

IMAGING THE BRAIN'S HIGHWAYS—DIFFUSION TENSOR IMAGING IN EPILEPSY

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Diffusion tensor imaging evaluates the motion of water at the voxel level and can provide data on the structural integrity of brain tissue, with quantitative measures of diffusion and fractional anisotropy. Imaging of the orientation of preferential diffusion of water in the brain can visualize major white matter pathways and infer the structural basis of cerebral networks. Thus, how these pathways and networks may be altered in specific epilepsy syndromes and in consequence to therapies can be assessed with the aid of these images.

The Principles of Diffusion Tensor Imaging

The diffusion of water in the brain is limited by intra- and extracellular boundaries, including membranes, macromolecules, and microcirculatory effects. In diffusion-weighted imaging, images are sensitized to the diffusion of water by adding pulsed magnetic field gradients into a standard spin echo sequence (1). It was soon found that apparent diffusion coefficient measurements depended on a subject's orientation relative to the magnet and gradient coils, giving rise to the concept of anisotropy of diffusion in three directions (2).

Diffusion tensor imaging quantifies the diffusion of water and characterizes the degree and direction of anisotropy (3). The diffusion tensor can be calculated from a nondiffusion-weighted image, plus six or more diffusion-weighted measurements, along noncollinear directions. It can give three eigenvectors, ε_1 , ε_2 , and ε_3 , representing the principal directions of diffusion and three eigenvalues, λ_1 , λ_2 , and λ_3 , representing the magnitude of diffusion along these directions. Mean diffusivity is a summary measure of the average diffusion in a

voxel and is equivalent to the estimated apparent diffusion coefficient over three orthogonal directions. Fractional anisotropy estimates the proportion of the magnitude of the diffusion tensor that is anisotropic. Parametric maps of these data can be constructed and compared between individuals or populations.

The anisotropy of diffusion is very variable in cerebral tissue because of many factors, including the concentration of macromolecules, organelles, density of nerve fibers and glia, the degree of myelination, and fiber diameter (4). In white matter, anisotropy primarily results from parallel bundles of axons and myelin sheaths, and water can diffuse more freely along the long axis of the fibers than perpendicularly. Congenital and acquired lesions disrupt the microstructural environment, which commonly results in reduced anisotropy and increased mean diffusivity.

Peri- and Postictal Changes in Diffusion

Seizures generally result in early postictal depression, followed by normalization, and then transient or chronic elevation of mean diffusivity (5). The early decline in diffusivity in prolonged seizures is thought to reflect cytotoxic edema (6). Seizures cause increased membrane ion permeability, leading to an influx of sodium, calcium, and water that cannot be compensated for by an energy deficient sodium–potassium ion ATP pump. Vasogenic edema also has been reported in subcortical white matter (7). Animal studies have demonstrated that seizures can trigger breakdown of the blood–brain barrier. This outcome, together with local vasodilatory effects, can give rise to vasogenic edema as well as an increase in intercellular space and diffusivity (8). Excitotoxic mechanisms eventually lead to cell lysis and death, which result in increased extracellular space and increased diffusion (9).

In status epilepticus, cytotoxic and vasogenic edema occurs, along with reductions of cortical diffusivity (10). In patients with complex partial status epilepticus, a correlation was identified between focal swelling and an increased signal on T_2 -weighted images, with reduced diffusivity and hyperperfusion (11). Diffusion changes often were more widespread, possibly indicating involved networks and secondary spread (12). Several studies of diffusion imaging following single seizures have been performed. The interpretation of these studies is limited by small numbers of heterogeneous patients, varying methods of analysis, lack of follow-up scanning, as well as by wide variations in the duration of seizures and of the interval from seizure to scan. In patients with focal epilepsy, postictal decreases were found in 52% seizures, but mean diffusivity increased after 17%. Postictal changes in mean diffusivity were often found

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distant to the putative seizure focus, inferring involvement of a widespread epileptic network. Repeated postictal scans showed a gradual return to baseline for both the increases and decreases in mean diffusivity (13). Reduced postictal apparent diffusion coefficient has been found in hippocampi and parahippocampal gyri, ipsilateral to the seizure onset, in patients with refractory temporal lobe epilepsy (TLE) (14). These studies suggest that the diffusion changes visualized with MRI after single seizures are more transient than those after status epilepticus and have a complex distribution and evolution of change. Technological advancements, such as real-time motion correction, open access scanners, and fast acquisitions, may overcome these limitations and result in postictal diffusion MRI becoming a useful clinical tool.

Interictal Studies

Diffusivity is increased in sclerotic hippocampi and in those patients who undergo surgery; thus, apparent diffusion coefficient measures may be a useful postoperative prognostic indicator (15). Anisotropy also is abnormal in hippocampal sclerosis, but to a lesser magnitude than mean diffusivity changes (16). Diffusion abnormalities have been found in hippocampi ipsilateral to seizure onset, which are normal on conventional MRI, suggesting that diffusion MRI may be more sensitive in identifying abnormal hippocampi than standard MRI sequences (17). Studies of normal appearing tissue in TLE patients have demonstrated bilateral and extratemporal abnormalities (18,19), indicative of structural or functional abnormalities that may extend beyond the seizure onset zone in TLE associated with hippocampal sclerosis. Voxel-based analysis of whole brain diffusion tensor imaging has shown extensive changes in patients with TLE with hippocampal sclerosis, principally in the ipsilateral temporal lobe and the limbic system but also in the arcuate fasciculus, the ipsilateral frontal lobe, and contralateral temporal lobe (20).

Diffusion tensor imaging also is sensitive to neocortical pathologies that underlie epilepsy. Areas of increased mean diffusivity and decreased fractional anisotropy correlate with abnormalities identified on visual inspection of conventional MRI and also often identify areas of pathology that appear normal on standard MRI (21). Both diffusion tensor imaging measurements and stereoelectroencephalographic recordings have found good spatial concordance between epileptiform activity and diffusivity abnormalities in nearly 50% patients (22,23).

Tractography and Epilepsy

Understanding the configuration of white matter tracts is fundamental to understanding cerebral function. Standard MRI does not identify specific white matter tracts. Tractography is a postacquisition processing extension of diffusion tensor imaging in which the directional information of the diffusion of

water in each voxel is used to infer the orientation of specific white matter tracts. Tractography is the only currently available technique for tracing white matter pathways in vivo. These maps are based on similarities between the diffusion properties of neighboring voxels in terms of shape (quantitative diffusion anisotropy measures) and orientation (principal eigenvector map), and algorithms have been devised to generate white matter tracts (24). Tractography does not trace fibers in the way that injected tracers do but rather visualizes the route of easiest water diffusion. For diffusion tensor imaging, the typical size of imaging voxels is a 2 to 3 millimeter cube, so a single voxel will contain thousands of axons. Most tractography methods assume that fibers in each voxel are described by a single orientation. This approach of course, will be an oversimplification if there are fibers running in different directions within a voxel, and it leads to difficulties with tracking in the event of tracts kissing or crossing. Tractography is an area of intense research and development; improvements are being made in orientational (25) and spatial resolution, in diffusion modeling (26,27), and tractography algorithms (28)—so these difficulties should be minimized.

Once specific pathways are isolated using tractography, the anatomy of the tracts can be visualized qualitatively, and quantitative information, such as volume, anisotropy, and connectivity indices, can be calculated (29). Tracts also can be spatially normalized and combined to generate group maps that indicate the reproducibility of a given tract across a group of subjects (30). Such data can be used to locate and assess the pathophysiological effects of chronic epilepsy on the white matter anatomy, including the structural reorganization of functions, such as language and memory. Tractography can be combined with functional activation studies to delineate white matter tracts connecting eloquent cortex (31,32), which can assist pre-operative planning to reduce the risk of damaging eloquent cortical functions.

Visualization of Language and Memory Networks in Epilepsy

TLE may be associated with disturbance of language functions, including changes in lateralization of language and of material-specific memory; these functions may be further impaired by anterior temporal lobe resection. Anterior temporal lobe resection in the speech-dominant hemisphere is followed by significant language deficits in up to 40% of patients (33) and often by a decline in verbal memory as well. Deficits in visual memory are common following nondominant temporal lobe resection (34). Functional MRI has shown the reorganization of memory (35) and language functions in TLE (36,37). Tractography has the potential to demonstrate the structural reorganization of networks involved in memory and language that mirror changes in cerebral function.

In a combined *f*MRI–tractography study, controls and right-hemisphere TLE patients had a left-lateralized pattern of both language-related activations and associated white matter organization. Left-hemisphere TLE patients showed more symmetrical language activations (with reduced left-hemisphere and increased right-hemisphere white matter pathways) in comparison with both controls and right TLE patients. Structure and function were correlated: subjects with more lateralized functional activation had more lateralized white matter pathways (38). The lateralization of the indices of connectivity for expressive language cortex predicted the development of language deficits after speech-dominant anterior temporal lobe resection (39). The connectivity of the parahippocampal gyrus has been demonstrated using tractography and in TLE: there is a relative reduction of structural connectivity (inferred by tractography) that correlates with memory performance (40).

In patients with unilateral TLE, there are bilateral changes in the fornix and cingulum bundle, with increased mean diffusivity and reduced fractional anisotropy, which is consistent with degeneration of pathways connecting to the hippocampus (41). The evolution of Wallerian degeneration has been shown in the limbic structures after corpus callosotomy (42) and temporal lobe resections (43). These data suggest that tractography-derived quantitative measures may have a significant role to play in the longitudinal evaluation of the effects of epilepsy on the brain and on cognitive functions, such as memory and language, particularly when correlated with neuropsychological measures (44).

Visual Pathways and Preoperative Planning

Visual field defects occur in up to 10% of patients as a result of anterior temporal lobe resection, and in 5% of patients, the defects may be severe enough to preclude obtaining a driving license, despite being seizure free (45). Typically, visual field defects following anterior temporal lobe resection are in the contralateral superior homonymous field, which is due to disruption of Meyer's loop of the optic radiation. The anterior extent of Meyer's loop varies from person to person and cannot be visualized on conventional MRI (46), so the occurrence and extent of a postoperative visual field defect might not be accurately predicted. Tractography can demonstrate the optic radiation (47) and its relationship to structural lesions (48). Tractography also has been used to visualize the optic radiation before and after anterior temporal lobe resection: 1) to demonstrate the disruption of Meyer's loop in a patient who developed a quadrantanopia (49), and 2) to show eloquent subcortical white matter tracts close to neoplasms (50). There are many technical obstacles, particularly the anatomical distortions inherent in echo planar imaging [EPI]-based acquisitions, to be overcome before tractography can be integrated into epilepsy

surgery and before accurate coregistration of preoperative tractography with the T₁-weighted MRI images can be used to guide neurosurgical interventions. Further, intraoperative MRI will allow the correction of the movement of tracts caused by craniotomy, to aid surgical planning and reduce the risks of postoperative deficits.

Conclusion

Diffusion tensor imaging and tractography provide further tools for imaging the brain. The interpretation of inter-, peri-, and postictal diffusion changes is complex but has the potential to improve understanding of seizure physiology and to have some localizing value in patients with focal epilepsy. Tractography produces beguiling images, which need to be interpreted with caution. The method, however, already has shown its potential to increase understanding of the structural and functional changes that occur in TLE. More work is needed to determine the role of tractography in presurgical planning, particularly correlation with *f*MRI of eloquent functions and postoperative findings.

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