

# What does diffusion tensor imaging (DTI) tell us about cognitive networks in temporal lobe epilepsy?

Kelly M. Leyden<sup>1</sup>, N. Erkut Kucukboyaci<sup>1,2</sup>, Olivia K. Puckett<sup>3</sup>, Davis Lee<sup>3</sup>, Richard Q. Loi<sup>4</sup>, Brianna Paul<sup>5</sup>, Carrie R. McDonald<sup>1,6</sup>

<sup>1</sup>Multimodal Imaging Laboratory, University of California, San Diego, CA, USA; <sup>2</sup>San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA; <sup>3</sup>Department of Cognitive Science, <sup>4</sup>Department of Biology, University of California, San Diego, CA, USA; <sup>5</sup>Comprehensive Epilepsy Center, Department of Neurology, University of California, San Francisco, CA, USA; <sup>6</sup>Department of Psychiatry, University of California, San Diego, CA, USA

*Correspondence to:* Kelly M. Leyden. Multimodal Imaging Laboratory, 8950 Villa La Jolla Drive, Suite C101, La Jolla, CA 92037, USA.  
Email: kleyden@ucsd.edu.

**Abstract:** Diffusion tensor imaging (DTI) has provided considerable insight into our understanding of epilepsy as a network disorder, revealing subtle alterations in white matter microstructure both proximal and distal to the epileptic focus. These white matter changes have been shown to assist with lateralizing the seizure focus, as well as delineating the location/anatomy of key white matter tracts (i.e., optic radiations) for surgical planning. However, only recently have studies emerged describing the utility of DTI for probing cognitive networks in patients with epilepsy and for examining the structural plasticity within these networks both before and after epilepsy surgery. Here, we review the current literature describing the use of DTI for understanding language and memory networks in patients with temporal lobe epilepsy (TLE), as well as the extant literature on networks associated with executive functioning and global intelligence. Studies of memory and language reveal a complex network of frontotemporal fibers that contribute to naming and fluency performance in TLE, and demonstrate that these networks appear to undergo adaptive changes in response to surgical intervention. Although studies of executive functioning and global intelligence have been less conclusive, there is accumulating evidence that aberrant communication between frontoparietal and medial temporal networks may underlie working memory impairment in TLE. More recently, multimodal imaging studies have provided evidence that disruptions within these white matter networks co-localize with functional changes observed on functional MRI. However, structure-function associations are not entirely coherent and may breakdown in patients with TLE, especially those with a left-sided seizure focus. Although the reasons for discordant findings are unclear, small sample sizes, heterogeneity within patient populations and limitations of the current tensor model may account for contradictory and null findings. Improvements in imaging hardware and higher field strengths have now paved the way for the implementation of advanced diffusion techniques, and these advanced models show great promise for improving our understanding of how network dysfunction contributes to cognitive morbidity in TLE.

**Keywords:** Diffusion tensor imaging (DTI); epilepsy; temporal lobe (TL); executive function; language; memory

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## Introduction

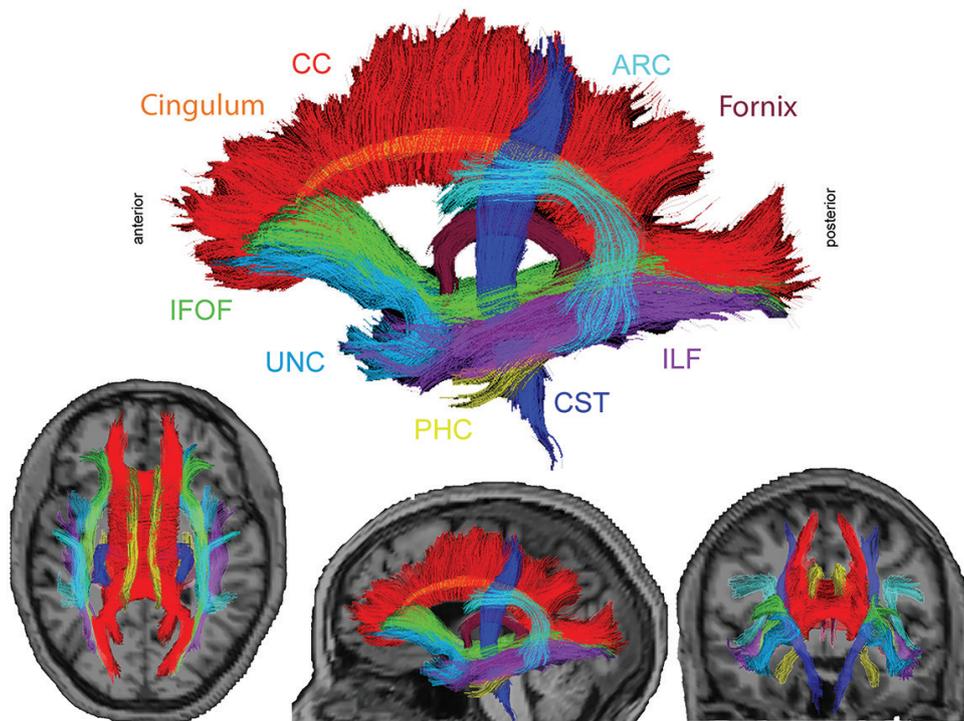
With greater appreciation of epilepsy as a network disorder, diffusion tensor imaging (DTI) has emerged as one of the most popular imaging modalities for studying network dysfunction associated with seizures in both children and adults. DTI has a broad range of applications in studying epilepsy-related networks, including lateralization of the seizure focus (1-5), delineating the location of key white matter pathways for surgical planning (e.g., optic radiations) [see (6) for a recent review; (7)], and understanding total white matter burden associated with different epilepsy syndromes (8-13). Emerging DTI literature also describes how disruptions in white matter networks contribute to cognitive morbidity and post-operative cognitive decline in patients with epilepsy, as well as how adaptive changes in white matter networks may allow for inter- and intra-hemispheric reorganization of function.

In this article, we review the current literature demonstrating the unique contributions of DTI to understanding cognitive dysfunction in patients with

temporal lobe epilepsy (TLE). Since the majority of work to date has surrounded language and memory networks in TLE this topic will be the primary focus of our review. We also survey the extant literature on how white matter microstructure can probe networks that underlie aspects of executive functioning and global intelligence in epilepsy. Finally, we address limitations of the tensor model and discuss how advanced diffusion techniques may improve white matter-cognitive associations in TLE.

## What can DTI tell us about language networks in TLE?

Perhaps the area that has received the most attention surrounds the use of DTI for mapping the structure and localization of language networks in healthy controls and patients with TLE. Several white matter tracts, including the arcuate fasciculus (ARC), uncinate fasciculus (UNC), inferior longitudinal fasciculus (ILF), and the inferior frontal occipital fasciculus (IFOF) have emerged as important fibers in the study of language networks (see *Figure 1*). In



**Figure 1** DTI fiber tracts that are commonly studied in relation to TLE and cognition. DTI, diffusion tensor imaging; TLE, temporal lobe epilepsy; CC, corpus callosum; ARC, arcuate fasciculus; ILF, inferior longitudinal fasciculus; CST, corticospinal tract; PHC, parahippocampal cingulum; UNC, uncinate fasciculus; IFOF, inferior fronto-occipital fasciculus.

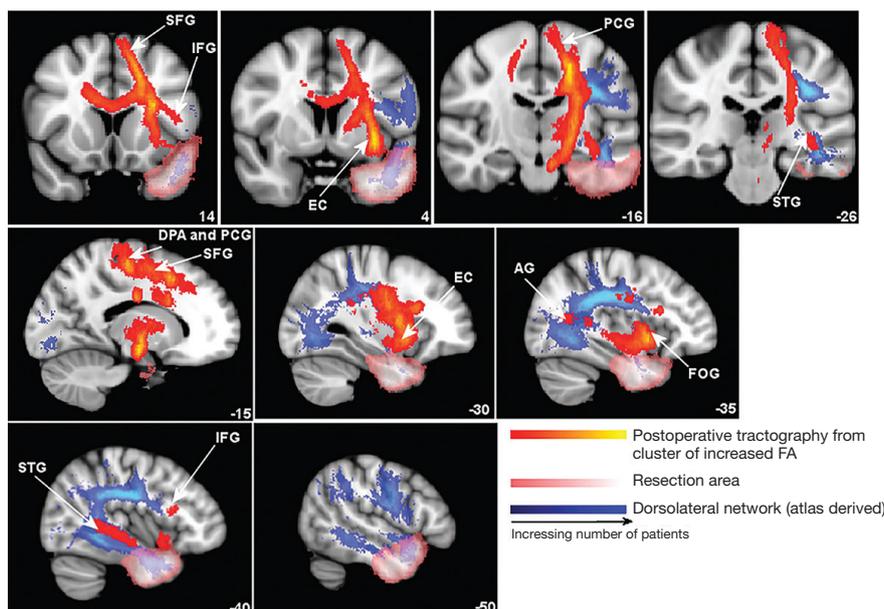
particular the ARC, which includes the frontotemporal portion of the superior longitudinal fasciculus (SLF), is a fiber long known to be important in language functioning as it connects areas involved in language comprehension (i.e., Wernicke's area) in the posterior superior temporal gyrus to areas involved in language expression (i.e., Broca's area) in the inferior frontal gyrus (14). Another commonly studied fiber is the UNC, a curved fiber that connects the anterior temporal lobes (TL) to the frontal lobes (15). The ILF connects the occipital lobe to the anterior TL running laterally and inferiorly above optic radiation fibers (16). Finally, the IFOF is a relatively long fiber running from occipital cortex passing through temporal/basal areas and the superior parietal lobe to the frontal lobe (17). The ARC, UNC, ILF and IFOF have all been implicated as facets of a complex network of fibers involved in language performance, where damage to one or more of these fiber tracts can lead to impairment in specific language skills.

Research using DTI to probe language networks in patients with TLE has used two basic approaches: either examining how DTI-derived metrics, typically fractional anisotropy (FA) or mean diffusivity (MD), correlate with impairment on neuropsychological measures of language (e.g., naming, fluency), or investigating how FA/MD laterality within frontotemporal fiber tracts corresponds to language laterality as determined by functional MRI (fMRI) or the intracarotid amobarbital procedure (IAP). With regard to the former, our lab applied probabilistic tractography to a group of 17 patients with TLE and 17 controls and demonstrated that increased MD of the ARC and UNC, along with decreased FA of bilateral ARC, UNC, and left IFOF were related to poorer naming performances in patients with TLE, but not controls (18). Not surprisingly, the strongest correlation was observed between FA of the left ARC and naming ( $r=0.80$ ,  $P<0.0001$ ) and this association held even after controlling for left hippocampal volume. We also found a strong correlation between integrity of the right ARC and visual naming in our patients. These data are commensurate with studies demonstrating right hemisphere contributions to language processing (3), and with studies suggesting partial reorganization of language to the right hemisphere in some patients with left TLE [LTLE; (19)]. Despite frontotemporal white matter correlations with naming, we did not find an association between fiber tract compromise and phonemic fluency impairments in our patient cohort. Conversely, Wang *et al.* (20) used a voxel-based approach and found that lower FA in regions of the left frontal lobe and right occipital lobe were associated with poorer semantic fluency in patients

with TLE. Although the reason for these divergent findings is unclear, it is possible that the use of different fluency measures (i.e., phonemic versus semantic) or the use of different DTI approaches (tract-based versus voxel-based) may explain these disparate outcomes.

Beyond the examination of DTI alone, Kucukboyaci *et al.* (21) took a multimodal imaging approach to understanding language impairment in TLE by examining the relative contributions of DTI-based versus structural MRI-based measures to predicting visual and auditory naming performances. Based on previous research implicating a network of frontotemporal fiber tracts in language performance (18), principal components analysis (PCA) was used to leverage the shared variance among multiple frontotemporal fiber tracts to evaluate language functioning in patients with TLE. This analysis showed that after controlling for the effects of left hippocampal volume, reduced frontotemporal FA was associated with poorer visual naming while increased MD was associated with poorer auditory naming. Neither cortical thickness nor gray-white contrast within frontotemporal regions explained language performances in TLE. These data supported our previous results demonstrating the value of DTI for understanding language performances and showed that measures of microstructural white matter integrity may be more sensitive than measures obtained from structural MRI for understanding language impairment in TLE.

A second approach to probing language networks in patients with TLE has been to examine the degree to which asymmetries in frontotemporal fiber tract FA/MD values are associated with asymmetries in fMRI language activations and results from the IAP. This approach is based on research demonstrating that in healthy individuals, a leftward asymmetry exists in frontotemporal FA and tract volumes (including the ARC, UNC, and IFOF), which correlates with typical leftward asymmetries in fMRI language activations (22,23). Thus, deviations from this expected asymmetry may imply language reorganization in TLE. Powell *et al.* (3) combined fMRI and probabilistic tractography in a cohort of patients with TLE to study language reorganization. Using fMRI tasks of verb generation and reading comprehension, they demonstrated that patients with LTLE had less lateralized language activation patterns relative to patients with right TLE (RTLE) and healthy controls. Reductions in language asymmetry were coupled with reductions in FA asymmetry within frontotemporal fiber tracts. The authors interpreted this finding as evidence of both structural and functional reorganization of language in patients with



**Figure 2** Yogarajah *et al.* (25). Group variability map (thresholded at 0.2) of tractography results after seeding from the local maxima of the cluster identified as showing an increase in FA after left anterior TLR. Tracts are superimposed upon the MNI152\_T1\_1mm\_brain image supplied with FSL. The group variability map (yellow-red, with yellow representing voxels identified by the tractography in all subjects) visualizes connections from the precentral gyrus via the internal capsule, and connections from the premotor and prefrontal areas, the superior and inferior frontal gyrus (including the deep frontal operculum), which pass via the external capsule to the posterior, superior temporal gyrus and angular gyrus. This network of connections is medial to the traditional dorso-lateral language pathway composed of the arcuate fasciculus and inferior longitudinal fasciculus. The latter pathway is shown for reference in blue and is derived from the JHU white matter tractography atlas supplied with FSL. Also shown is the group variability map for the surgical resection area (dark pink to light pink) created from the postoperative  $b=0$  images (thresholded at 0.3). It is evident that after an anterior TLR the dorso-lateral language connections may be more susceptible to resection and damage than the ventro-medial connections. FA, fractional anisotropy; TLR, temporal lobe resection; MNI coordinates are shown on each slice. DPA, dorsal premotor area; PCG, precentral gyrus; SFG, superior frontal gyrus; EC, external capsule; AG, angular gyrus; FOG, fronto-orbital gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

LTLE. Rodrigo *et al.* (12) used a similar approach and found a leftward asymmetry in FA of the ARC that was associated with leftward fMRI language activations in patients with RTLE and controls. However, this relationship did not hold for patients with LTLE. Despite reduced microstructural and functional asymmetry of the ARC in patients with LTLE, there was a lack of coherence between functional and DTI measures, which underlines the complexity of language reorganization in patients with LTLE. In a third multimodal study, Ellmore *et al.* (24) examined whether white matter microstructure of several frontotemporal fiber tracts, including the ARC, UNC, and ILF, could be used to predict asymmetric language representation, as determined by the IAP. They found that laterality indices computed from asymmetry of the ARC, but not other pathways, correctly classified 82.6% (19 of 23) patients when using the

IAP language index as the gold standard. When FA of the ARC was combined with fMRI language activation patterns and handedness, 95.6% (22 of 23) of patients were correctly classified. Overall, results of these studies indicate that increased FA and decreased MD of left frontotemporal fiber tracts are associated with better performances on measures of language functioning in patients with TLE. However, there appears to be a decreased asymmetry of language networks in many patients with LTLE that is reflected in both functional and microstructural measures and may indicate a partial or complete language reorganization associated with chronic TLE.

#### *Pre-post surgical changes in language networks*

Clinically, the greatest value of understanding language

networks in patients with TLE lies in the ability to predict the likelihood and nature of language decline following epilepsy surgery. However, few studies have addressed this in a systematic way. Yogarajah *et al.* (25) measured white matter networks and language performances before and after (average of 4.5 months) anterior temporal lobectomy (ATL) in patients with TLE and found widespread decreases in FA surrounding the resection zone, in addition to increases in FA after left ATL in a cluster of regions that included the ipsilateral external capsule, posterior limb of the internal capsule, and corona radiata (see *Figure 2*). Mean pre- and post-operative FA and parallel diffusivity (i.e., diffusion parallel to primary fiber orientation) in this cluster were significantly correlated with postoperative verbal fluency and naming scores in patients with LTLE. Specifically, greater increases in parallel diffusivity following left ATL were associated with smaller declines in language performances. The authors suggest that this cluster of altered diffusion following left ATL corresponds to a ventromedial language network located medial to the dorsolateral language network, which may be less susceptible to injury following ATL and have a greater propensity for structural reorganization. In a more recent study, Pustina *et al.* (19) used DTI to measure white matter changes before and up to several years after ATL, examining the relationship between changes in FA and verbal fluency. In patients with LTLE, better preoperative phonemic fluency was related to higher FA in the left superior corona radiata, right SLF, and right UNC. However, better post-operative phonemic and semantic fluency were associated with higher FA of the right SLF only. Given the relationship of all three clusters with language performance before surgery but only the right SLF after surgery, the authors suggest that an adaptive inter-hemispheric shift occurs following left ATL. Thus, although left ATLEs increase risk for postoperative language decline, there is a high likelihood of functional and structural reorganization to the contralateral side that may help to preserve language in many patients.

Taken together, studies using DTI to examine language networks in patients with TLE have supported the idea that multiple frontotemporal fiber tracts play a role in naming, fluency and reading comprehension, whether using neuropsychological measures or fMRI language tasks. However, the left ARC remains the fiber tract most associated with language performances in healthy controls and patients with TLE. Although there does not appear to be a one-to-one correspondence between functional and microstructural asymmetries, patients with LTLE are more likely to have

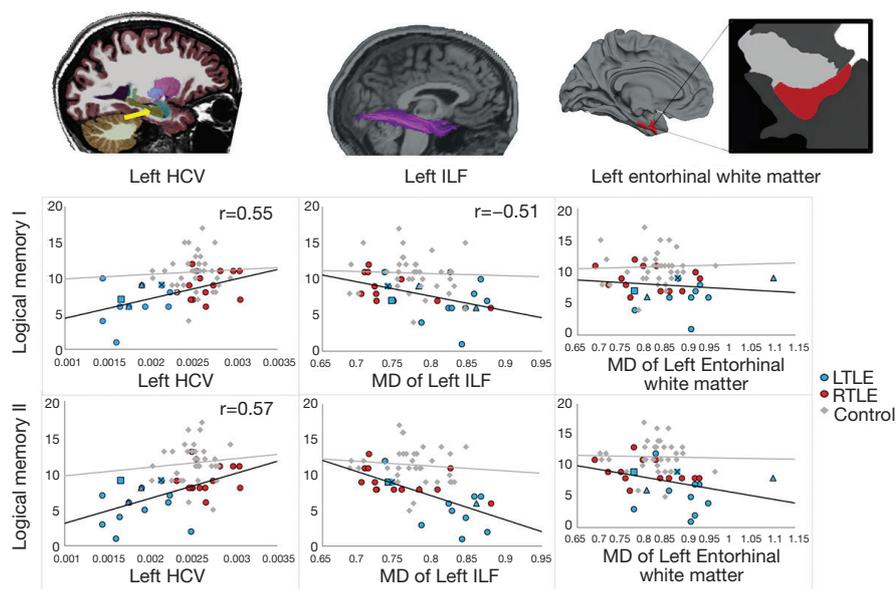
less left-lateralized DTI and fMRI patterns, consistent with the concept of inter-hemispheric language reorganization in TLE. In addition to new insights into pre-operative language reorganization, DTI has provided evidence that post-operative reorganization and adaptive changes may occur within parallel language networks following left ATL, and this reorganization may occur within intra-hemispheric (3,25) or inter-hemispheric (12,19) networks.

### What can DTI tell us about memory dysfunction in TLE?

Between 29-47% of patients with TLE present with verbal and/or nonverbal impairments in episodic memory (26,27), making memory dysfunction the most common cognitive co-morbidity in TLE. Thus, imaging of networks that underlie memory functioning has received considerable attention in the epilepsy literature.

Microstructural damage to the hippocampus itself, as well as to fiber tracts that originate in or course through the TL, have been implicated in memory dysfunction in TLE. Lui *et al.*, (28) examined the relationship between medial temporal and whole brain diffusion abnormalities in TLE patients and found that the apparent diffusion coefficient (ADC) of the ipsilateral hippocampus and parahippocampus was significantly increased in patients. ADC within the hippocampus, particularly the left hippocampus, was related to poorer verbal and visuospatial memory in patients. There was also a strong trend between visuospatial memory and ADC of the right hippocampus that did not reach significance ( $P=0.08$ ). Work from our lab has supported the importance of hippocampal MD in verbal memory, showing that hippocampal volume and MD of the left hippocampus contribute unique variance to memory scores (29).

The UNC has received considerable attention in studies of memory functioning due to its connections between prefrontal and medial temporal regions associated with memory (30). Diehl *et al.* (31) explored the relationship of the UNC to auditory and verbal scores of both immediate and delayed memory abilities in patients with TLE, finding that reduced FA of the left UNC was associated with poorer auditory memory in both LTLE and RTLE, while increased ADC and radial diffusivity were associated with poorer auditory memory in LTLEs only. For the right UNC, reduced FA was associated with poorer performance on visual delayed memory in LTLE, but no associations were found in patients with RTLE. This study provides evidence that damage to fiber tracts that emanate from the medial



**Figure 3** McDonald *et al.* (33). Scatterplots depicting the relationship between left hippocampal volume (HCV) (left), MD of the left ILF (middle) and MD of the pericortical entorhinal white matter (right) with LM I and LM II scores for patients and controls. Magnification of the left entorhinal white matter shows the distance below the cortical surface in which the white matter was sampled. Left-handed patients are coded as triangles, patients who have bilateral language dominance according to the IAP are coded as squares, and one patient who is both left handed had bilateral language dominance is coded as a square with an X in the middle. MD, mean diffusivity.

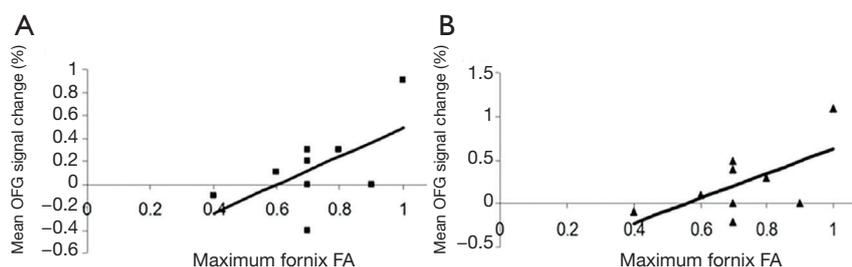
TL, in addition to the hippocampus, contribute to memory impairment in patients with TLE and that there is some material-specificity in these associations (i.e., left UNC damage is associated with verbal memory impairment, whereas right UNC damage is associated with visual memory impairment).

More recent studies have examined multiple fiber tracts and found broader associations with memory performances in TLE (18). Work from our lab has shown that increases in MD of the left UNC, parahippocampal cingulum (PHC), IFOF, and bilateral ARC, as well as decreases in FA of the right ARC are associated with poorer delayed memory for prose passages in patients with TLE. Similarly, in a cohort of 12 individuals primarily composed of LTLE patients (10 LTLE, 2 RTLE), Riley *et al.* (32) found a strong trend ( $P=0.053$ ) for reduced FA in the ipsilateral anterior TL, which includes portions of these tracts, to be associated with poorer delayed verbal memory scores.

One question of clinical importance is how well DTI measures predict memory performances relative to other imaging measures described in the literature. Our lab sought to examine the contribution of DTI relative to structural-MRI for explaining verbal memory

performance (33). We found that MD of the left ILF was a stronger predictor of verbal memory scores compared to morphometric measures including medial temporal cortical thickness, gray-white contrast and left hippocampal volume. The best model for predicting verbal memory performance included left hippocampal volume, MD of left ILF, and MD within left entorhinal white matter (see *Figure 3*). Together, these structures explained 60% of the variance in delayed memory performances. These results suggest that DTI and structural MRI may provide complementary information, as both the size of the hippocampus and microstructural integrity of surrounding white matter appear to be important to verbal memory in TLE.

Voets *et al.* (34) combined DTI with fMRI to examine reorganization within memory networks in LTLE and to determine the coherence between functional and diffusion measures. Using a tensor independent component analysis on fMRI activations from a complex scene encoding task, they were able to conduct a voxel-based analysis of FA along the UNC and fornix. Results showed that maximum FA along the fornix was associated with altered functional connectivity between unilateral medial TL and the ipsilateral orbitofrontal cortex (see *Figure 4*). No relationship was



**Figure 4** Voets *et al.* (34). Correlation between fornix coherence measures and orbitofrontal fMRI signal change during memory task performance. Measures of white matter coherence along the fornix in LTLE patients correlated significantly ( $P < 0.05$ ) with task-related mean (A) and maximum (B) BOLD percent signal change in an orbitofrontal region showing altered functional connectivity with the medial TL in LTLE patients. OFG, orbitofrontal gyrus; TL, temporal lobes.

found between UNC FA and functional activations, or between any of the DTI measures and neuropsychological scores. However, increased medial temporal-prefrontal activations ipsilateral to the seizure focus were associated with better performances on immediate and delayed story recall. The authors concluded that (I) LTLE is associated with adaptive changes within medial temporal-prefrontal memory networks ipsilateral to the seizure focus rather than inter-hemispheric shifts in memory; and that (II) white matter integrity of a primary hippocampal efferent pathway (i.e., fornix) may underlie these functional changes. Although no direct relationship was demonstrated between fornix FA and memory measures, the authors acknowledge that their small sample size ( $N=9$ ) may have attenuated any potential effects.

#### *Pre-post surgical changes in memory networks*

Although many studies have examined changes in memory networks following ATL using functional imaging [(4,35-39) for a review see (40)], no studies have systematically used DTI to examine the relationship between pre- to postoperative changes in memory networks and changes in memory performances in TLE. In a recent post-hoc analysis of five patients with LTLE (33), we show that changes in left hippocampal volume, MD of left ILE, and MD of left entorhinal white matter all appear to correlate with change in memory performances one year following left ATL. However, our sample size was too small to draw reliable conclusions. Furthermore, this analysis was restricted to the subset of regions that were significant pre-surgical predictors of memory performance. Therefore, whether or not change in memory was associated with an increase in contralateral or adjacent ipsilateral regions (suggestive

of inter- or intra-hemispheric reorganization) was not evaluated. Nevertheless, these preliminary data indicate that diffusion of left TL white matter and hippocampal volume may both be important to the prediction of verbal memory outcomes, at least following left ATL.

In summary, hippocampal volume and diffusivity seem to be sensitive predictors of memory performance in patients with TLE. Furthermore, efferent and afferent tracts of the hippocampus, in addition to those that course through the lateral TL, appear to contribute uniquely to the memory performance in patients with TLE. Finally, microstructural integrity within medial temporal fibers (i.e., fornix) may underlie functional plasticity in memory networks, suggesting some coherence between structural and functional measures.

#### **What can DTI tell us about working memory/ executive function networks in TLE?**

Executive functioning refers to a broad category of higher-level cognitive abilities that includes fluency, set-shifting, decision-making, reasoning, and response inhibition, as well as working memory (41). The use of DTI to investigate executive functions in patients with TLE is an area of emerging interest since impairment in any of these complex cognitive processes can be associated with lower educational attainment, employment and social functioning in epilepsy (42). It is now recognized that 25-30% of patients with TLE show evidence of executive dysfunction (27,43), and a similar proportion demonstrate white matter changes in frontal networks (44). However, to date, the majority of studies have focused on the extent of white matter diffusivity or executive dysfunction in TLE. Only recently have some groups started to examine the complex executive

function-DTI associations in TLE in a systematic manner.

Unlike memory and language networks, there is less consensus as to which fiber networks underlie executive dysfunction in TLE. Wang *et al.* (45) found that increased MD in multiple deep nuclei (i.e., caudate, putamen, thalamus) and decreased FA in the left frontal and occipital lobe were associated with poorer phonemic fluency in patients with TLE. They also found that impaired working memory was associated with increased MD in the splenium of corpus callosum (CC) and left putamen, and increased MD in the posterior limb of internal capsule bilaterally was associated with slower inhibition/switching performance. However, in a follow-up study, the same group (20) did not find any associations between white matter microstructure and similar measures of executive dysfunction in TLE. Dulay *et al.* [2009] examined associations between cingulum FA and working memory, problem solving, mental flexibility, phonemic fluency and learning performances in 8 patients with TLE. They found that the patients with executive dysfunction (defined as an average z-score of  $-1.64$  or lower) had significantly lower mean FA values in their right and left cingulum. They also found that increased FA in the left cingulum was associated with poorer working memory, problem solving, and phonemic fluency. Similarly, Widjaja *et al.* (46) analyzed lobar diffusion in a mixed sample of children ( $N=40$ ) with predominantly frontal, temporal and frontotemporal epilepsy in conjunction with an extensive neuropsychological battery. In this study, FA decreases in right temporal FA regions were associated with both language and executive function impairment ( $r=0.535$ ,  $P<0.001$ ;  $r=0.617$ ,  $P<0.001$ ). In addition, there were correlations between FA and executive function in bilateral frontal, left temporal, right parietal, and the body of the CC ( $r=0.500-0.542$ , all  $P$  values between  $0.001$  and  $0.005$ ). In nine patients with TLE, Riley *et al.* (47) analyzed rule learning, switching, and inhibition/switching performance together with less conventional DTI metrics (e.g., mean proportion of fibers connecting the caudate to a number of prefrontal regions). In this small sample, they found that reduced caudate volume was associated with higher perseveration on rule learning and switching, while reduced microstructural connections between left caudate and the dorsal prefrontal cortex were associated with slower inhibition/switching performance.

Combining fMRI and DTI, Winston *et al.* (48) studied working memory impairment in 54 patients with TLE and unilateral hippocampal sclerosis using a combination of a visuospatial n-back fMRI paradigm and a composite

measure of working memory from the Weschler Adult Intelligence Scale-III (WAIS-III; see *Table 1*) to create a single working memory index. In all patients with TLE, white matter integrity (FA and MD) within a frontoparietal network, in addition to the integrity of the contralateral TL, was associated with working memory performance. Similar to Widjaja *et al.*'s (46) findings in the TL, Winston *et al.* interpreted these results as supporting the importance of both a frontoparietal network and TL structures beyond the hippocampus in working memory performance. Taking a connectivity approach, Stretton *et al.* (49) examined both functional connectivity and structural connectivity of the underlying white matter tracts emanating from the hippocampus (see *Figure 4*). They found that in controls, lower FA within both left and right hippocampal networks were associated with greater ipsilateral frontoparietal functional connectivity. Interestingly, LTLE patients demonstrated the opposite effect, where greater FA within right hippocampal networks was related to increased right frontoparietal functional connectivity, suggesting potential structural compensation of the contralateral hippocampus.

Despite some evidence that white matter microstructure within frontal networks (i.e., frontoparietal and/or frontotemporal) contributes to executive functions, numerous studies have not found reliable associations between reductions in prefrontal FA and executive dysfunction in TLE (46,50). As described above, Widjaja *et al.* found executive dysfunction (i.e., impaired divided attention, response inhibition, problem solving, and mental flexibility) to be primarily associated with reductions in right TL, but not frontal lobe FA. Kucukboyaci *et al.* (50) examined canonical correlations between frontotemporal fiber tracts (e.g., IFOF, UNC, ARC, and PHC) and measures of executive functioning and found that worse visuomotor set-shifting performance was associated with decreased FA of the left IFOF, whereas worse verbal set-shifting performance was associated with decreased FA in the left ARC and left UNC, but only in controls. Conversely, this relationship appeared to be absent in patients with TLE, suggesting a breakdown in typical microstructural-function associations that could reflect aberrant developmental or degenerative processes associated with TLE.

#### ***Pre-post surgical changes in executive function networks***

Despite evidence suggesting changes in executive functioning in many patients following ATL (51), as well as

Table 1 Articles that examine DTI metrics and cognition in TLE				
Author and year	N (LTLE, RTLE)	Cognitive measures <sup>†</sup>	ROI placement <sup>‡</sup>	Cognitive correlates
Alexander et al. [2014]	13, 5, 3 bilateral	AVLT, CVMT, DSym, symsearch	Fx, cingulum	Increased FA of the Fx was associated with increased processing speed index
Diehl et al. [2008]	18, 10	Auditory: LM, VPA; visual: faces, family pictures	UNC	Reduced FA of left UNC and increased ADC of bilateral UNC in all patients. Auditory immediate index was related to left UNC ADC. Auditory delayed was correlated with left UNC ADC, RD, and FA
Dulay [2009]	4, 4	Measures of working memory, problem solving, mental flexibility, and verbal learning	Bilateral cingulum bundles	Lower mean FA values were significantly associated with executive dysfunction. Lower FA of the left cingulum was associated with working memory, problem solving, mental flexibility, lexical fluency, semantic fluency, and verbal learning. Reduced right cingulum FA was only associated with spatial learning impairment
Ellmore et al. [2010]	15, 8	fMRI: visual and auditory naming; IAP laterality indices	ARC, ILF, UNC	Model based on fMRI and DTI laterality and handedness can accurately predict IAP indices in 95.6% of patients
Kucukboyaci et al. [2012]	15, 17	CF, TMT, VF,	ARC, cingulum, IFOF, UNC	No significant results between FA and neuropsychological measures in patients
Kucukboyaci et al. [2014]	25, 27	ANT, BNT, CF, LF, WASI	CC, Fx, IFSFC, ILF, IFOF, SLF, UNC; striatum, anterior thalamic radiations, forceps minor, cingulum	Reduced FA and increased MD associated with visual and auditory naming deficits
Lui et al. [2005]	11, 9	BWMT, CVLT, LM, Rey-O	Hippocampus & parahippocampus	Negative relationships were demonstrated between ADC of the left hippocampus and delayed recall, new word recognition, and visuospatial memory, as well as ADC of the right hippocampus and new word recognition. A trend between ADC of the right hippocampus and visuospatial memory was also found
McDonald et al. [2008]	9, 8	BNT, faces, LM, VF	ARC, CST, Fx, IFOF, PHC, UNC	Increased MD was related to poorer immediate verbal memory in the left UNC, PHC, and IFOF, as well as bilateral ARC. Lower delayed verbal memory scores were related to decreased FA of the right ARC, and increased MD of left UNC, PHC, IFOF and bilateral ARC. Impaired visual naming was related to reduced FA in left IFOF, and bilateral ARC and UNC; as well as increased MD in left UNC and bilateral ARC. Verbal fluency scores were correlated with FA of the left CST
McDonald et al. [2014]	13, 13	LM	Fx, IFOF, ILF, PHC, UNC; medial and lateral temporal lobes	Impaired verbal memory was related to left hippocampal volume, and increased MD of the left ILF and left entorhinal white matter

Table 1 (continued)

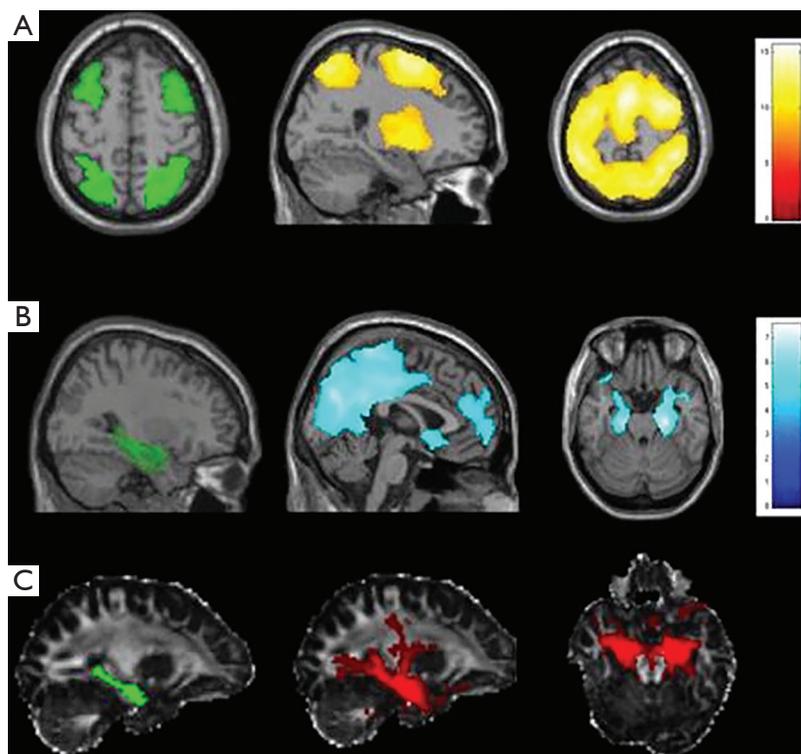
Table 1 (continued)				
Author and year	N (LTLE, RTLE)	Cognitive measures <sup>†</sup>	ROI placement <sup>‡</sup>	Cognitive correlates
Powell et al. [2007]	7, 7	fMRI language laterality	SLF	Patients with LTLE showed more symmetrical language activations, along with reduced left hemisphere and right hemisphere structural connections. Patients with stronger laterality also had highly lateralized connecting tracts
Pustina et al. [2014]	12, 12	COWAT	SLF, UNC	After anterior temporal resection, non-dominant tracts experience significant reorganization. In particular, multiple tracts that are significantly correlated with phonemic and semantic fluency pre-operatively reduce to only the right SLF maintaining significance
Riley et al. [2010]	10, 2	COWAT, peg, RBANS, stroop	Voxel-wise (whole-brain)	Mean FA was positively correlated with delayed memory in the anterior temporal lobe, and immediate memory in the mesial temporal lobe
Riley et al. [2011]	9, 2	TMT, WCST	ARC, Fx, ILF, UNC	Decreased volumes of the right Caudate were related to increased amounts of perseverative errors on the WCST. Reduced connections between the left caudate and left dorsal prefrontal regions correlated with poorer performance on trails B
Rodrigo et al. [2008]	8, 12	fMRI language laterality	ARC, IFOF	FA of the ARC was positively correlated with fMRI lateralization indices in patients with RTLE
Stretton et al. [2013]	30, 22	Working memory composite score derived from DSp, gesture span, MSeq, and fMRI task	Whole brain emanating from Hippocampus seeds	Functional connectivity between superior parietal lobe and ipsilateral hippocampus was associated with worse working memory performance in patients; structural connectivity of the hippocampus was negatively associated with intra-hemispheric functional connectivity of the superior parietal lobe
Voets et al. [2009]	9 LTLE	AMIPB, fMRI visual memory encoding, VF, WAIS-III,	Fx, UNC	No direct significant associations between diffusion based measures and neuropsychological tests due to small sample size
Wang et al. [2007]	N/A	DSp, DSym, stroop, TMT, VF	Sub-cortical structures	VF is negatively correlated with MD of left caudate, right thalamus and bilateral putamen, and positively correlated with FA of left frontal and left occipital lobes. TMT is positively correlated with MD of the posterior limb of the internal capsule. Digit span is negatively correlated with MD of the splenium and left putamen
Wang et al. [2010]	27, N/A	CF, DSf, DSym, TMT, Stroop	Normal appearing white matter (NAWM) including frontal & occipital lobes, internal & external capsules	Category fluency scores were positively correlated with FA of the left frontal lobe and right occipital lobe
Widjaja et al. [2013]	6, 3	BNT, CMS, CCPT II, CVLT, DKEFS, EVT2, Peg, PPVT IV, WASI, WCST	Genu, body & splenium of CC; bilateral frontal, temporal, parietal & occipital lobes	Right temporal FA was positively correlated with executive function and language measures. Left parietal MD was also negatively correlated with language in patients

Table 1 (continued)

Table 1 (continued)

Author and year	N (LTLE, RTLE)	Cognitive measures <sup>†</sup>	ROI placement <sup>‡</sup>	Cognitive correlates
Winston et al. [2013]	29, 25	Working memory composite score derived from DSP, gesture span, MSeq, and fMRI task	CST, SLF, cingulum	In patients, FA and MD of the frontoparietal network is associated with working memory performance, especially in the SLF, cingulum, and contralateral lobe
Yogarajah et al. [2010]	26, 20	CF, fMRI language task, LF, MGNT	FA skeleton, whole-brain tractography analysis	Mean FA decreases in tracts related to resection, and mean FA increases of ipsilateral external capsule and posterior limb of the internal capsule, and corona radiata were associated with post-operative verbal fluency and naming scores. The percentage change in PD was negatively correlated with the degree of change in verbal fluency after surgery

<sup>†</sup>, cognitive measures: AMIPB, adult memory and information processing battery; ANT, auditory naming test; BNT, Boston naming test; BVMT, brief visuospatial memory test; CVLT II, California verbal learning test II; CCPT II, Conner's continuous performance test II; CVMT, continuous verbal memory test; COWAT, controlled oral word association test; DKEFS, Delis-Kaplan executive function system; VF, verbal fluency; CF, category fluency; LF, letter fluency; EVT II, expressive vocabulary test second edition; MGNT, McKenna graded naming test; MSeq, motor sequencing task; Peg, Purdue pegboard; PPVT IV, Peabody picture vocabulary test, fourth edition; AVLT, Rey auditory verbal learning test; Rey-O, Rey-Osterrieth complex figure; RBANS, repeated battery for the assessment of neuropsychological status; Stroop, Stroop test; TMT, trail making test; WASI, Wechsler abbreviated scale of intelligence; WMS-III/IV, Wechsler memory scale III or IV; LM, logical memory; VPA, verbal paired associates; DSP, faces, family pictures, digit span; DSym, digit symbol; WCST-IV, Wisconsin card sorting test IV. <sup>‡</sup>Region of interest (ROI) placement: ARC, arcuate fasciculus; CC, corpus callosum; CST, corticospinal tract; Fx, fornix; IFOF, inferior frontal-occipital fasciculus; IFSFC, inferior frontal superior frontal cortex; ILF, inferior longitudinal fasciculus; PHC, parahippocampal cingulum; UNC, uncinata fasciculus. AD, axial diffusivity; ADC, apparent diffusion coefficient; FA, fractional anisotropy; MD, mean diffusivity; PD, parallel diffusivity; RD, radial diffusivity.



**Figure 5** Stretton *et al.* (49). Functional and structural connectivity seed regions and maps. (A) Task-positive seed regions of the bilateral middle frontal gyri and superior parietal lobes (green, axial slice) and control group FC maps showing co-activation of a fronto-thalamo-parietal network between each region (yellow); (B) task-negative seed region of the medial temporal lobe (green, sagittal slice) and control group FC map showing co-deactivation of default mode network regions and bilateral hippocampus (blue). Images are overlaid on a single-subject T1 image provided by SPM8; (C) SC seed regions of the hippocampus (green, sagittal slice) and individual control SC map showing areas connected to each hippocampus (red). The mean FA value was calculated in each subject for each hippocampal SC map and used for subsequent analyses. Images are overlaid on a control subject FA image. SC, structural connectivity; FA, fractional anisotropy.

separate studies finding changes in fiber tracts thought to underlie various aspects of executive functioning [see (42) for a review; (44)] none of these studies have examined how changes in executive function relate to changes in diffusion measures following ATL.

### What can DTI tell us about global functioning in epilepsy?

In addition to studies examining the relationship between DTI measures and performance within specific cognitive domains, a few studies have explored how white matter microstructure relates to more global measures of cognitive functioning. Vaessen *et al.* (52) applied graph theoretical analysis to examine how widespread white matter connectivity relates to full scale IQ (FSIQ; WAIS-III) and overall level of cognitive impairment in a cohort of patients

that included both TLE and frontal lobe epilepsy. Patients classified with severe cognitive impairment (N=7) showed lower clustering (a measure of brain network segregation) and higher path length (a measure of brain network integration) compared to controls and patients with little to no cognitive impairment. They found that higher FSIQ was associated with higher clustering and lower path lengths, but there was no significant relationship between whole brain white matter volumes and IQ (see *Figure 5*). They suggest that microstructural measures of network topology may provide a more sensitive measure of impairment than whole brain white matter volume alone. Using a broad range of neuropsychological measures, Alexander *et al.* (53) found that increased FA of the left fornix was related to higher processing speed, yet when analyzing memory tasks they did not find any significant correlations. In further analysis of their results, the authors found that the

association between the left fornix and processing speed was only present in patients without hippocampal sclerosis.

The relationship between DTI measures and global intelligence has also been examined in children with epilepsy. In a study described previously, Widjaja *et al.* (46) took a broader look at cognitive function in children with localization related epilepsy (LRE) and found that FA of the CC was associated with both verbal IQ and performance IQ. In general, the authors note that LRE of childhood onset is associated with more global cognitive deficits compared to LRE of adult onset, and that aberrant development of critical white matter tracts may underlie these broader impairments. Evidence of atypical diffusion and its relationship to poorer cognition in children with epilepsy suggests that seizures or other precipitating events may disrupt the typical developmental trajectories of many white matter tracts early on, and this may underlie an atypical course of cognitive development for children with epilepsy. Longitudinal studies of DTI and cognition in pediatric populations can shed light on these issues, while also providing greater insight into the nature of structural and functional reorganization in children with specific epilepsy syndromes. Ultimately, this information will facilitate our understanding of the nature of structure-function relationships in epilepsy across the lifespan.

### **Current limitations of DTI and the promise of advanced diffusion imaging for better understanding network dysfunction in TLE**

Since its inception, DTI has generated considerable interest among researchers and clinicians for its unique ability to probe the underlying structure of white matter and to quantify the nature and location of network dysfunction in patients with epilepsy. Despite its promise, there are several limitations of the tensor model that may lessen its clinical application and the degree to which DTI measures relate to clinical variables.

First, standard DTI has a low spatial resolution relative to the underlying white matter structure. That is, the voxel size is typically 2-3 mm and the tensor model assumes that all fibers within a voxel are well-described by a single orientation estimate. In reality, a single voxel is likely to include multiple fiber tracts with unique orientations, and therefore, DTI is not well equipped to resolve crossing fibers. Second, partial voluming of gray matter, white matter, and cerebrospinal fluid is often problematic, complicating the measurement of tissue structure,

particularly in peripheral white matter and gray matter (54). Third, the standard tensor models diffusion as a Gaussian distribution (55), which does not appear to reflect biological reality. A number of additional limitations of DTI include distortions resulting from motion, eddy currents, and inhomogeneous static magnetic fields. For excellent reviews of both technical and model-based limitations of DTI, see Winston (56) and Abhinav *et al.* (57).

These known limitations of DTI have led to the emergence of a number of advanced diffusion models with greater promise for resolving crossing fibers and quantifying more specific intravoxel tissue properties. Among these advanced diffusion measures, the ball-and-stick model, diffusion kurtosis imaging (DKI) and restriction spectrum imaging (RSI) have gained recent popularity for measuring network pathology associated with neurosurgical populations and neurodegenerative disease (57). The ball-and-stick method is a specific form of multiple tensors that models free diffusion (ball) and axons (sticks) and is implemented within the FSL software package. DKI is another extension of conventional DTI, which utilizes multiple diffusion weightings (b-values) to quantify the non-monoexponential decay in diffusion data and is sensitive to changes in non-Gaussian components of water diffusion (58). RSI is a model-based, multiple b-value approach that can separate cylindrically-restricted diffusion within axons from other tissue properties (e.g., vasogenic edema), allowing for improved visualization and quantification of fiber tracts in regions of edema or associated pathology (59). These are just a few of the emerging methods that may provide additional insight into the complex mechanisms underlying network damage in epilepsy.

These advanced diffusion techniques have only begun to emerge within the epilepsy literature and be used to examine network dysfunction in TLE. Lee *et al.* (60) used DKI to examine the microstructural integrity of early myelinating versus late myelinating tracts in TLE and found greater reductions in mean kurtosis (MK), parallel kurtosis, and axial kurtosis in late vs early myelinating tracts, including the ILF and SLF. Furthermore, kurtosis metrics were more sensitive to group differences in late myelinating tracts relative to FA, which may reflect their greater sensitivity to complex changes in heterogeneous tissue compartments (i.e., axonal loss and permeability changes between intra- and extra-axonal tissue compartments) relative to standard diffusion measures. Thus, advanced diffusion measures show great promise for improving the quantification of fiber bundles with complex anatomy as well as providing more

specific measures of pathology in TLE, and it is possible that they will also provide greater insight into how network changes lead to cognitive dysfunction in TLE.

### Summary and future directions

Over the past two decades, DTI has provided considerable insight into the relationship between network changes and cognitive dysfunction in TLE, particularly with respect to language and memory. In concert with fMRI, DTI has increased our understanding of pre- and postoperative reorganization of language and memory networks and indicated the possibility that these adaptive network changes may occur both inter- or intrahemispherically. In particular, language studies have shown that, in addition to the ARC, a number of other frontotemporal tracts including the UNC, ILF and IFOF are important for naming and fluency performances. Furthermore, DTI studies have demonstrated that in addition to the hippocampus, the UNC, ILF, ARC, PHC, IFOF and fornix appear to be part of a complex memory network. The literature has been far less conclusive as to which white matter networks are associated with executive dysfunction and global cognitive impairment in TLE, or how changes in white matter networks following ATL influence these domains. These studies have been complicated by relatively small sample sizes, the diverse aspects of executive functioning surveyed in the literature (i.e., inhibition, task switching, working memory, etc.) and heterogeneous patient cohorts. Thus, future studies that address intricate associations between white matter integrity and these more complex cognitive functions in TLE are greatly needed.

Finally, there are a myriad of unanswered questions of theoretical and clinical importance to the field of epilepsy that DTI studies are uniquely poised to address, alone or in combination with other imaging modalities. Among the most provocative are the following: What are the network changes that occur in response to initial precipitating injuries (IPIs) in epilepsy, and how do these changes set the course for functional reorganization? Can specific preoperative markers of network integrity in TLE help to quantify individual risk of cognitive decline following different surgical approaches (e.g., ATL versus laser ablation)? Does cognitive rehabilitation of memory or other cognitive impairments in TLE result in adaptive network changes that map onto measurable cognitive gains? Answering these questions could have a pivotal impact on the field by providing insight into the development of

cognitive dysfunction in TLE, as well as how cognitive networks are altered by surgical, pharmacological, and neuropsychological interventions. In doing so, multi-site projects with larger patient samples and funding structures that encourage both reproducibility and translational applications will be essential for obtaining results that are both statistically and scientifically meaningful.

### Conclusions

Improving structural-cognitive correlations in TLE will likely depend on a variety of factors that include further development of imaging hardware, diffusion models, and post-processing algorithms/analytic models. As noted, advanced diffusion models show great promise for providing better quantitative data with regards to crossing fibers and intravoxel tissue microstructure, and they may strengthen microstructural associations with cognition in TLE. However, most cognitive processes are complex and likely recruit multiple cortical and subcortical networks that may vary across individuals (61). Furthermore, partial or atypical reorganization of function may occur in many patients, further complicating even the more reliable structure-function associations (i.e., language). Given that no single neuroimaging measure is without limitations, multimodal imaging studies that combine information from functional, structural, and diffusion imaging may provide the greatest insight into network dysfunction in patients with TLE.

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