Review Article

White matter in temporal lobe epilepsy: clinico-pathological correlates of water diffusion abnormalities

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Abstract: Using magnetic resonance imaging, it is possible to measure the behavior of diffusing water molecules, and the metrics derived can be used as indirect markers of tissue micro-architectural properties. Numerous reports have demonstrated that patients with temporal lobe epilepsy (TLE) have water diffusion abnormalities in several white matter structures located within and beyond the epileptogenic temporal lobe, showing that TLE is not a focal disorder, but rather a brain network disease. Differences in severity and spatial extent between patients with or without mesial temporal sclerosis (MTS), as well as differences related to hemispheric seizure onset, are suggestive of different pathophysiological mechanisms behind different forms of TLE, which in turn result in specific cognitive disabilities. The biological interpretation of diffusion abnormalities is based on a wealth of information from animal models of white matter damage, and is supported by recent reports that directly correlate diffusion metrics with histological characteristics of surgical specimens of TLE patients. Thus, there is now more evidence showing that the increased mean diffusivity (MD) and concomitant reductions of diffusion anisotropy that are frequently observed in several white matter bundles in TLE patients reflect reduced axonal density (increased extra-axonal space) due to smaller-caliber axons, and abnormalities in the myelin sheaths of the remaining axons. Whether these histological and diffusion features are a predisposing factor for epilepsy or secondary to seizures is still uncertain; some reports suggest the latter. This article summarizes recent findings in this field and provides a synopsis of the histological features seen most frequently in post-surgical specimens of TLE patients in an effort to aid the interpretation of white matter diffusion abnormalities.

Keywords: Epilepsy; temporal lobe; diffusion magnetic resonance imaging; diffusion tensor imaging (DTI); white matter histology

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Introduction

One goal of neuroimaging in epilepsy is to identify focal lesions that are responsible for the disorder, with the hope that it can be surgically resected, rendering the patient seizure-free. Temporal lobe epilepsy (TLE), the most common form of focal epilepsy (1), is often accompanied by mesial temporal lobe sclerosis (MTS), a particular lesion of the hippocampus, amygdala, and entorhinal cortex characterized by specific patterns of neuronal loss and gliosis (2). The identification of an epileptogenic lesion such as MTS considerably improves the chances of seizure freedom following surgery (3). However, this specific lesion (identified in routine magnetic resonance imaging (MRI) as hippocampal atrophy, T2 signal hyperintensity, or both) is seen in only 25% of outpatients in a hospital-based setting (4), and in around 70% of TLE patients referred to a tertiary care center (5-8). For these reasons, there have been great efforts to improve neuroimaging techniques such that subtle lesions become apparent and surgery can be considered.

Having revolutionized the field of stroke, diffusion-

weighted magnetic resonance imaging (dMRI) entered the field of epilepsy, with many hoping it would shed light on epileptogenic lesions and aid treatment decisions. While in some cases dMRI can accomplish this goal (9-12), it also showed that TLE patients have white matter abnormalities in several brain regions within and beyond the temporal lobe. Suddenly, TLE ceased to be a focal disorder with a clear unilateral lesion; these findings force us to conclude that TLE is truly a brain network disorder, and that the classically recognized MTS lesion is accompanied by micro-architectural abnormalities of several fiber bundles that interconnect remote brain areas.

In highly organized tissue such as white matter, the membranes and overall coherence of biological structures modulate the behavior of diffusing water molecules, and thus impart a particular signature to their displacement (13). In voxels occupied by a single fiber population, the resulting preferred direction of diffusion corresponds to the orientation of the fibers therein, which can be used to reconstruct the trajectories of macroscopic fiber tracts using tractography (14). Thus, dMRI is able to simultaneously provide information regarding macroscopic brain connectivity and microscopic features of the underlying tissue. There are numerous methods to analyze the behavior of water diffusion, but diffusion tensor imaging (DTI) (15) has been, by far, the most widely used for the study of TLE due to its relatively low demands in terms of data acquisition (which is generally performed in a clinical setting and therefore limited in time), but also due to its seemingly straightforward biological interpretation. In the tensor model, the diffusion profile is portrayed as an ellipsoid; its long axis (eigenvalue) is oriented parallel to the direction of fibers, and its magnitude relative to the two orthogonal eigenvalues provides a measure of anisotropy (i.e., the degree of directionality of diffusion imposed by the tissue). Analysis of the spatial profile of the diffusion of water, such as the shape of the tensor, provides important information that can be intuitively related to tissue characteristics. For instance, the largest eigenvalue is generally thought to reflect axonal integrity, while the remaining eigenvalues are modulated by axonal density, axonal membranes and myelin sheaths, with mean diffusivity (MD) and fractional anisotropy (FA) (the mean and a normalized ratio of eigenvalues, respectively) often used as summary metrics (16-18). These are, however, over-simplistic biological interpretations of the tensor model; as many different and concomitant underlying factors may account for particular metrics derived from the tensor (16,19-21).

The numerous reports of white matter diffusion abnormalities in patients with TLE have been reviewed before (22,23) and it is not necessary to repeat them here, except to provide context for the most commonly found alterations of white matter. The two objectives of this article are (I) to comment on some recent findings that extend our knowledge of white matter abnormalities in TLE; and (II) to collate histological confirmation of white matter abnormalities that could underlie the abnormal water diffusion patterns seen in TLE patients. As we focus on the microscopic features of tissue revealed by dMRI, we will not comment on the use of tractography to infer long-range anatomical connectivity to aid surgical resections or to infer the network properties of the epileptic brain, as those topics have been reviewed recently (24,25).

Diffusion abnormalities of white matter in TLE patients

Abnormalities of the three-dimensional diffusion profile of water molecules have been reported in several white matter structures of TLE patients for more than a decade, since the first demonstration of reduced FA of the external capsule and corpus callosum (26), with a large degree of consistency among publications. Most studies have shown that diffusion abnormalities are not confined to the epileptogenic temporal lobe, with many association, projection and commissural fibers showing alterations. Recently, Otte *et al*. performed a meta-analysis that included 13 cross-sectional studies and confirmed the existence of temporal and extra-temporal white matter DTI abnormalities (27). The evidence showed that reductions of FA and increases of MD are most prominent in white matter structures closely related to the epileptogenic temporal lobe, such as the uncinate and arcuate fasciculi, cingulum and external capsule, but that contralateral structures as well as the corpus callosum are also affected, albeit to a lesser degree. Further, there seems to be a centrifugal decrease of the degree of abnormalities as tracts extend away from the epileptogenic temporal lobe (27,28). The fornix is the main connection to and from the hippocampus and in some patients it shows volumetric abnormalities (29); notably, the fornix did not prove to be significantly abnormal in this meta-analysis. However, most reports included in the analysis did not use any form of correction for partial volume averaging with the neighboring cerebro-spinal fluid (CSF), an artifact that can on its own mask underlying tissue characteristics and potentially obscure differences between groups (30,31).

Indeed, following suppression of the CSF signal, DTI metrics of the fornix in patients with unilateral TLE show clear bilateral abnormalities that do not resolve following seizure freedom and that have been validated by histology of the ipsilateral tract (32-35). Further, the fornix abnormalities seen in adult TLE patients are partially mirrored in an animal model of post-status epilepticus TLE of juvenile rats, who developed transient DTI abnormalities in the corpus callosum, but also chronic reductions of FA in the fornix that corresponded to decreased myelin content (36). A similar study also showed early reductions of FA of the fornix bilaterally after status epilepticus but, notably, these abnormalities were exclusive to the subgroup of rats who ultimately developed spontaneous seizures (37).

Most DTI studies of TLE had, until recently, included patients with TLE regardless of the presence or absence of MTS. However, there is now considerable evidence supporting the idea that DTI abnormalities are more pronounced in patients with radiological evidence of MTS than in patients with non-lesional TLE (nlTLE). Widespread and bilateral reductions of FA do occur in nlTLE patients (38) but, for example, fornix and cingulum DTI abnormalities are much milder in nlTLE patients (34) than in patients with MTS and more evident in the ipsilateral tract (39). Using tract-based spatial statistics (TBSS), Scanlon *et al*., showed that TLE patients with MTS have more widespread DTI abnormalities than nlTLE patients (40), a finding that was also observed using tractography of several structures, with nlTLE patients showing DTI abnormalities only in the inferior portion of the cingulum and the tapetum (41). Moreover, in patients with MTS, several white matter structures exhibit progressive white matter diffusion abnormalities, suggesting a gradual degenerative process in response to recurrent seizures (42).

Previous studies have pooled TLE patients with left and right hemisphere onset as a homogeneous group, although it has long been recognized that clinical signs and symptoms of TLE differ depending on the hemisphere of onset. While both groups of TLE patients exhibit white matter DTI abnormalities, they are distinguished by degree and spatial pattern. Tractography of eight paired tracts indicated that those most affected are ipsilateral to seizure onset; however, TLE patients with right hemisphere onset showed a more marked tendency to have ipsilateral abnormalities, while patients with left hemisphere onset tend to have bilateral involvement. This information was enough to correctly lateralize 90% of the patients included using a linear discriminant analysis (43). Another study, in contrast, showed that right TLE patients had DTI abnormalities in more tracts than patients with left TLE, with bilateral involvement more prevalent in right TLE (41). A greater involvement of the limbic system, as well as more widespread abnormalities were seen in left TLE patients in a TBSS study (44), but TLE patients with right hemisphere onset had bilateral temporal lobe DTI abnormalities. FA of the tapetum was recently found to correlate with contralateral interictal spikes in TLE only in patients with left hemisphere onset, suggestive of chronic white matter damage by ongoing seizures and distinct neuroplastic mechanisms depending on hemispheric seizure onset (45). Other studies have corroborated the widespread affections and stronger lateralization of DTI abnormalities in left TLE, as compared to right TLE (42,46,47), and an increased inter-tract correlation in left TLE, such that FA reductions in one tract are likely to be accompanied by reduced FA in other tracts (48). The somewhat conflicting results do not allow us to conclude if left or right onset TLE shows greater severity. Moreover, the experimental design needed to answer this question is complex: by discriminating patients according to seizure onset side, patients with or without MTS are often grouped together although, as we reviewed above, the presence of MTS also influences the degree and spatial pattern of abnormalities, and some patients show bilateral electrophysiological evidence of seizure activity. In a voxel-based analysis that included patients with and without MTS who were also grouped by seizure onset side, the most widespread and prominent DTI abnormalities were seen in patients with MTS and left hemispheric onset; no DTI abnormalities were detected in right nlTLE patients (49). As patient groups were not compared directly but only contrasted to healthy controls, it is difficult to ascertain the interaction between MTS and hemispheric seizure onset. Further studies are needed, in which an adequate number of patients are included in each of these four groups, ideally with clear and objective confirmation of both the presence of MTS (e.g., post-surgical histological confirmation or pre-surgical T2 relaxometry), and unequivocal electrophysiological lateralization.

Some studies have directly interrogated the effect of surgical resection on the structure of white matter (*Figure 1*). In the ipsilateral hemisphere, the fornix and other tracts intimately related to the resected tissue show DTI changes compatible with expected Wallerian degeneration (33,52-55). What is most intriguing, however, is that more superiorly, particularly in the corona radiata, there is an increase of FA (due to increased parallel and

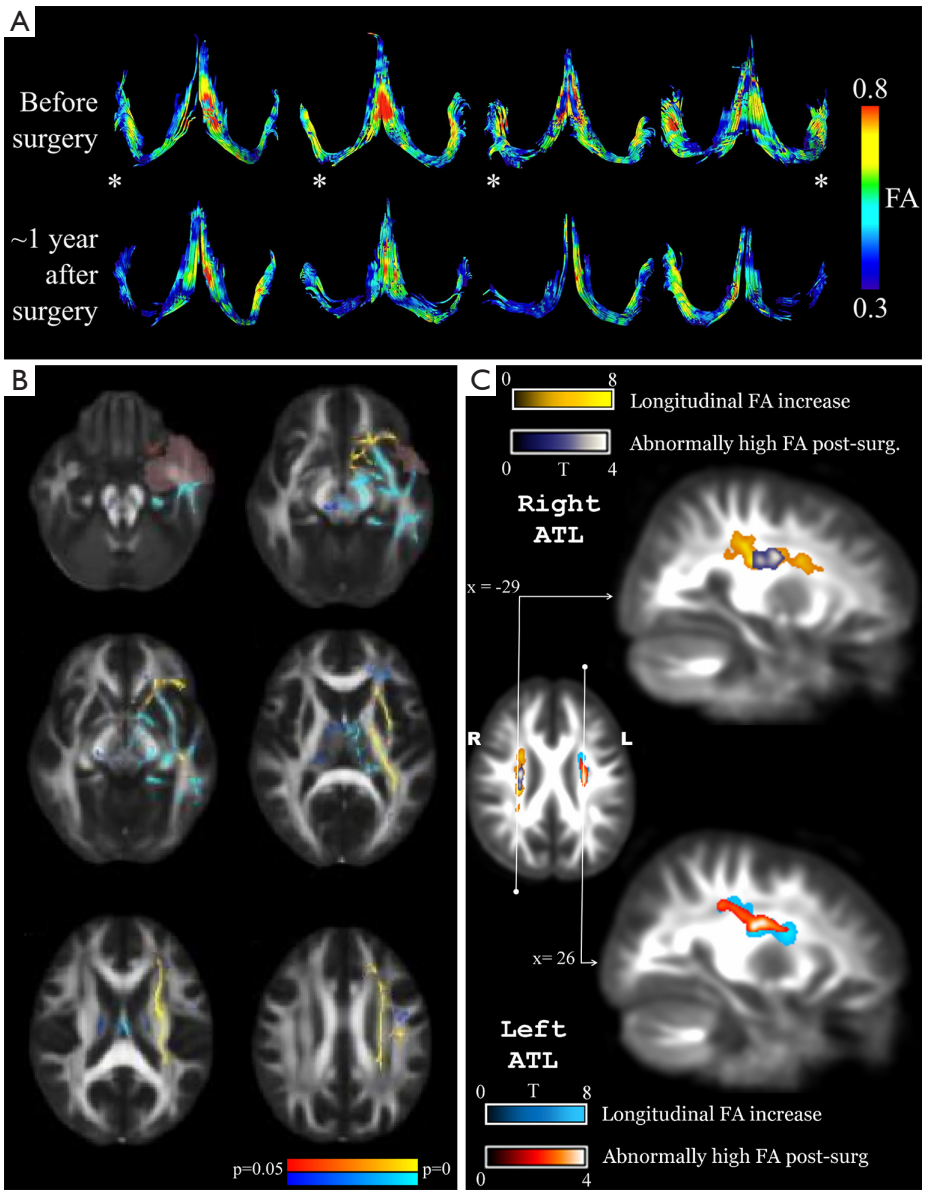

Figure 1 Post-surgical changes of diffusion anisotropy. (A) Marked reductions of FA are seen on the fornix ipsilateral to surgical resection of MTS (*) one year after surgery, likely reflecting Wallerian degeneration; the contralateral fornix fails to normalize even after seizure freedom; (B) one year after surgical resection of the anterior temporal lobe (red mask), reductions of FA (cool colors) are seen near the resection site, while increased FA (hot colors) are evident in more distant ipsilateral regions including the external capsule and corona radiata; (C) the corona radiata shows a post-surgical increase of FA reaching values even higher than those seen in controls. Panel A adapted from (33), panel B adapted from (50), panel C adapted from (51).

reduced radial diffusivities) (50,55). Nearby tracts such as the uncinate fasciculus and external capsule also showed FA increase post-surgically. Similar findings were also reported by Pustina *et al*. (51), with the post-surgical FA increase in the coronal radiata exceeding the normal values of healthy controls; this, along with analysis of the tensor mode, suggests a reorganization of fibers in that region, with degeneration of a group of fibers in this region of crossing fibers. Moreover, patients with left TLE had a post-surgical normalization of FA in the contralateral

superior longitudinal and uncinate fascicles, with the former showing a correlation with postoperative verbal fluency; this phenomenon was not observed in right TLE patients, which points to a certain degree of plasticity of the non-dominant language tracts. While it is certainly possible that some white matter fascicles undergo plastic changes following surgery, the paradoxical improvement of FA values in regions of known fiber crossings highlights the inability of the tensor model to fully capture information in regions of complex architectural configurations, and the importance of careful biological interpretations of non-invasive assessments of white matter through diffusion MRI in general (16,20,56).

DTI of pediatric TLE

An intriguing question regarding white matter diffusion abnormalities is whether they precede or are a consequence of seizures, and pediatric studies begin to provide information in this regard. Although dMRI and tractography can be reliably performed in pediatric epilepsy (57,58), their use in pediatric TLE has not been as extensive as in adults. The shorter duration of disease in pediatric TLE patients should minimize any potential progressive abnormalities of white matter secondary to seizures, but it must be considered that unlike adult TLE, the etiology of pediatric TLE is often secondary to specific lesions such as focal cortical dysplasia (FCD), tumors or malformations, making a direct comparison to adult TLE less straightforward (59,60). Despite this limitation, TLE patients have shown bilateral temporal lobe white matter diffusion abnormalities characterized by an increase of MD, but no changes of FA (61), as well as bilateral extra-temporal DTI abnormalities (62). In another study, the ipsilateral uncinate, arcuate and inferior longitudinal fascicles, as well as the corticospinal tract, showed bilateral diffusion abnormalities, with correlations of left uncinate and arcuate fascicles with disease duration (63). Diffusion kurtosis imaging (DKI) seems to be more sensitive than DTI in children with TLE, who showed normal tensor-derived parameters, but bilateral diffusion kurtosis abnormalities of the temporal lobe white matter, with greater reductions of radial kurtosis on the ipsilateral hemisphere (64). As in adults (65), other forms of pediatric epilepsy also show diffusion abnormalities of white matter. The cingulum and splenium are abnormal in children of 8-18 years, with several forms of idiopathic epilepsies (66) and reduced FA has been found in right fronto-occipital white matter in children with frontal lobe epilepsy, which was associated with poorer cognitive abilities (67). White matter DTI abnormalities are found in the same lobe as FCD in slightly more than half of pediatric patients (12) and in white matter adjacent to areas of hypometabolism (68). It is very interesting that in some forms of idiopathic epilepsy, white matter diffusion parameters normalize following remission but not in patients with ongoing seizures; while this finding cannot be directly extrapolated to adult TLE patients, who show persistent abnormalities of the fornix after seizure freedom (33), it is possible that some diffusion abnormalities are transient and secondary to epileptic activity.

Whether childhood febrile status epilepticus (FSE) leads to TLE is still unknown and debated. Hippocampal T2 hyperintensities and increased volume are seen soon after the occurrence of febrile status epilepticus in 11.5% of patients, many of whom show hippocampal sclerosis one year later (69). Moreover, children with a history of FSE have a larger prevalence of hippocampal malformations, particularly malrotation (70). In a longitudinal study (71), children who presented FSE had FA reductions throughout the brain one month after the event, but these abnormalities essentially disappeared after one year. The authors of said study suggest that these findings could reflect a temporary pause of white matter development which resumes if the insult is not repeated, or they may indicate an underlying pre-existing structural abnormality that renders these children more prone to FSE. As unprovoked seizures occur only several years after FSE, it is still too early to know how many of those patients will develop TLE.

Neuropsychological implications of white matter abnormalities

Cognitive functions rely on the association of multimodal information, a task that is supported by the long-range connections provided by white matter fascicles. With the robust evidence of widespread white matter microstructural abnormalities in TLE patients, it should not come as a surprise that these patients exhibit cognitive disabilities in several domains (72,73). Memory, both delayed and immediate, correlates with FA of the anterior and medial portions of the temporal lobe, respectively (74), and verbal memory deficits are associated with diffusion abnormalities of the uncinate, arcuate and inferior fronto-occipital fascicles, the inferior portion of the cingulum and the white matter directly underneath the entorhinal cortex (75-77). Patients with left TLE tend to have more pronounced

deficits of working memory (78), which could be due to the extensive white matter abnormalities seen in this patient group (42). Additionally, patients with hyperintense temporal lobe white matter and blurring of the gray/white matter interface show more neuropsychological deficiencies than patients without blurring (79). The fronto-parietal network that supports working memory is known to be disrupted in patients with TLE (80), with specific diffusion abnormalities in the interconnecting white matter. Specifically, the diffusion characteristics of the superior longitudinal fasciculus, cingulum and contralateral temporal lobe were associated with working memory performance in patients with left TLE and MTS (81). Although the fornix is intimately associated with the hippocampus, its diffusion parameters do not correlate with memory performance (77,82), yet they do correlate with processing speed, particularly in TLE patients without MTS (82).

There is considerable evidence of language impairments in patients with TLE (83), which is somewhat to be expected considering the alterations of white matter bundles involved in its perception and production (84). The spatial organization of the functional cortical language networks are disrupted in TLE patients, particularly with left hemispheric onset, who show increased right hemisphere structural connections and reduced ipsilateral connectivity (85). These differences in brain connectivity are likely explained by the altered diffusion parameters (namely reduced FA and increased MD) seen in the uncinate, arcuate and inferior fronto-occipital fasicles, as well as the inferior portion of the cingulum (75,77,86). Additionally, hemispheric dominance can sometimes be difficult in TLE patients and may require the use of the invasive Wada test, but this test can be superseded by imaging. Combining dMRI metrics of frontal and temporal white matter bundles and morphologic data, language hemispheric dominance can be lateralized non-invasively (87), and language function can be accurately predicted (88). Finally, the extent of surgical resection of the fiber bundles involved in language predicts postsurgical naming deficits (89).

As dMRI becomes more widely utilized during pre- and postsurgical evaluation of TLE patients, it will provide more information on the association of white matter pathology and cognitive decline associated with or caused by this neurological disorder.

Histological white matter features behind dMRI abnormalities

The interpretation of white matter diffusion abnormalities (seen in epilepsy or other conditions) is generally based on previous studies that related tissue microstructure and ultrastructural characteristics to the spatial profile of water diffusion (13), but often the diffusion abnormalities are over-simplistically related to a "loss of tissue integrity" (56). Few studies have directly correlated dMRI metrics with histological features of human specimens in specific white matter regions within the temporal lobe (35,79). These studies, along with the histopathological features described in brain specimens of TLE patients provide relevant information regarding the mechanisms that cause water diffusion to behave abnormally in several white matter bundles in TLE patients. The most common histological abnormalities within the temporal lobes are described below; notably, each of these features is seen in only 17-36% of surgical specimens, but evidence of at least one abnormality is detected in nearly 63% of all cases (90).

White matter gliosis

Gliosis is observed in most FCD, but it is also a common finding in the white matter of TLE patients (91-93) although it has no apparent relation to the severity of the disorder (94). Astrocytic gliosis, traditionally assessed by the expression of glial fibrillary acidic protein (GFAP), has been found in 18% to 100% of specimens of TLE patients, with severity ranging from mild to marked gliosis (79,94,95) and associated with enlarged glial cell nuclear volume (96,97). Even though gliosis is often seen in TLE specimens, it does not seem to be related to T2 signal changes or diffusion metrics of the temporal lobe white matter (98). Nevertheless it was proposed that the diffuse gliosis found in the temporal lobe white matter of patients with TLE could be an extension of temporal lobe dysplasia in patients with MTS (99), or an adaptive compensatory reaction to frequent seizures (92,94).

Oligodendroglia is prominently increased in the white matter of TLE patients as compared to controls, but it is equally high in TLE patients with or without MTS (100). Oligodendrogliosis in white matter is often found as clusters of cells (90,91,100-103), and they appear to be slightly more common in patients with gray/white matter blurring and related to reduced myelin content (91). Further, oligodendrocytes (OL) can be observed as groups or rows of small round cells along white matter vessels (perivascular clusters) and around a single neuron (perineural OL) (92,100-102,104). Even though the main function of OL in the central nervous system is myelination, their increased

numbers in white matter tissue in TLE needs further investigation, as it could be due to a pathophysiological or compensatory mechanism in epileptogenesis, and their increased number may be a sign of an active attempt to compensate for ongoing myelin loss (79,91,105).

Heterotopic neurons in white matter

Normally, a few neurons are interspersed within the white matter fascicles (106,107), but their density is often increased in brain specimens of TLE patients as compared to controls (92,93,108-111) and is independent of white matter gliosis (90,93). These neurons are frequently seen in the yuxtacortical white matter; they blur the border between the gray and white matter in specimens of FCD type IIa, IIb, and IIIa (112), but they do not seem to cause blurring in TLE specimens (79). Similar to white matter gliosis, these ectopic white matter neurons do not seem to be associated with temporal lobe white matter hyperintensities or reduced diffusion anisotropy, likely because their dimensions and numbers are not sufficient to substantially affect the diffusion of water in white matter.

Temporal gray/white matter demarcation (blurring)

Blurring of the border between gray and white matter is a common finding in conventional MRI of patients with TLE, particularly in patients with earlier onset of the disorder (79,110,113), and in patients with FCD type IIa, IIb, and IIIa. As previously stated, heterotopic neurons can be responsible for this feature, although blurring in TLE specimens is also secondary to reduced myelin content and reduced axonal density (79,93,112). Blurring is present in MRI images of 32-65% of TLE patients with MTS (91,113,114), and it is of great lateralizing value, as it tends to be on in the same hemisphere as the sclerotic hippocampus and, in cases of bilateral hippocampal damage, it follows the more severely affected mesial temporal lobe (113).

Myelin and axon abnormalities

Hypomyelination or dysmyelination are presumed to be responsible for temporal lobe white matter hyperintensities and blurring of the temporal grey/white matter border (79,91,113) and are associated with FCD Type II (115). Overall myelin content can be reduced by decreasing its production, increasing its degradation, or reducing the number of myelinated axons (116), with the latter being the most likely in patients with TLE. A study by Garbelli *et al*. of surgical specimens of TLE patients showed evidence of large patches of reduced myelin content in the white matter underlying the temporal neocortex, as well as prominently reduced axonal density of both myelinated and non-myelinated axons (*Figure 2A-J*) (79). Reduced axonal density decreases the overall coherence of the white matter and minimizes the barriers that hinder water diffusion, thus allowing a more isotropic diffusion profile, which was also demonstrated in this study by acquiring dMRI of the excised temporal lobes at 7 T. These findings confirm the previously reported positive correlation between cummulative axonal membrane circumference and pre-surgical FA of the fornix of TLE patients with and without MTS (*Figure 2K-O*) (35). Supporting the finding of axonal loss in TLE, an electron microscopy study of the fornix of cadavers of patients who had TLE showed axonal density to be significantly reduced bilaterally, as compared to non-TLE specimens, with myelinated and non-myelinated axons affected equally (117). An interesting finding in these and other studies (105,111) is the preferential loss of small-diameter axons; the large caliber axons are spared, albeit with abnormal morphology and alterations in their myelin sheaths (*Figure 3*). In an animal model of TLE, myelinated fibers within the hippocampus showed loss of fibers with diameters of less than one μm, reduced myelin basic protein content, and stratification, collapse and disruption of the myelin sheaths (105). Although these architectural abnormalities of myelin are evident and have been reported repeatedly (*Figure 3*), it is important to mention that myelin layers are particularly sensitive to differences in tissue processing methods (118) and therefore abnormalities can only be assessed with judiciously selected control tissue that has undergone equal procedures, and caution must be exercised when attempting to compare the characteristics of myelin across studies.

Despite differences in methodological procedures, reduced axonal density is a robust finding in the temporal lobe white matter of TLE patients, and the subsequent increase of extra-cellular space is sufficient to reduce diffusion anisotropy and increase MD at the expense of increased diffusivity perpendicular to the axons, which are precisely the characteristic findings of DTI studies in TLE patients. The nature, origin and function of the affected axons are unknown, as is the mechanism that underlies progressive structural damage in TLE, which could include excitotoxic effects from seizure activity (63,119,120), or deafferentation resulting from mesial temporal cell loss (121,122).

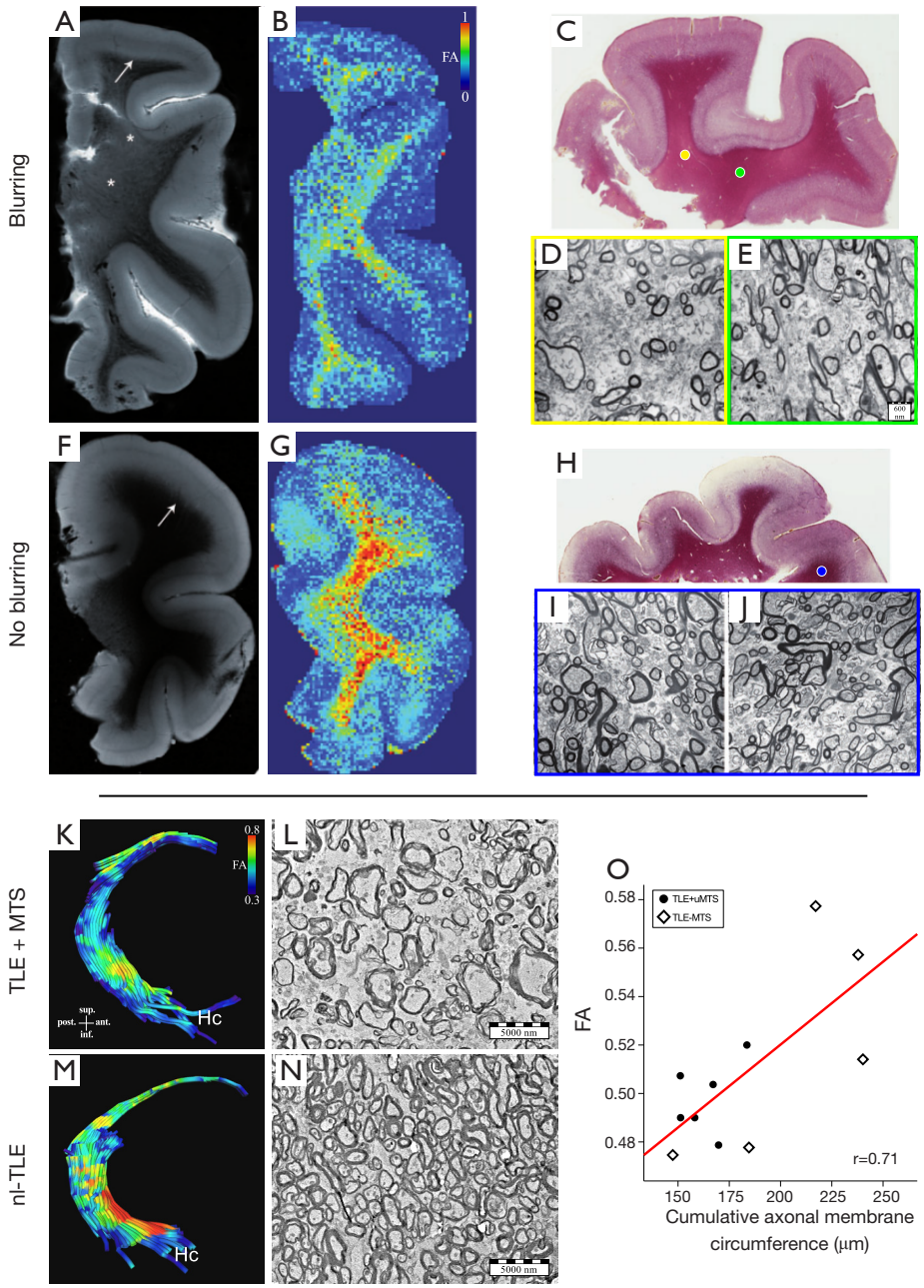

Figure 2 Histological correlates of diffusion abnormalities in temporal lobe white matter. Top panel: *ex vivo* T2-weighted and FA maps obtained at 7 T from temporal lobe specimens with (A-E) and without (F-J) blurring of the gray/white matter boundary. There is reduced diffusion anisotropy in the white matter of the specimen with blurring, which corresponds to dishomogeneous staining (C and H) and markedly reduced axonal density and increased extra-axonal spaces as seen with electron microscopy (D, E, I and J, taken from regions shown as colored dots in C and H). Bottom panel: *in vivo* pre-operative tractography, and corresponding electron microscopy of the surgically-resected fornix of a TLE patient with MTS (TLE + MTS) and a patient with non-lesional TLE (nl-TLE). The patient with TLE + MTS shows lower diffusion anisotropy of the fornix as compared to the nl-TLE patient (K and M). Electron microscopy of the specimens showed reduced axonal density and higher extra-axonal fraction in the patient with MTS (L), as compared to the nl-TLE patient (N). Analysis of eleven specimens showed a positive correlation between overall axonal membrane circumference and FA (O). A-J adapted from (79), K-O adapted from (35).

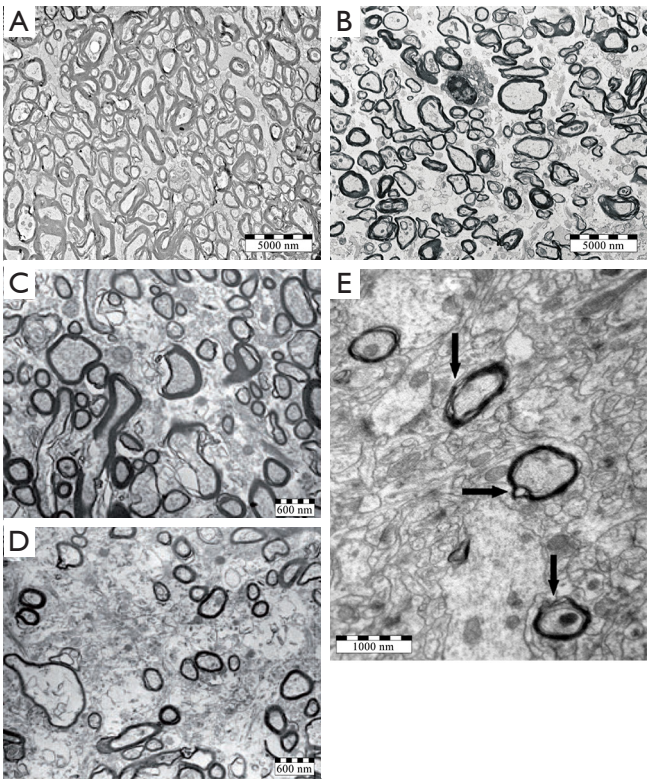

Figure 3 Electron microscopy of white matter abnormalities in TLE. The fornix of a TLE patient with MTS (B) shows reduced axonal density, increased extra-axonal space and disruption of myelin sheaths as compared to an exemplar TLE patient without MTS (A). Temporal lobe white matter shows reduced axonal density in regions of blurring between gray and white matter (D) as compared to regions without such blurring (C). (E) Myelinated hippocampal fibers of a rodent model of epilepsy show disrupted myelin sheaths (arrows). Panels A and B taken (35), panels C and D adapted from (79), E adapted from (105).

Conclusions

While the impact of dMRI on clinical decisions regarding patients with TLE has not been as dramatic as with stroke patients, it has certainly proved to be an invaluable research tool in the study of white matter in TLE. It has enabled us to shift our perception of this particular form of epilepsy from a focal to a brain network disorder, which in turn allows us to better understand its associated cognitive, psychological and psychiatric repercussions. There is considerable evidence of extensive white matter diffusion abnormalities in many brain regions which, backed by direct correlations with histology and a wealth of information derived from histopathological examinations of surgical and post-mortem specimens, very likely reflect reduced axonal density and disruption of myelin sheaths.

Given the low data requirements of the tensor model, DTI has played a prominent role in the field. However, its theoretical assumptions limit its use and interpretability in regions of white matter crossings, which are in reality the majority of white matter (123). The problems of DTI can be overcome by new analytical methods that allow sufficient data to be acquired in time intervals suitable for the clinical setting (124). Moreover, many of these methods provide more insight into tissue microstructure than the tensor model, and they are increasingly being refined and extended.

As more information regarding the microstructure of white matter in TLE patients is gathered through dMRI and extended by tractography and network-based analyses, we will be able to form a picture of their nature, temporal evolution, and whether they represent secondary damage due to ongoing seizures or a predisposing factor for their presentation. Further studies may subdivide and correlate the spectrum of TLE according to specific white matter abnormalities and the underlying epileptogenic process, be it acquired, congenital or developmental.

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