Clinical Applications of Diffusion MRI in Epilepsy

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Introduction

Seizures represent abnormal, unregulated discharges of neurons in the brain that disrupt normal function (5% of the population experience at least one seizure before age 80). **Epilepsy** refers to a chronic condition where seizures repeatedly occur in the absence of a reversible systemic cause (~1% of the population suffers from epilepsy). The International League Against Epilepsy (ILAE) criteria for epilepsy include: At least two unprovoked seizures >24 h apart, one unprovoked seizure and a probability of future seizures similar to the general recurrence risk after two unprovoked seizures or diagnosis of an epilepsy syndrome [1–3] (Fig. 43.1). The morbidity and mortality of epilepsy are high. Epilepsy patients have an increased risk of sudden death [4] and epilepsy ranks second only to stroke when comparing years of life lost [5].

MRI plays an important role in the clinical evaluation of epilepsy patients [6]. However, conventional anatomic MRI lacks sensitivity for detecting epileptogenic lesions in a substantial portion of patients ("MRI-negative" epilepsy) and after 40 years of use may be less likely to produce novel insights into disease detection or pathophysiology. Diffusion MRI can be sensitive to both acute nervous tissue water changes associated with excess neuronal activation and to chronic alterations to the functional organization of the tissue from axonal and synaptic loss—these latter changes can lead to further seizure initiation, propagation and synchronization. Diffusion MRI is a sensitive structural imaging method to assess the impact of epilepsy on the in vivo functional organization and connectivity of the hippocampus, cortex, and white matter.

This chapter reviews how diffusion MRI has been applied to different epilepsy disorders. We first provide an overview of the key technical concepts for diffusion MRI and the white matter pathways that are most commonly involved in epilepsy. We review diffusion MRI changes in the peri-ictal state. The bulk of the chapter addresses various applications of diffusion MRI to temporal lobe epilepsy, the most common adult form of epilepsy. The use of diffusion MRI in malformations of cortical development is then considered briefly. Finally, we suggest potential future directions for research of diffusion imaging in epilepsy disorders.

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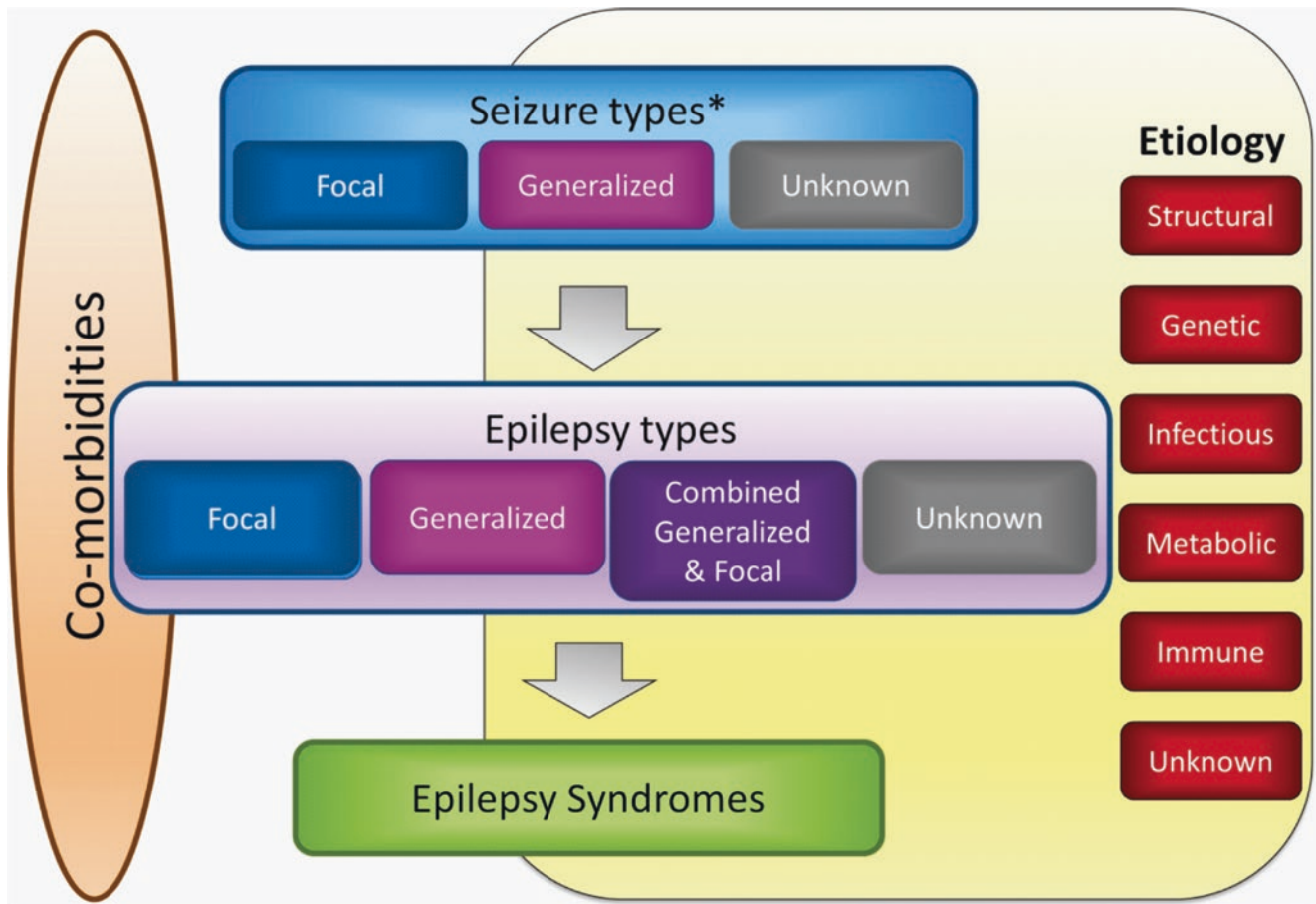e-mail: timothy.shepherd@nyumc.org

Fig. 43.1 Current classification of epilepsies as defined by the International League Against Epilepsy. Adapted with permission from Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521. doi: https://doi.org/10.1111/epi.13709

Fundamental Concepts in Diffusion MRI

In its most simplified form, the addition of two balanced spatially encoding gradients across a spin echo creates an MRI sequence that is sensitive to tissue water diffusion. We review the key concepts for understanding water diffusion observable by MRI in nervous tissue—the more technical details are well described by several reviews for the interested reader [7]. Water molecules in a glass of water will diffuse in a random Brownian motion. In healthy nervous tissue, however, **mean diffusivity** will appear reduced (relative to "free water" or CSF) as water movement is altered when it encounters and interacts with large proteins, organelles and semi-permeable cellular membranes. This "sampling" of the local tissue structure on the mesoscopic length scale by MRI-observable water is the reason diffusion MRI has become so fundamental to clinical neuroradiology. The sensitivity of a diffusion MRI sequence to water diffusion changes is generally determined by the maximum ***b*-value** (a scalar value determined by the size, duration and separation of the diffu-

sion gradients; a typical clinical value is 1000 s/mm^2). In acute pathology, like ischemic stroke, mean diffusivity is reduced—the exact biophysical basis for this is not understood, but attributed to simultaneous dynamic changes in the restrictive properties of cellular membranes, altered tortuosity from macromolecules, and changes associated with water re-distribution between the intra- and extracellular compartments [8]. The use of diffusion MRI to detect reduced diffusivity in ischemic stroke remains its most important clinical application [9]. In chronic pathology (like hippocampal sclerosis), mean diffusivity is increased due to neuron loss, gliosis, extracellular space expansion and a loss of normal tissue organization. Unlike acute changes, chronic diffusion MRI changes correlate better with changes observed by histology. Recent analytical methods using diffusion MRI acquisitions with higher b-values (e.g., 2000 s/mm^2) also can characterize the non-Gaussian diffusion behavior of water molecules in tissue—this diffusion **kurtosis** may be more sensitive than diffusivity for subtle changes to nervous tissue complexity in chronic conditions [10].

Myelin provides a formidable barrier to water movement such that diffusivity will appear much lower transverse to membranes, particularly myelinated axons—this orientation-dependence of water diffusivity is defined as **anisotropy**. Interpretation of diffusion MRI in nervous tissue, particularly in white matter, can be confounded by anisotropy. The diffusion MRI sequence can be made sensitive to water diffusion anisotropy by increasing the number and varying the spatial orientation of the diffusion gradients relative to the brain (increasing the "**angular resolution**"). The orientation-dependence of observed water diffusion within an image voxel in clinical data is most commonly described using a tensor representation (**diffusion tensor imaging**; DTI) that provides measures of mean diffusivity and fractional anisotropy (the latter using a scale between 0 and 1, where that glass of water has a value close to "0" and the densely myelinated corpus callosum approaches "0.8"). A dominant vector orientation for diffusion anisotropy in a voxel is also determined. Algorithms can be created to follow the vector orientations voxel-by-voxel through a 3D image dataset under certain user-defined conditions (e.g., fractional anisotropy remains above 0.3) to create diffusion tractograms that capture large portions of known brain white matter pathways (**diffusion tractography**) [11]. Table 43.1 provides an overview of white matter pathways possibly involved by seizures and epilepsy. Improvements in computational analyses of DTI allows for studies of structural connectivity or "connectomics," and combining DTI with functional imaging has the potential to expand our understanding of large scale networks and connectivity in patients with epilepsy [12, 13] (Fig. 43.2). Over the past 20 years, diffusion MRI acquisition strategies and the analytical representations of the data have become increasing complex with multiple different models of the underlying nervous tissue microstructure that estimate selective properties for the intra- and extracellular volume fractions. The specific models, their assumptions and limitations, and the data supporting their validation are beyond the scope of this review. It should be noted that these models thus far have largely focused on white matter, which is likely easier to model than gray matter structures.

The signal-to-noise is limited in clinical MRI compared to other imaging techniques. In diffusion-weighted MRI, the signal is reduced ~90% between images obtained with b-value of 0 and 1000 s/mm^2. Because of these limitations, clinicians and researchers must choose compromises between the strength of diffusion weighting (resolution in "q-space"), degree of angular resolution and the spatial resolution of the image—this is a key challenge when using diffusion MRI to investigate epilepsy. Further, image discrimination of small temporal lobe structures, the most common lobar substrate for seizures, are particularly confounded by partial volume averaging of the diffusion signal from brain tissue with adjacent isotropic diffusion signal

Table 43.1 Summary of white matter pathways

Tract	Course	Function
Superior longitudinal fasciculus	U-shaped fiber around the sylvian fissure connecting the frontal, parietal and temporal cortices	*Right*—Visuospatial processing *Left*—Language processing
Cingulum	Courses within the cingulate and parahippocampal gyrus to interconnect the ventral temporal lobe, retrosplenial cortex, cingulate cortex, and frontal lobe	Regulation of emotion; long-term consolidation of memories
Fornix	Arises from the alveus and fimbria of the hippocampus and travels ventral to the corpus callosum to connect to the medial thalamus and septal nuclei	Memory function
Uncinate fasciculus	Extends from the ventral portion of the extreme capsule to the claustrum connecting the anterior temporal lobe, amygdala, and hippocampus to the orbitofrontal cortex	Emotional processing, episodic memory consolidation and retrieval
Inferior fronto-occipital fasciculus	Central white matter pathway between the orbitofrontal cortex to the occipital lobe	Possibly reading and visual processing
Inferior longitudinal fasciculus	Central white matter pathway between the temporal lobe to occipital lobe	Visual recognition of faces, objects and written language
Meyer's loop	Extends from the lateral geniculate nucleus to the occipital lobe visual cortex, with three components. The anterior component passes anterior over the temporal horn (Meyer's loop)	Visual sensory information to the visual cortex

from surrounding cerebrospinal fluid. The fornix, a major output of the hippocampus, is poorly resolved even in normal patients with current advanced diffusion MRI resolutions (2-mm isotropic resolution). The fornix is reduced in size ipsilateral to fronto-temporal seizures [14] making partial volume confounds to diffusion MRI data even worse. Some groups have advocated the use of CSF suppression techniques in diffusion MRI [15], but this approach further reduces SNR by up to 30% [16]. A recent study used relatively low diffusion-weighting and limited coverage to obtain 1-mm isotropic diffusion parameter maps of medial temporal lobe structures in controls [17]—presumably such an approach also will be applied to patients with epilepsy in the near future. Simultaneous multislice acquisitions [18] compressed sensing image reconstructions [19] and recent novel image denoising methods [20] should improve our ability to push spatial, angular or q-space resolution for epilepsy investigations in the near future.
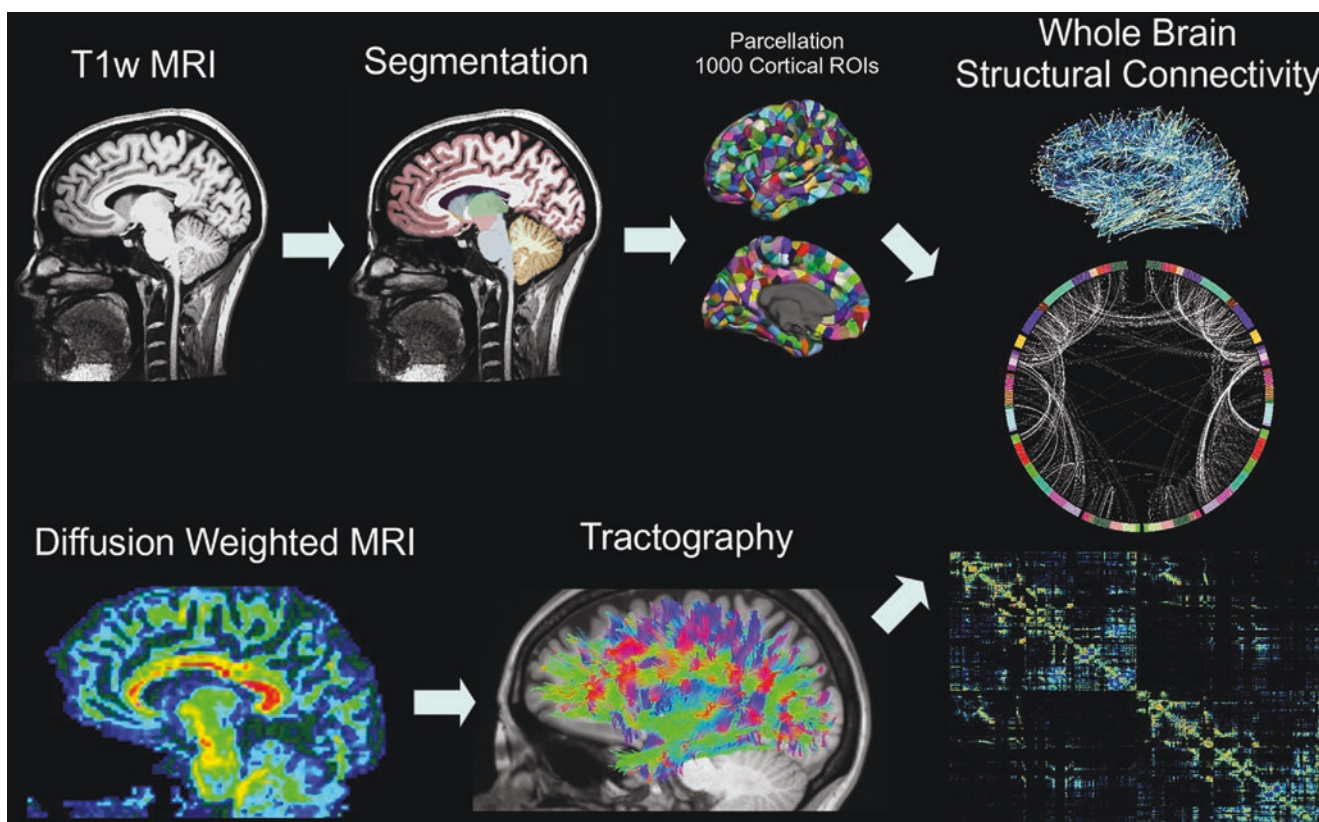
Fig. 43.2 Flowchart that illustrates the steps of connectivity analysis. MP-RAGE sequence is segmented into ROIs, which are then parcellated into cortical and subcortical ROIs. Whole-brain white matter tractography is performed after voxel-wise tensor calculation, and the density of fibers that connect each pair of cortical ROIs is used to calculate structural connectivity. Reproduced with permission from DeSalvo MN, Douw L, Tanaka N, Reinsberger C, Stufflebeam SM. Altered Structural Connectome in Temporal Lobe Epilepsy. *Radiology*. 2014;270(3):842–848. doi: https://doi.org/10.1148/radiol.13131044

Eddy current, patient motion, geometric distortion and low signal-to-noise (SNR) inherent to commonly used echoplanar imaging sequences [7] also create challenges for diffusion MRI characterization of certain parts of the brain frequently involved in seizure disorders. The medial temporal lobes are especially vulnerable to susceptibility-induced blurring and geometric distortion due to air-filled structures within the underlying temporal bones. These artifacts, which partially depend on the number of phase encoding steps and readout duration, can be mitigated to some degree with improved gradient coil performance, partial Fourier acquisition and parallel imaging [21]. Multishot echoplanar imaging (EPI) [22–24] also can significantly reduce distortion at the expense of increased imaging time. 3D and ultrahigh field acquisition methods also have the potential to improve SNR [25]. Periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) is a multishot technique that can be used to decrease susceptibility artifacts [26] with the added benefit of reduced sensitivity to rigid-body patient motion that may help to improve visualization of medial temporal lobe structures [27]. Finally, when whole-brain imaging is not required, reduced field-of-view diffusion (rFOV) imaging can be used to image clinically important medial temporal lobe structures with high spatial resolution [15].

Peri-ictal Diffusion MRI of Seizures

The ionic changes, increased energy demands and increased presence of extracellular glutamate associated with sustained, repetitive electrical activity may lead to the development of cytotoxic edema within nervous tissue in seizures [28, 29] that can be detected as reduced water diffusion using MRI. Diffusion MRI studies of patients suffering from status epilepticus and children with complex febrile seizures (e.g., sustained seizures) have shown reduced diffusivity in a number of brain structures [29–31]. Peri-ictal studies, obtained shortly after a more discrete seizure, present a less consistent pattern, especially in patients with longstanding epilepsy [32–35]. Detection of acute seizure-induced water diffusion changes appears to depend both on the seizure duration and rapid MRI follow-up [32, 36, 37]. Mean diffusivity changes can resolve even within 1–2 h [32, 36]. In patients with uni-

lateral localization-related epilepsy, peri-ictal reduced diffusion may be concordant with epileptogenic lesion localization [30, 35]; however, other studies have suggested limited concordant diffusion and EEG seizure localization [34]. Poor diffusion MRI localization of the seizure focus may be attributed to rapid, widespread involvement of neuronal networks by seizures (similar to what is often observed with EEG). It is impractical to image patients immediately following a seizure; therefore, typical seizure episodes may not be detected with peri-ictal diffusion MRI if they are associated with only transient diffusion changes. With even longer initial follow-up intervals, it appears that most acute seizure-induced diffusion changes have resolved [30, 31, 38]. Less often, changes in water diffusion may progress or be associated with permanent MRI signal changes, particularly if there was excitotoxic injury, such as following prolonged status epilepticus [29]. Peri-ictal reductions in water diffusivity seem to be associated with more severe seizures and suggest increased risk for atrophy on subsequent follow-up imaging [31, 39]. This supports the hypothesis that individual seizure episodes can cause long-term structural damage to the brain.

Diffusion MRI may add to our understanding of the association between complex febrile seizures in children and the subsequent development of temporal lobe epilepsy, the most common adult seizure disorder. A complex seizure lasts greater than 15 min and/or was associated with focal seizure onset or recurrent seizures within 24 h. Between 2% and 8% of children with complex febrile seizures develop epilepsy and 30%–50% of temporal lobe epilepsy patients had complex febrile seizures as children (versus only 6% of the normal population) [40]. Complex febrile seizures can give rise to transient peri-ictal reductions in hippocampal diffusion that progress to atrophy on follow-up imaging months later [31, 39, 41]. Complex febrile seizure patients also do not demonstrate normal age-dependent decreases in hippocampal diffusivity compared to controls at later time points [42]. These data suggest hippocampal damage induced during febrile seizures may progress to hippocampal sclerosis [40] or increase a patient's susceptibility to developing epilepsy by altering normal neuropil and axonal organization in the hippocampus during development [40]. DTI of children following prolonged febrile seizures at 1 and 6 months demonstrate diffusely reduced FA at 1 and 6 months, which normalized at 12 months post seizure [43]. Diffusion MRI 8 years postfebrile seizures found increases in FA in early maturing white matter tracts and increased AD and MD in peripheral white matter tracts that mature later in life [44]. These studies also suggest febrile seizures may affect white matter maturation. Some studies of patients with perinatal injury or familial predilection for febrile seizures suggest that complex febrile seizures occur because the hippocampus was *already* abnormal [40]—if true, diffusion may be able to characterize these differences.

Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most common adult seizure disorder that is often associated with epigastric auras, behavioral arrest, altered consciousness, amnesia and behavioral automatisms [42]. Many TLE patients do not achieve seizure control with medical therapy, but can achieve seizure-free outcomes, or at least significant reduction in seizure frequency and secondary generalization, by unilateral temporal lobectomy [45]. Conventional MRI plays a major role in the identification of mesial temporal sclerosis (MTS) in patients with longstanding TLE. Architectural distortion, T2 prolongation and atrophy on MRI in MTS correlate with gliosis and neuronal loss in several cell layers, granule cell dispersion and mossy fiber sprouting observed on postresection surgical pathology [46]. Medically refractory TLE patients with concordant lateralization by EEG and hippocampal sclerosis on MRI have the highest postresection seizure-free success rates. Preoperative MRI also can sometimes detect "dual pathology," whereby epileptogenic lesions are present beyond the mesial temporal structures in 15% of patients—failure to resect this second lesion diminishes postsurgical seizure freedom or control. Patients with a clinical diagnosis of TLE, but without MTS (or other structural MRI abnormalities) are described as "MRI negative" and have less favorable seizure-control following temporal lobectomy. Applications of diffusion tensor imaging and tractography in the temporal lobe epilepsy patient population have focused on improved characterization (or detection) of the mesial temporal lobe pathology, understanding the impact of TLE on white matter connectivity, and prediction of surgical outcome utilizing these techniques.

Hippocampal Pathology

One of the first applications of diffusion MRI to epilepsy was to characterize hippocampal disease in patients with known temporal lobe epilepsy [47, 48]. Conventional MRI findings in hippocampal sclerosis correlate to relatively macroscopic histological features. T2 prolongation is attributed to gliosis and extracellular space expansion, while hippocampal atrophy and loss of normal architecture on MRI correlates with neuronal loss. Water diffusion and fractional anisotropy measurements in the normal hippocampus and its layers depend on specific cytoarchitectural features of pyramidal and granule cell neurons, their surrounding neuropil, and local axonal connectivity (Fig. 43.3) [49, 50]. These features reflect the specific functional organization of the hippocampus so it is reasonable to hypothesize that diffusion MRI may be more sensitive to early or subtle changes associated with seizures (e.g., granule cell dispersion, mossy fiber sprouting and synaptic loss). Diffusion MRI then might have clinical value for accurate seizure lateralization and localization, as
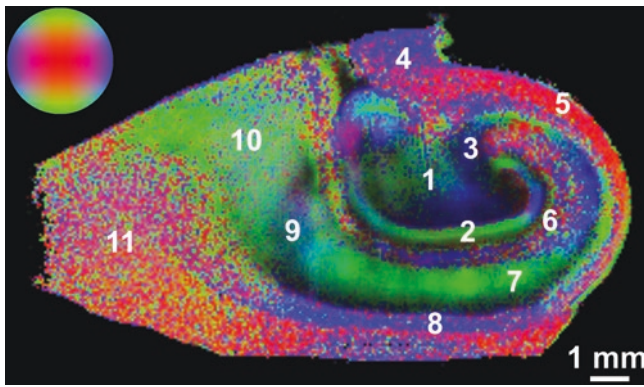
Fig. 43.3 Color fiber orientation map demonstrates the functional cytoarchitectural organization of the ex vivo human hippocampus (1 = hilus, 2 = molecular layer, 3 = mossy fibers, 4 = fimbria, 5 = alveus, 6 = stratum lacunosum-moleculare, 7 = stratum radiatum and pyramidale, 8 = stratum oriens, 9 = prosubiculum, 10 = subiculum, 11 = angular bundle). Developing similar in vivo high-resolution DTI of the hippocampus may increase its specificity and sensitivity for changes related to hippocampal sclerosis and temporal lobe epilepsy. Note, color intensity depends on fractional anisotropy and the color scheme differs from the clinical standard (here, left-right = blue, anterior-posterior = red, and cranio-caudal = green). Reproduced with permission from Shepherd TM, Ozarslan E, Yachnis AT, King MA, Blackband SJ. Diffusion tensor microscopy indicates the cytoarchitectural basis for diffusion anisotropy in the human hippocampus. *AJNR Am J Neuroradiol* 2007 May;28(5):958–964

well as correlating with specific clinical features, functional impairments and prognosis.

In unilateral temporal lobe epilepsy, interictal MRI studies have reported 10%–25% elevations in mean diffusivity in hippocampal sclerosis compared with controls or the contralateral hippocampus [31, 48, 51–57]. Ipsilateral hippocampus FA also is reduced compared to controls or the contralateral hippocampus in unilateral temporal lobe epilepsy patients [36, 52, 57–59]. Reductions in FA in the ipsilateral posterior cingulum and fornix have been identified in patients with MTS [60], as well as the parahippocampal gyrus, bilateral thalami and posterior callosum with connections to the temporal lobe [61]. Increased diffusion and reduced FA within the ipsilateral hippocampus of TLE patients may reflect loss of synaptic complexity and neuronal connectivity, but early studies with low spatial resolution also may have observed such changes just from increase intravoxel contributions from CSF due to hippocampal volume loss [51]. The head, body and tail of the hippocampus have all demonstrated elevated diffusion in unilateral TLE [62], with the anterior portion or hippocampal head demonstrating more substantial changes to diffusion [56] and fractional anisotropy [36]. The amygdala does not demonstrate associated diffusion changes in most TLE patients [56, 63]. Evaluating the dentate gyrus or CA1 region, which are selectively vulnerable to seizure pathology [64], may increase the specificity and/or sensitivity of diffusion MRI for temporal

lobe epilepsy with or without hippocampal sclerosis. Ex-vivo ultra-high field imaging and DTI have elucidated hippocampal organization [65] and demonstrated disruptions in hippocampal connectivity [66] in TLE. A high-resolution 7-T diffusion MRI study also found layer specific changes in MRI negative TLE patients [67] (see further discussion below).

Ipsilateral diffusion changes in hippocampal sclerosis suggest diffusion MRI has the potential to independently lateralize temporal lobe epilepsy. Visual recognition by neuroradiologists for intensity changes or asymmetries in diffusion-weighted images, though, may not be as sensitive as absolute quantification for detecting mean diffusivity abnormalities in temporal lobe epilepsy patients [51, 56]. Our experience also is that B1 heterogeneity, poor fat saturation and skull base artifacts from 3-T MRI can make the medial temporal lobe structures in normal individuals appear asymmetrically bright on both FLAIR and diffusion trace images. Several quantitative studies have demonstrated asymmetric unilateral elevations of hippocampal diffusion above study-specific thresholds can have high sensitivity and specificity (>80%) for correct lateralization in TLE based on semiology and EEG as reference standards [56, 68–70]. Combining machine learning in combination with graph theoretical analysis of diffusion MRI also has recently demonstrated >70% accuracy for correct lateralization of right and left TLE [71]. Diffusion kurtosis imaging, which may be more sensitive to subtle epilepsy-induced reductions to nervous tissue complexity, detected additional differences in TLE patients not captured by conventional DTI [72, 73] (Fig. 43.4). When combined with support vector machine (SVM), diffusion kurtosis outperformed diffusivity and FA when classifying TLE [74]. One would predict that deep learning methods, potentially using diffusion MRI data, also will perform well classifying TLE.

Could diffusion MRI be more sensitive than conventional MRI for structural medial temporal lobe abnormalities underlying temporal lobe epilepsy, particularly in MRI-negative patients? In one study, diffusion was increased and FA reduced compared to controls in one-third of MRI-negative focal epilepsy patients [75]. Similarly, observations of increased ADC without other MRI abnormalities were attributed to early tissue changes in a subset of five TLE patients [76]. More recently, diffusion tensor imaging applied to TLE patients with HS and MRI negative TLE patients have detected decreased FA in the ipsilateral cingulate gyrus and fornix for both groups, with decreased FA in the hippocampus in the MRI negative group [59]. Increased MD also was found in the ipsilateral hippocampus in both groups; however, this was more significantly increased in patients with HS [59]. In contrast, several early studies of MRI-negative TLE patients did not detect significant underlying water diffusion changes [48, 54, 62]. This may have been
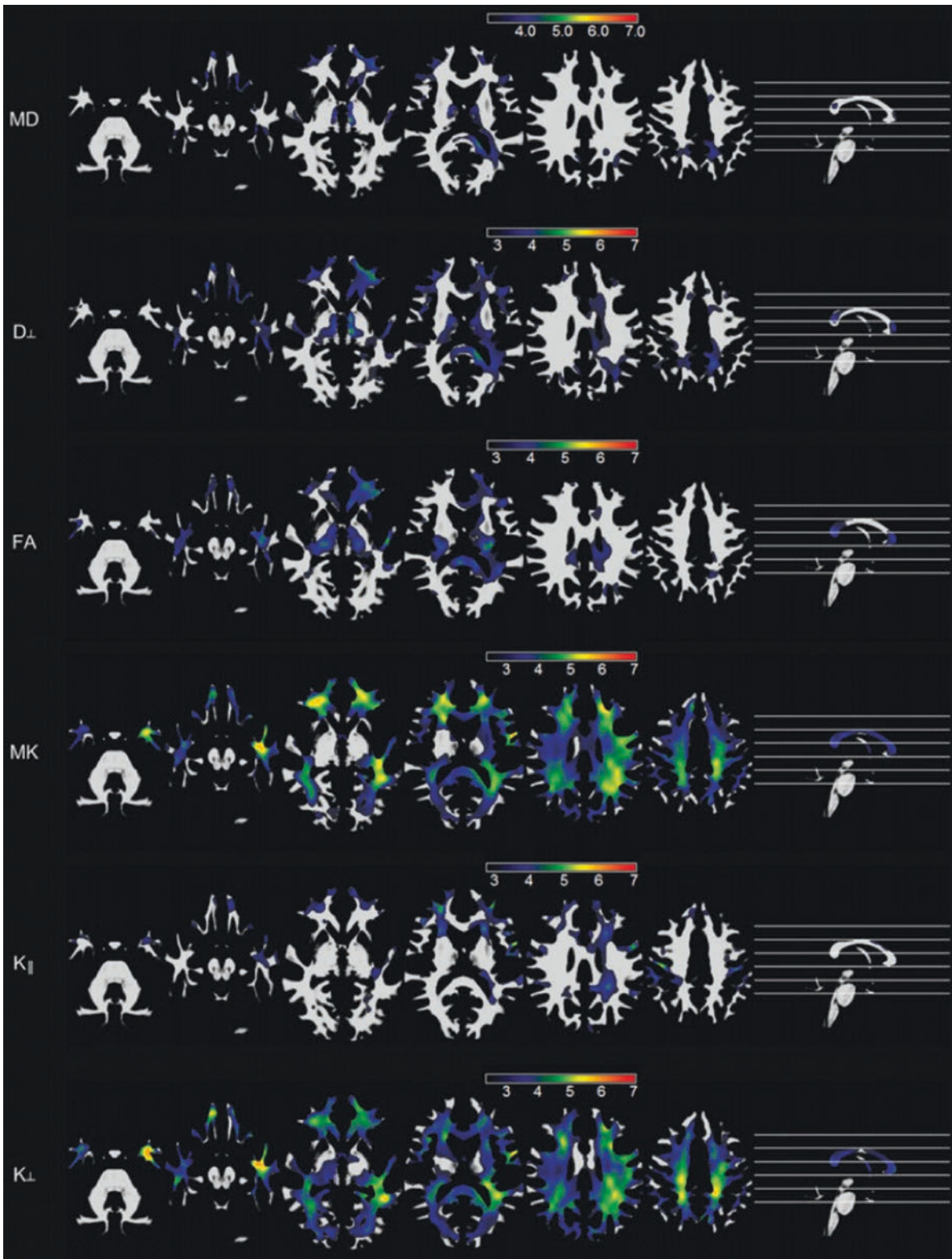
Fig. 43.4 Voxel-wise maps of white matter abnormalities in patients with TLE compared with controls. Statistical maps are overlaid on an average of probabilistic white matter maps from all subjects. The scale bars represent absolute values of t scores. The first and second rows demonstrate areas with an increase in MD and radial diffusion. The third row demonstrates areas with reduced FA in patients, while the fourth, fifth, and sixth rows demonstrate areas of reduced mean kurtosis, axial kurtosis, and radial kurtosis. Reproduced with permission from Bonilha L, Lee CY, Jensen JH, et al. Altered Microstructure in Temporal Lobe Epilepsy: A Diffusional Kurtosis Imaging Study. *American Journal of Neuroradiology*. 2015;36(4):719–724. doi: https://doi.org/10.3174/ajnr.A4185

due to technical and study design limitations at the time; however, publication bias may limit the number of reports that have failed to observe diffusion changes in MRI negative patients and a priori placement of ROIs in known TLE patients limits the external validity of the positive studies. Assessing the sensitivity of diffusion contrast in MRI-negative patients is challenging, since most studies are unable to obtain pathological confirmation of the non-MRI localized epileptogenic lesion. One study reported MRI-negative, diffusion-negative resected hippocampi had gliosis without associated neuron loss [62]—this suggests more substantive tissue changes may be required for detection with diffusion MRI. Recently, high-resolution 7T tractography in patients with MRI-negative TLE demonstrated decreased connectivity in the contralateral CA1 region and subiculum with increased connectivity of ipsilateral subfields such as the subiculum, presubiculum and parasubiculum when compared to controls [67]. Increasing the spatial resolution of diffusion MRI and/or combining it with accurate volumetry (and other quantitative MRI methods) may increase correct localization of MRI-negative TLE patients [77].

Water diffusion changes indicate altered functional organization of the hippocampus and may correlate with certain clinical or prognostic features of TLE. Ipsilateral diffusivity negatively correlated with performance on cognitive tests of recognition and delayed recall [55]. Increased hippocampal diffusivity and reduced FA correlates with increased seizure duration and earlier age at seizure onset [54, 61]. Another interesting result was that TLE patients with the highest ipsilateral hippocampal ADC more frequently reported epigastric sensation auras [57]. Two studies with 40 and 55 patients contradict one another whether increased hippocampal ADC correlated with better temporal lobectomy outcomes [63, 68]. Clinical correlations with diffusion changes in the ipsilateral hippocampus or thalamus may relate to connected neural networks that are involved in seizure epileptogenesis or propagation. In the future, structural connectome studies may help to clarify these seizure networks.

Diffusion changes in the hippocampus also can be associated with increased diffusion in the ipsilateral thalamus [78, 79], parahippocampal gyrus [55, 78], or other temporal lobe structures [57, 78]. Diffusion changes in the contralateral hippocampus of patients with unilateral TLE have been reported as unchanged [52, 78], elevated [51, 62], or decreased [57, 61, 80]. FA also can be reduced in the contralateral hippocampus compared with controls [58]. The counterintuitive reductions in water diffusion reported in the contralateral hippocampus by one group reversed 8 months following resection of the sclerotic, opposite hippocampus, and were attributed to swelling due to neuronal dysfunction without actual cell loss [57, 80]. Other studies have reported bilateral diffusion changes to the adjacent fornix in unilateral TLE patients that did not reverse with surgery [81, 82]. It has been shown that the contralateral hippocampus can demonstrate delayed decline in FA and increase in MD several years after epilepsy surgery, although the clinical significance of this is not yet determined [83]. As diffusion MRI techniques become more sensitive, more changes are observed in more structures—this may reflect the widespread pathology associated with TLE.

White Matter Pathology

Diffusion tensor imaging, diffusion kurtosis and diffusion MRI-based graph theoretical analysis demonstrate widespread white matter abnormalities in TLE patients that are difficult to appreciate using conventional MRI contrast mechanisms (see Table 43.2 for key references). A meta-analysis of diffusion imaging of white matter abnormalities in epilepsy demonstrated that there are greater white matter

Table 43.2 Ten recommended publications for diffusion tensor imaging of patients with epilepsy

Authors	Subjects	Diffusion MRI paradigm	Results
Catani et al. (2008) [84]	22 right-handed male controls	200-direction DTI at 1.5-T with deterministic tractography of multiple white matter pathways	Atlas for virtual in vivo dissection of human brain white matter anatomy. Includes specific instructions and landmarks for reproducibly dissecting specific pathways
Ahmadi et al. (2009) [85]	21 TLE patients (5 negative by conventional MRI) and 21 age-matched controls	51-direction DTI at 1.5-T with probabilistic tractography of multiple white matter pathways	Detailed characterization of white matter differences between patients with right and left TLE. Cingulum and parahippocampal white matter changes also lateralized 90% of patients based on these differences (including 5 of 5 "MRI-negative" patients)
Yogarajah et al. (2009) [86]	21 TLE patients after anterior temporal lobectomy (9 with visual field defects) and 20 controls	52-direction DTI at 3.0-T with probabilistic tractography of Meyer's loop	Probabilistic tractography of the optic radiations demonstrated that distance from tip of Meyer's loop to the temporal pole and the extent of resection help predict postoperative visual field defects

Table 43.2 (continued)

Authors	Subjects	Diffusion MRI paradigm	Results
Concha et al. (2010) [69]	11 TLE patients (6 with hippocampal sclerosis) undergoing temporal lobe resection	6-direction DTI at 1.5-T with fluid-suppression, then deterministic tractography of the fornix	Rare anatomic correlation in the fornix/fimbria pathway of decreased FA on presurgical DTI to axon and myelination changes demonstrated by electron microscopy of the resected samples
Ellmore et al. (2010) [77]	23 epilepsy patients (17 with TLE) undergoing WADA testing for language localization	32-direction DTI at 3.0-T with deterministic tractography of the arcuate fasciculus	Asymmetry in the arcuate fasciculus by DTI tractography concordant with WADA language lateralization in 19 of 23 patients. Adding fMRI activation of Broca's area & handedness improved lateralization to 22 of 23 correct (96%)
Keller et al. (2012) [61]	62 patients with unilateral TLE with HS and 68 healthy controls	60-direction DTI at 3.0 T with tractography of multiple white matter pathways	Microstructural changes observed in TLE with HS may correlate with duration of disorder and age of seizure onset
McDonald et al. (2014) [87]	26 patients with TLE and 35 healthy controls	51-direction DTI at 1.5T with probabilistic tractography of multiple white matter pathways	Combination of hippocampal volume and MD of the inferior longitudinal fasciculus was the strongest predictor of verbal memory
DeSalvo et al. (2015) [13]	24 patients with left TLE and 24 healthy controls undergoing evaluation of whole-brain connectome	60-direction DTI at 3.0T with deterministic tractography and MP-RAGE sequences were acquired. Graph theory network analysis performed for connectivity	Distant connectivity was reduced in patients with TLE compared to controls; however, local connectivity medial and lateral frontal cortices, insular cortex, posterior cingulate cortex, precuneus, and occipital cortex were increased
Bonilha et al. (2015) [73]	32 left TLE patients and 36 health age-matched controls	30-direction DKI at 3.0T with measurement of DKI and DTI parameters of multiple white matter pathways	Diffusion kurtosis imaging (DKI) in temporal lobe epilepsy revealed cortical and gray matter abnormalities that extended beyond previous findings with DTI
Hutchings et al. (2015) [88]	22 patients with left TLE and 39 healthy controls	64-direction DTI at 3.0T with deterministic tractography used in a computational model	Computational models that include DTI data may be predictive of better surgical outcomes

differences in focal epilepsies than generalized epilepsy and that changes were age- and duration-dependent [89]. Both right and left TLE are associated with abnormal white matter diffusion in the corpus callosum [90–93], ipsilateral temporal lobe white matter [68, 94–85], and external capsule [90, 91]. Statistical parametric mapping demonstrated shared diffusion abnormalities in the ipsilateral limbic system and inferior frontal gyrus for either right or left TLE [78]. DTI tractography studies have demonstrated diffusion changes to the uncinate fasciculus [96] and cingulum for both right and left TLE patients [82, 95, 85]. Further, FA is reduced in the ipsilateral inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and arcuate fasciculus for both right and left TLE patients [85]. A study using voxel-based and track-based postprocessing of diffusion images demonstrated changes in the superior longitudinal fasciculus (SLF), ILF, IFOF, and uncinate fasciculi, with differences mainly in fractional anisotropy and radial diffusivity, suggesting that multiple parameters should be used to evaluate for white matter changes in epilepsy [97]. The fornix may [82, 98] or may not [99] be affected in all patients with TLE. In histopathologic correlation studies, FA reductions in the ipsilateral fornix in TLE patients undergoing temporal

lobectomy correlated with myelin sheath irregularities, increased extracellular space, more variable axonal size [100] (Fig. 43.5) and reduced axonal density [101]. Comparison of postoperative patients with seizure-free outcome to patients with persistent seizures demonstrated significant diffusivity differences in the dorsal ipsilateral fornix and contralateral parahippocampal white matter, and were associated with smaller resections of the uncinate fasciculus [102]. Increased ADC, reduced FA, and/or reduced fiber tract density in the white matter of TLE patients have been attributed variously to edema, gliosis, occult cortical dysplasias, demyelination, and/or neuronal loss.

Using graph theoretical analysis to evaluate topological and complex networks in TLE has demonstrated overall increased path length and decreased global efficiency, indicating disrupted normal white matter networks [103]. Additionally, graph diffusion based models have been used to predict areas of propagation of neuronal degeneration in TLE with and without MTS [104]. Differences in white matter alteration also are present between patients with clinically established TLE with or without mesial temporal sclerosis. Those with MTS demonstrated more extensive white matter changes with decreased FA in the cingulum,
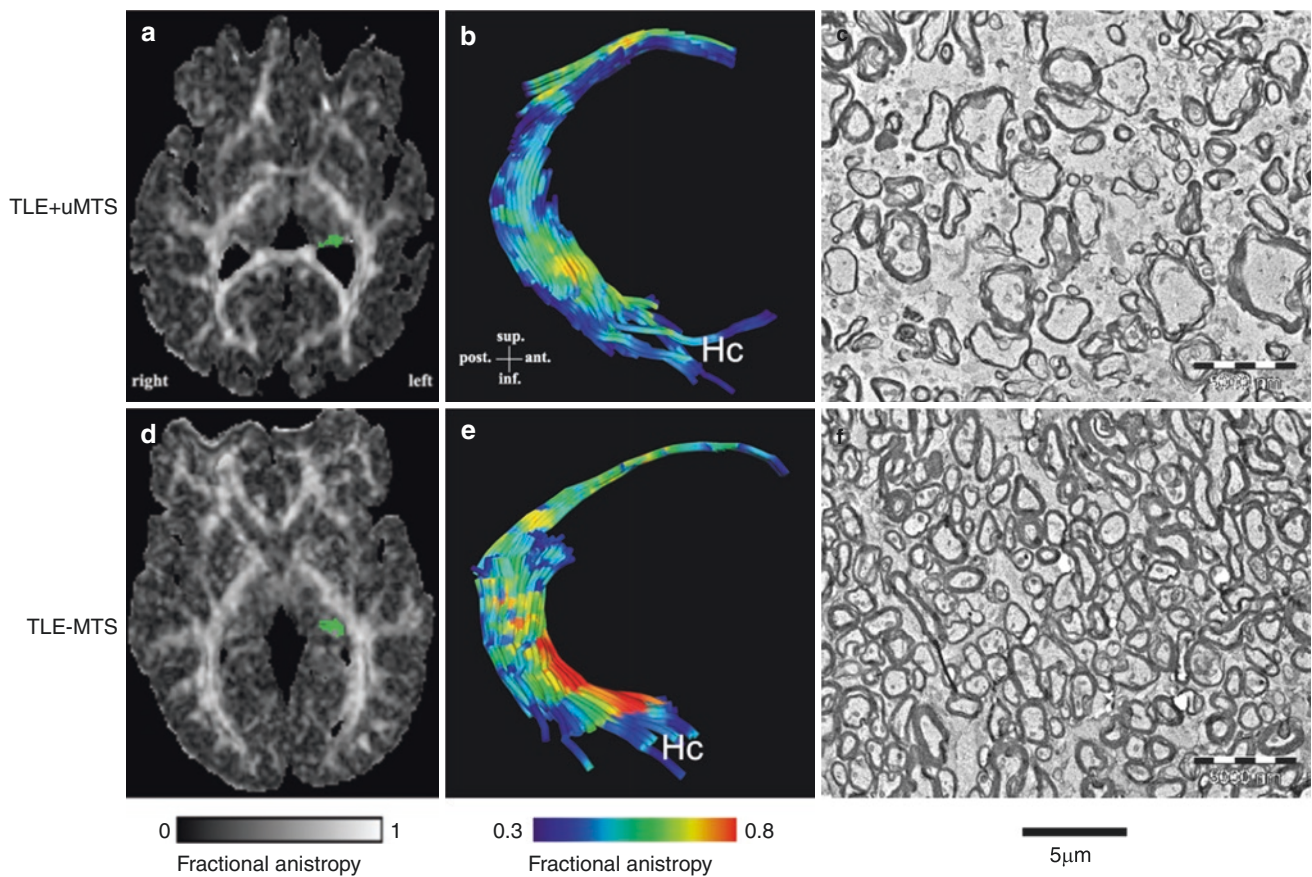
Fig. 43.5 Correlation of fractional anisotropy (**a**, **d**) and deterministic DTI tractography findings (**b**, **e**) from the fimbria-fornix pathway with postsurgical electron microscopy of the more rostral fimbria (**c**, **f**) for temporal lobe epilepsy (TLE) patients with and without mesial temporal sclerosis (MTS) (HC = hippocampal commissure). TLE patients with MTS had decreased axonal density, membrane circumference, and myelin fractions compared to patients without MTS ($P \leq 0.05$). These white matter microscopy changes also showed some statistic correlations with fractional anisotropy in the fimbria-fornix DTI tracts. Reproduced with permission from Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW. In vivo diffusion tensor imaging and histopathology of the fimbria-fornix in temporal lobe epilepsy. *J Neurosci* 2010 January 20;30(3):996–1002

external capsule, internal capsule and uncinate fasciculus that were not seen in patients without MTS [105] Furthermore, studies demonstrated reduced FA in ten major WM tracks in patients with MTS as compared to only changes in the parahippocampal cingulum and tapetum in patients without MTS [106]. Restriction Spectrum Imaging (RSI) studies of patients with temporal lobe epilepsy have shown decreased neurite density in similar locations to changes in FA; however, with greater reductions of neurite density (ND) in the ipsilateral hemisphere, as well as correlation with disease duration [107].

DTI studies also have emphasized the bilateral extent of white matter pathology in *unilateral* TLE. Both right and left TLE demonstrate increased diffusion in the bilateral temporal lobe white matter [78] and uncinate fasciculus [96]. The bilateral cingulum and fornix demonstrated reduced FA in right or left TLE patients [82]. In patients with unilateral hippocampal sclerosis, there is reduction of cingulum fibers connecting the cingulate gyrus and parahippocampal gyrus [108]. A separate study in adults found bilateral cingulum DTI changes only for left, but not right TLE patients [85]. Children with TLE, but normal conventional MRI, also demonstrate bilateral DTI changes in the uncinate fasciculus, arcuate fasciculus, ILF and corticospinal tracts [109]. Some bilateral white matter diffusion abnormalities in unilateral TLE persist after resective surgery [81, 110], refuting the early hypothesis that extensive white matter changes are only due to neuron dysfunction and edema. In a few studies, white matter diffusion abnormalities did not correlate with differences to postsurgical seizure-free outcomes [81, 91]; however, in more recent studies, patients with poor postsurgical outcomes had more changes in the ipsilateral fornix and contralateral parahippocampal white matter [111]. Widespread white matter changes, often remote from structural abnormalities, suggest widespread involvement of neural networks during seizure propagation. It also has been speculated that

bilateral white matter disease detected by DTI represents abnormal connectivity that may precede clinical seizures and predisposes patients to epilepsy [40, 81].

Many DTI studies have highlighted specific connectivity differences between right and left TLE patients. Left TLE patients demonstrate additional FA reductions in the ipsilateral IFOF, arcuate fasciculus, fornix and anterior thalamic radiation, and contralateral changes to the cingulum, anterior thalamic radiation and IFOF [85]. Similar extensive white matter changes were present in a pediatric cohort of TLE patients [109]. Although contralateral white matter changes are not always reported for left TLE [112], several DTI studies have also detected more extensive changes with left compared to right TLE [78, 113–116]. One study demonstrated more significant changes in the hippocampus and cingulum with right TLE, but more prominent remote changes in left TLE [117]. The more extensive white matter changes associated with left TLE may be the result of more widespread seizure propagation in the dominant left hemisphere due to its greater connectivity [78]. A study comparing DTI and PET activity in preoperative TLE-HS patients demonstrated abnormalities on both modalities involving similar regions [118]. Patients with anterior temporal hypometabolism had abnormalities in anterior association and commissural tracts, while those with posterior temporal hypometabolism had differences in anterior and posterior tracts. DTI probabilistic tractography in left TLE demonstrates loss of asymmetry in the arcuate fasciculus associated with increased bilateral connections compared to controls. In patients after anterior temporal lobectomy, those with left TLE demonstrated normalization in the SLF and uncinate fasciculus FA compared to right TLE, indicating that there is potential for reorganization [119]. These changes reflect side-specific reorganization of language networks underlying verb generation and reading comprehension as demonstrated by functional MRI, whereas right temporal lobe epilepsy patients were similar to controls [120]. An additional study using DSI to evaluate whole brain connectivity demonstrated different structural alterations in right and left TLE [121].

Several studies have tried to localize (or lateralize) TLE based on white matter DTI differences, many of which also combine clinical data and multimodality imaging with PET or MEG. An early report found concordant increased diffusion and reduced anisotropy in the ipsilateral temporal lobe white matter [75]. However, another study demonstrated that increased diffusion in the ipsilateral temporal stem white matter was less accurate than hippocampal diffusivity measurements for lateralization of epilepsy concordant with semiology, EEG, and conventional MRI findings [68]. Utilizing discriminate function analysis of DTI tractography lateralized TLE patients concordant to video EEG with 90% accuracy. Further, this study was 100% accurate for right

TLE patients and for a small subset of five patients that were MRI-negative for hippocampal sclerosis [85]. Combination of MEG with diffusion imaging may help as a means of non-invasive lateralization [122]. In MRI-negative children with TLE, extensive white matter diffusion abnormalities were present in the bilateral uncinate fasciculus, arcuate fasciculus, ILF and corticospinal tracts [110]. Another study of adult TLE patients without hippocampal sclerosis demonstrated reduced FA in the fronto-temporal components of the corpus callosum and external capsule, plus reduced diffusion in the cingulum compared with controls. More extensive white matter abnormalities were present in patients with hippocampal sclerosis, but these patients also had longer durations of epilepsy [120]. Multiple studies to date suggest that DTI can detect white matter structural and functional connectivity abnormalities without detectable structural lesions by conventional MRI contrast mechanisms. Additional studies are necessary to determine the clinical relevance of these differences between the various imaging manifestations of temporal lobe epilepsy, which include patients with or without hippocampal sclerosis, cortical dysplasias, dual pathologies, and/or bilateral disease.

Similar to diffusion changes in the hippocampus of TLE patients, some studies of white matter diffusion abnormalities have shown correlations with age of onset or duration of seizure disorder. Higher magnitude reduced anisotropy and increased diffusivity in the posterior corpus callosum correlated with early seizure onset [123]. Similarly, FA decreases in the uncinate fasciculus correlate with the age of onset [112]. Early onset of TLE also is associated with a larger volume of bilateral arcuate fasciculus connections, which may reflect altered language development (discussed later) [124]. A recent study evaluating thalamic connectivity in TLE patients using diffusion imaging demonstrated differences in MD and FA in patients with <15 years of seizures compared to those with >15 years of seizures. Differences in MD and FA also were found in those with better Engel classification following surgery [125]. In a separate study, increased diffusivity in both the uncinate fasciculus and arcuate fasciculus positively correlated with duration of seizures in children with left TLE [110]. Duration of epilepsy has also been correlated to increased mean diffusivity within the left hippocampus in left TLE [117]. One group has suggested unlike diffusivity, FA changes may only occur in the temporal lobe and cingulum white matter after longer durations of disease [85]. Further, patients with longer durations of clinical epilepsy (27 versus 18 years) had reduced anisotropy in the bilateral fornix and cingulum, although this result may be confounded by the presence of hippocampal sclerosis [120]. DTI changes from age of onset and duration of TLE can be hard to disentangle from each other in small patient cohorts, but both factors may relate to a dose-related

progressive damage from repetitive seizures [126]. These chronological correlations also could reflect seizure-induced derangement of normal white matter development in children or young adults [123]. Similar to hippocampal diffusivity clinical correlations, findings have not been consistent and there may be a publication bias in the literature, especially since small patient populations limit the statistical power to disprove a small or weak correlation. Unlike hippocampus diffusion changes, white matter connectivity changes may be more amenable to systems-based clinical correlations with specific cognitive abilities (e.g., language and memory). DTI studies of white matter changes also can be combined with functional MRI methods to simultaneously examine concordant activation and structural connectivity changes in TLE [94, 120, 127]. In a study analyzing 24 patients with left TLE in comparison to controls, decreased distant connectivity was found in the medial orbitofrontal cortex, temporal cortex, posterior cingulate, and precuneus, whereas increased local connectivity was found in the medial and lateral frontal cortices, insular cortex, posterior cingulate cortex, precuneus, and occipital cortex [13].

DTI studies also have begun to correlate specific changes to verbal memory and naming ability to the white matter changes observed in TLE. In TLE patients, ADC or FA of the left parahippocampal gyrus white matter correlated with verbal memory [99, 100]. The parahippocampal gyrus white matter may contain several fiber tracts associated with the hippocampus or limbic system, including the uncinate and arcuate fasciculi. The uncinate fasciculus and arcuate fasciculus demonstrate increased diffusion and reduced anisotropy in both adults [112] and children [109] with TLE. Further, TLE is associated with a loss of the normal left-right asymmetry in the diffusion properties of the arcuate fasciculus [109, 128] and uncinate fasciculus [96, 129]. Poor verbal memory performance correlated with increased diffusion in the left uncinate fasciculus for patients with either left or right TLE, but also correlated with increased diffusion in the left IFOF and bilateral arcuate fasciculus [99]. An additional study in patients with L TLE have found alterations in the left arcuate fasciculus in patients during cognitive processes, including decreased connectivity in the left fronto-temporal components of the arcuate fasciculus and increased parietal connectivity [130]. Alternatively, the ILF also has been proposed as the strongest predictor of verbal memory [87]. Additionally, combining hippocampal volume and MD of the ILF may also model prediction of verbal memory impairment [87]. Decreased FA within the left UF in patients with TLE [131] and DTI microstructural change in the thalamocortical pathways [132] was associated with poor executive function on multiple clinical tasks. Alternatively, uncinate fasciculus diffusion changes correlated with Wechsler Memory Scale scores in left, but not right TLE patients [96]. This was further validated in another

study demonstrating that patients with left TLE had positive correlations between WM diffusivity characteristics and cognitive performance and that patients with significant diffusion abnormalities had decreased cognitive performance [133]. Poor naming ability correlated with increased diffusivity and decreased anisotropy in the both uncinate and arcuate fasciculus [99]. In patients with left TLE, overall poor executive function correlated with decreased FA of the uncinate fasciculus [131]. Another study suggested verbal naming ability in TLE patients might correlate better with more lateralized arcuate fasciculus asymmetry [124]. In contrast, there is conflicting data whether correlations exist between nonverbal memory and white matter diffusion changes. In TLE patients, volume and fractional anisotropy of the right parahippocampal gyrus white matter correlated with nonverbal memory [134], but another study found no correlations between nonverbal memory or fluency and different white matter tracts [99].

It is helpful clinically to understand the impact of TLE on patient's cognitive abilities when determining treatment options. In patients with medically refractory seizures, surgical resection of the ipsilateral temporal lobe structures (hippocampus, amygdala, parahippocampal gyrus, and/or entire temporal pole) can eliminate or significantly decrease the frequency of seizures [45]. There are a number of studies evaluating white matter changes postsurgery, with the goal of being able to predict patients that will be seizure-free postoperatively. Both right and left TLE patients free of seizures after resection of hippocampal sclerosis demonstrate reduced fractional anisotropy in the corpus callosum, ipsilateral arcuate fasciculus, cingulum, uncinate fasciculus, inferior frontal-occipital fasciculus, and corticospinal tracts compared with controls [112]. In one published longitudinal follow-up after surgical resection of hippocampal sclerosis, DTI changes to the corpus callosum, external capsule, contralateral fornix, and cingulum persisted despite 1-year seizure-free outcomes, suggesting a persistent and/or predisposing developmentally abnormal network for seizure propagation in these patients [81]. Continued work is needed to better understand how epileptogenic networks are affected by surgical resection of presumed epileptogenic foci in pediatric and adult patients, especially in the patient population that demonstrates seizure recurrence at more chronic follow-up time points.

Surgical Planning

Presurgical planning for TLE patients involves a multimodality, interdisciplinary assessment of the patient to establish medically refractory disease, localize the epileptogenic focus, and accurately predict risk for complications from resection. Complications result from injury to eloquent, still-

functional temporal lobe structures or pathways from the surgical dissection required to reach and resect the hippocampus and other medial temporal lobe structures.

Previous studies evaluating hippocampal and white matter changes in pre- and postsurgical cases of temporal lobe epilepsy were limited. In one study, bilateral white matter changes to the cingulum and fornix in preoperative DTI did not portend poor postsurgical prognosis [81, 91], in contrast to the known poor prognosis associated with resective surgery in patients with bilateral hippocampal sclerosis. With regard to the hippocampus, one study has reported a positive correlation between increased hippocampal ADC and positive surgical outcomes in 55 patients [63] yet another study of 40 patients failed to detect a similar relationship [68].

More recently, multiple studies have focused on predictive features of TLE with positive postsurgical outcomes. Using functional resting state and DTI imaging, a connectivity model was used to predict outcomes postepilepsy surgery on a small sample size [135]. Although larger studies are necessary, patients with DTI images prior to and postsurgery, with connectivity aberrations outside of the surgical resection, demonstrate poorer prognosis postsurgically [136]. Combining DTI data with clinical data has shown up to 88% accuracy in predicting patients with a positive postsurgical outcome [136]. Computational models based upon DTI imaging have been proposed to improve surgery success rates in TLE [88]. Machine learning algorithms in temporal lobe epilepsy have reported seizure-free outcome with 79% accuracy and 65% sensitivity in a small retrospective study [137] with predictive models identifying important features involving ipsilateral and contralateral structures [138]. Patients with altered DTI involving bilateral thalamotemporal connections are not as likely to have a seizure-free outcome in the postsurgical state [139]. Comparison of postoperative patients with seizure-free outcomes and those with continued seizures demonstrated significant diffusivity differences in the dorsal ipsilateral fornix and contralateral parahippocampal white matter, as well as smaller resections of the uncinate fasciculus [111].

An additional topic that requires future research involves determining structural changes associated with different surgical approaches. Previously reported, resecting the anterior two-thirds of the temporal pole causes further reduction in fractional anisotropy of the inferior longitudinal fasciculus compared with selective amygdala-hippocampectomy [112]. Yet, another small study did not detect a significant relationship between type of surgery and white matter changes, particularly in the limbic system [81]. Many patients experience decline in naming ability following anterior temporal lobectomy. Initial studies suggest that the greatest decline in naming ability occurs for individual temporal lobe epilepsy patients that undergo temporal lobectomy in the dominant hemisphere as assigned by differences in fMRI activation and DTI assessment of the arcuate fasciculus (Fig. 43.5) [124]. Direct correlation between surgical disruptions of the arcuate fasciculus (or other language-related pathways) detected by DTI with the severity of postoperative naming difficulties has not yet been reported.

Patients undergoing temporal lobectomy also develop visual field deficits due to surgical disruption of Meyer's loop. Ironically, driving privileges that patients hoped would be restored with seizure-free outcomes then may be denied due to surgery-induced visual field defects. Surgeries for temporal lobe epilepsy often resect the most anterior portions of this fiber bundle leading to contralateral superior homonymous quadrantanopsia that can spread from the medial to lateral sector depending on the extent of injury [140]. DTI-based tractography studies demarcate the anterior extent of Meyer's loop between 32 and 37 mm posterior to the temporal pole tip, but there is significant individual patient variation [140–142]. Also, the left Meyer's loop may extend slightly more anterior compared to the right, consistent with more visual field defects reported following left anterior temporal lobectomies [142]. Comparison between pre- and intraoperative DTI demonstrated that the position of Meyer's loop also shifts several millimeters cranially and medially during the majority of anterior temporal lobectomies [141]. Postoperative DTI has demonstrated decreased fractional anisotropy in the ipsilateral sagittal stratum correlated with the severity of visual field defects after anterior temporal lobectomy [142]. The severity of visual field defects following surgery correlated both with the anterior extent of Meyer's loop [86] and the distance the resection extends into an individual's Meyer's loop as determined by DTI tractography [142]. These results suggest preoperative DTI may have an important role in the preoperative assessment of individual risk for visual impairment following anterior temporal lobectomy.

Malformations of Cortical Development

Malformations of cortical development represent a heterogeneous spectrum of disorders with abnormal cerebral cortex laminar or columnar structure due to deranged neuronal proliferation, migration or cortical network organization [143]. The underlying etiology may be perinatal ischemia or infection, versus germline or somatic mosaic gene mutations. The MRI-visible spectrum of abnormalities includes lissencephaly, focal cortical dysplasia, subependymal, subcortical or band gray matter heterotopias. Individual patients have variable clinical presentations with partial and/or generalized seizures [144]. Focal cortical dysplasia can represent dual pathology in a subset of temporal lobe epilepsy patients that reduces seizure-free prognosis following temporal lobe resection [145]. Conventional MRI of cortical dysplasia may

demonstrate visible focal cortical thickening, gray-white junction blurring and T2 prolongation in the underlying white matter radiating from the lateral ventricle to the cortical surface concordant to localization by EEG. Overall, advanced diffusion MRI investigations of cortical malformations have been more limited than TLE, but have demonstrated increased diffusivity and reduced fractional anisotropy within lesions visible on conventional MRI when compared to controls or contralateral homologous brain regions [75, 146–148]. Limited data suggested band heterotopias may be the only visible cortical malformation that do not have these diffusion abnormalities [146]. Water diffusion changes are consistent with decreased neuronal density, the presence of abnormal cells and loss of diffusion anisotropy due to abnormal functional organization.

Similar to temporal lobe epilepsy, conventional MRI fails to detect all epileptogenic cortical abnormalities [144], or underestimates the full extent of abnormal nervous tissue. This latter problem could affect seizure-free outcomes if surgical resection fails to remove the full margins of epileptogenic tissue. Subtle structural abnormalities not visible with conventional MRI may demonstrate DTI abnormalities due to the associated abnormal functional organization of the tissue. Diffusion or fractional anisotropy changes in normal-appearing brain tissue were concordant with EEG localization in 7 of 30 MRI-negative patients with partial seizures. However, in this study, three additional diffusion abnormalities were discordant with EEG localization [75]. Voxel-based analysis demonstrated diffusion and fractional anisotropy changes in refractory epilepsy patients without structural abnormalities, but only 50% of those findings were concordant with EEG [79]. Changes to mean diffusivity may be more sensitive than altered anisotropy in MRI-negative patients with partial seizures [75], perhaps due to the low intrinsic fractional anisotropy in normal cortex. DTI studies of extratemporal epilepsy also have suggested involvement of the thalamocortical network [149]. Overall these results suggest DTI may increase sensitivity for epileptogenic cortical malformations in MRI-negative patients, but has limited specificity.

Several groups have reported white matter subjacent or surrounding malformations of cortical development has increased diffusivity and/or decreased anisotropy [146, 150, 151]. All but one study have reported diffusion abnormalities extended beyond white matter with abnormal T2 prolongation. Further, white matter diffusion abnormalities may extend several centimeters remote to the conventional MRI lesion [152], involve deep white matter projecting from the cortical lesion [151], or affect adjacent large fiber bundles such as the posterior corona radiata [152], uncinate fasciculus, SLF, and IFOF [153]. White matter subjacent to seizure activity on MEG (beyond the conventional MRI lesion) also

has increased diffusion and reduced anisotropy [150]. Diffusion MRI at 7T demonstrated decreased u-fibers in patients with nonlesional focal epilepsy [154]. Abnormal white matter diffusion in patients with cortical malformations may have multiple etiologies including the presence of dysplastic neurons, decreased axonal density and increased extracellular space due to failed neurogenesis, abnormal neuronal migration and/or subsequent cell loss from chronic repetitive seizures. Specific changes to diffusion perpendicular to the principal eigenvector suggests these normal-appearing white matter lesions also may reflect abnormal myelination [151]. Neurite orientation dispersion and density imaging (NODDI) suggested decreased intracellular volume fraction in cortical malformations with normal conventional MRI [155, 156].

Similar to temporal lobe epilepsy, DTI findings also suggest malformations of cortical development may have more widespread and potentially bilateral white matter abnormalities. One study examined 23 patients with histopathologically confirmed FCD and determined that there was decreased FA involving the corpus callosum, bilateral IFO, ILF, and SLF compared to controls with a greater decrease in the side of the SLF corresponding to the FCD. In a connectivity meta-analysis, patients with focal epilepsy were determined to have reduced integration and increased segregation on network organization [157]. It remains to be determined whether a component of the cortical or white matter lesions detected by DTI that extends beyond the conventional MRI lesion is epileptogenic or just represents a pathway of preferred seizure propagation. Currently, EEG, magnetoencephalography (MEG), and/or electocorticography are used to guide the surgical margins for curative resection of epileptogenic focal cortical malformations. The role for DTI in such preoperative assessment has not been established.

Diffusion MRI also has been applied to tuberous sclerosis (TSC) patients. Tubers demonstrate increased mean diffusivity compared with either contralateral cortical regions in patients [158, 159] or control subjects [160]—these diffusion changes may not be appreciated on visual inspection [158]. Further, several studies have suggested the tuber or perilesional white matter with highest diffusivity corresponded to the epileptogenic lesion on EEG [158, 161, 162], although to our knowledge this has not been implemented clinically as a strong selection factor for tuber resection. The supratentorial white matter in TSC patients has increased mean diffusivity [163, 164] and reduced fractional anisotropy [165] well away from conventional MRI-detected lesions when compared to age-matched control subjects. Structural whole-brain connectivity in 20 patients with tuberous sclerosis demonstrated increased diffusivity throughout the brain that correlated with tuber load. Additionally, TSC patients with developmental delay or autism have higher dif-

fusivity for the interhemispheric connections [166]. Further studies are warranted to determine whether differences in tuber or white matter connectivity by diffusion tractography correlate to seizure origin, propagation, network and prognosis.

Conclusion: Future Directions

Diffusion tensor imaging and tractography have provided many novel insights into epilepsy-induced changes to the functional and structural organization of the hippocampus, cortex and underlying white matter. These changes appear more widespread with diffusion MRI techniques compared to conventional MRI. Diffusion may be more sensitive at detecting seizure-induced cytotoxic edema in epileptogenic regions during the peri-ictal period and detecting subtle chronic structural alterations to brain tissue not visible with conventional MRI contrast mechanisms. DTI has demonstrated extensive, often bilateral white matter and extrahippocampal changes in temporal lobe epilepsy. Further, right and left temporal lobe epilepsy have significant white matter structural differences. Seizure propagation and white matter reorganization appears more widespread when seizures are generated in the dominant cerebral hemisphere due to greater pre-existing connectivity. White matter changes can correlate with the duration or age of onset of seizures, supporting the hypothesis that seizures may damage the brain in a dose-dependent fashion. Normal-appearing white matter in malformations of cortical development or tuberous sclerosis remote from visible structural lesions also can be abnormal. White matter assessment in temporal lobe epilepsy patients prior to temporal lobe resection can predict visual field defects based on the extent of resection and provide objective surrogate findings for language lateralization, verbal, and memory function. Additionally, better understanding of white matter changes in the preoperative period may aid in determination of which patients will benefit from surgical resection.

The most advanced DTI and tractography methods have been applied to cross-sectional studies of adult patients with unilateral temporal lobe epilepsy well localized by semiology, EEG, and sometimes conventional MRI, but one of the challenges to research and clinical imaging of epilepsy is the heterogeneous nature of the patient population. Thus, significant further insight into temporal lobe epilepsy may be gained by applying advanced diffusion methods and analysis to more longitudinal studies and to larger cohorts of specific patient populations including MRI-negative patients, patients with bilateral disease, or dual pathology. It would be interesting to compare white matter involvement in medically refractory temporal lobe epilepsy patients to those with suc-

cessful pharmacologic management. More diffusion studies of children with complex seizures or families with increased incidence of temporal lobe epilepsy may give insight into predisposing connectivity differences or early pathological changes. Over the last several years, mathematical models have used diffusion MRI probabilistic tractography data to assess connectivity of whole brain neural networks by analyzing its topological properties with graphical theoretical approaches. Future studies with large cohorts and evaluation of subtypes of epilepsy will help to elucidate clinical prognosis and treatment strategies.

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