The behavioral and cognitive comorbidities of epilepsy are increasingly recognized, but their etiologies remain elusive. Advances in structural and functional neuroimaging have led to increasing understanding of the brain systems that may be abnormal in individuals with epilepsy and that contribute to these cognitive difficulties.1

In this issue of Neurology®, McDonald et al.2 relate performance on tests of memory and language to white matter fiber tract integrity in 17 patients with temporal lobe epilepsy (TLE). The investigators used diffusion tensor imaging (DTI), an MRI technique that measures the movement of water molecules along white matter tracts, and quantified two DTI measures of tract integrity: fractional anisotropy (FA, which decreases in disease) and mean diffusivity (MD, which increases in disease) in TLE. They focused on fibers with connections related to the temporal lobe: the uncinate fasciculus (UF), arcuate fasciculus (AF), fornix (FORX), parahippocampal cingulum (PHC), and inferior fronto-occipital fasciculus (IFOF). Moreover, they related DTI measures of tract health to neuropsychological tests that can be impaired in TLE: immediate and delayed verbal and nonverbal memory, verbal fluency, and confrontation naming.

The investigators found significant DTI changes in temporal lobe fiber tracts of patients with TLE relative to controls, although no differences were seen in the corticospinal tract. Moreover, patients with TLE showed significant correlations between these DTI changes and poor performance on neuropsychological measures. Lower verbal memory scores were associated with abnormalities in left UF, PHC, and IFOF, for example, and lower nonverbal memory scores were associated with abnormalities in bilateral AF and left UF, PHC, and IFOF. Confrontation naming scores were associated with abnormalities of bilateral AF and UF, and with left IFOF. Hierarchical regression showed that left hippocampal volume (corrected for intracranial volume) predicted verbal memory scores. After the contributions of age and hippocampal volume were accounted for in the model, the left IFOF was a predictor of delayed verbal memory; multiple fiber tracts, both in the left hemisphere (left AF, left IFOF) and bilaterally (UF), predicted confrontation naming scores.

Previous groups also have found that the integrity of UF3 and parahippocampal gyrus4 are related to verbal memory. McDonald et al. extend these observations to additional frontotemporal projections that are increasingly recognized as important for episodic memory, and to language processing. White matter changes thus may play a crucial role in the cognitive deficits of patients with TLE. These results also underscore the growing realization that focal epilepsy affects brain systems that may call on multiple anatomic regions.

The most important limitation of the study is that the findings are correlative, and do not speak to causation. It might have been useful to identify the exact location of the seizure focus (i.e., mesial vs lateral temporal), for example, and thus inform the relationship of the focus to the integrity of the studied tracts. This information might have helped to answer whether the abnormal tracts shared a typical anatomic relationship to the seizure focus, or whether tract integrity was similarly affected for patients with any seizure focus within the temporal lobe. Another factor that can have significant effects on both cognitive function and brain volume is chronic antiseizure medication use; in a larger patient group, perhaps this potential confound could be explored further.

These observations nevertheless open a new chapter in studies of the root cause of cognitive dysfunction in epilepsy. Prior work attributed cognitive difficulties to nociferos cortex in the area of a seizure focus. McDonald et al.2 suggest that another factor is the disruption of the large-scale neural networks that involve neighboring regions as well as distant functional circuits in cognitive functions. This study also highlights the question of whether the spread of
seizures and cognitive abnormalities both arise from a common pathology affecting white matter tracts. These are the critical questions that we must struggle toward answering. Being able to stop seizures is paramount, and this report suggests that we may be able to address the significant morbidity associated with epilepsy-related cognitive decline at the same time.

REFERENCES