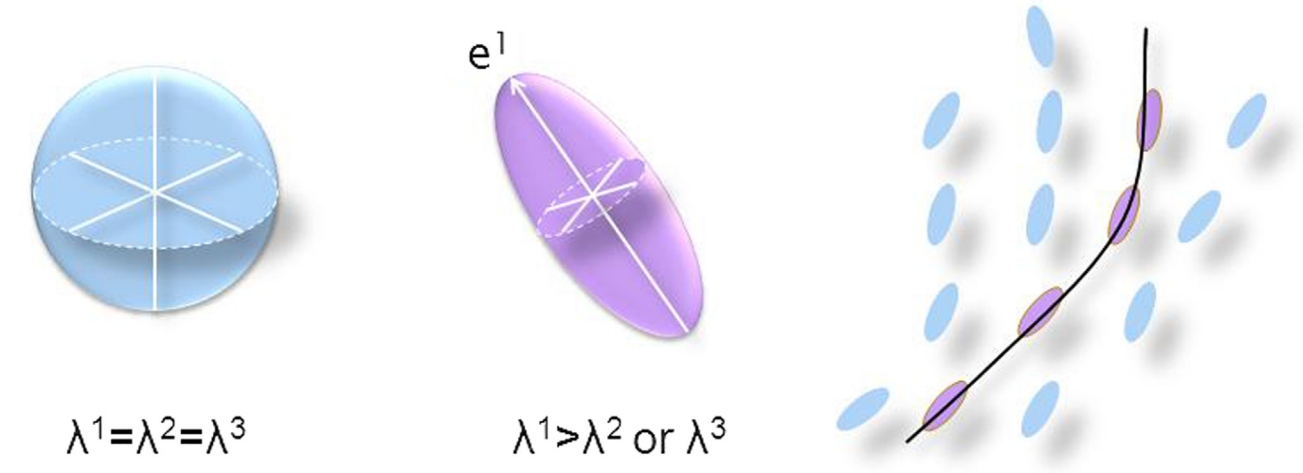

Figure 1. Diffusion ellipsoid tensors and fiber assignment by continuous tracking. (**A**) Unrestricted, isotropic diffusion is represented as a sphere as all of the eigenvalues (λ) or diffusion coefficients are equal, so there is no directionality and the fractional anisotropy (FA) is zero. (**B**) In biologic tissue, diffusion is often anisotropic, and the diffusion coefficient is different when measured along different directions. FA is calculated from the eigenvectors (e1) and measures the fraction of the magnitude of the diffusion tensor that is anisotropic and its directionality, which is often illustrated as an ellipsoid. (**C**) Fiber tracking is initiated at a pixel or region of interest (ROI) and tracking is propagated along adjacent ellipsoids that meet certain thresholds for FA and trajectory curvature.

also precluded widespread use of HARDI and Q-ball for clinical applications; however, recent technical advancements and increased adaptation of high-performance hardware give hope for future inclusion of these techniques in clinical practice.

DTI-based tractography techniques can be classified broadly into two methods: deterministic and probabilistic (138). Deterministic algorithms, such as fiber assignment by continuous tracking, were the first to be introduced and remain the most widely used. In deterministic techniques, a starting or "seed" point is designated in three-dimensional space and tracking is terminated when "stop criteria," such as a pixel with low FA or a predetermined trajectory angle between two contiguous vectors is attained. A distinct limitation of most deterministic algorithms is the inability to produce more than one reconstructed trajectory per seed point. Researchers are investigating methods of overcoming this limitation (113).

Probabilistic tractography techniques incorporate uncertainty of fiber direction to create a probabilistic map of "likely" tracts, which has the benefit of allowing for branching fibers. For neurosurgical planning purposes, the probabilistic method has some limitations (11). First, it cannot be used interactively because of the greatly increased computational complexity compared with deterministic methods. Second, rather than creating discrete geometric pathways, the probabilistic method creates a three-dimensional volume of potential connectivities that may leak into unexpected regions of the brain. This makes visual interpretation of fibers more difficult and requires judgment to determine relevance.

A major factor that must be considered when using tractography is the lack of robust clinical validation. It is likely that the deterministic algorithm may underestimate the fiber tracts visualized (69). Although the probabilistic technique appears to have the potential to address this limitation, this has yet to be proven.

CHALLENGES

Phase effects resulting from coherent macroscopic or bulk motion present a great technical challenge for DWI. DWI pulse sequences must be sensitive to microscopic molecular motion, but this sensitivity also causes signal loss, phase changes, and ultimately ghost artifacts when there is any motion from either cardiac pulsatility or patient movement during the diffusion-encoding periods. Single-shot methods, such as single-shot echo planar imaging (EPI), are used to prevent phase variation between shots and decrease ghost artifact (6). In addition, single-shot EPI has extremely fast image formation capability, which is needed when more than a thousand images are acquired for DTI. Disadvantages of EPI include its lower spatial resolution (~128 × 128), image blurring, geometric distortions, and signal loss at interfaces of tissue and air due to magnetic field inhomogeneity (37). As field strength increases, these artifacts become more apparent. Eddy currents produced by rapid switching of diffusion-encoding gradients cause local field changes, which can result in misregistration of individual images. These effects are reduced by modifying DWI pulse sequences (103) or by registration-based postprocessing methods (1, 53). In addition, other imaging techniques, such as parallel imaging and the PROPELLER technique, offer potential solutions for these problems (4, 6, 7, 99, 132).

Reproducibility of DTI metrics also has been recognized as a significant limitation in clinical and research applications of this technique. DTI metrics may vary when