Connectomics 2.0: Connected or Not, Is This the Question?

Preoperative Automated Fibre Quantification Predicts Postoperative Seizure Outcome in Temporal Lobe Epilepsy.

Keller SS, Glenn GR, Weber B, Kreilkamp BAK, Jensen JH, Helpern JA, Wagner J, Barker GJ, Richardson MP, Bonilha L. *Brain* 2017;140 (1):68–82.

Approximately one in every two patients with pharmacoresistant temporal lobe epilepsy will not be rendered completely seizure-free after temporal lobe surgery. The reasons for this are unknown and are likely to be multifactorial. Quantitative volumetric magnetic resonance imaging techniques have provided limited insight into the causes of persistent postoperative seizures in patients with temporal lobe epilepsy. The relationship between postoperative outcome and preoperative pathology of white matter tracts, which constitute crucial components of epileptogenic networks, is unknown. We investigated regional tissue characteristics of preoperative temporal lobe white matter tracts known to be important in the generation and propagation of temporal lobe seizures in temporal lobe epilepsy, using diffusion tensor imaging and automated fibre quantification. We studied 43 patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis and 44 healthy controls. Patients underwent preoperative imaging, amygdalohippocampectomy and postoperative assessment using the International League Against Epilepsy seizure outcome scale. From preoperative imaging, the fimbria-fornix, parahippocampal white matter bundle and uncinate fasciculus were reconstructed, and scalar diffusion metrics were calculated along the length of each tract. Altogether, 51.2% of patients were rendered completely seizure-free and 48.8% continued to experience postoperative seizure symptoms. Relative to controls, both patient groups exhibited strong and significant diffusion abnormalities along the length of the uncinate bilaterally, the ipsilateral parahippocampal white matter bundle, and the ipsilateral fimbria-fornix in regions located within the medial temporal lobe. However, only patients with persistent postoperative seizures showed evidence of significant pathology of tract sections located in the ipsilateral dorsal fornix and in the contralateral parahippocampal white matter bundle. Using receiver operating characteristic curves, diffusion characteristics of these regions could classify individual patients according to outcome with 84% sensitivity and 89% specificity. Pathological changes in the dorsal fornix were beyond the margins of resection, and contralateral parahippocampal changes may suggest a bitemporal disorder in some patients. Furthermore, diffusion characteristics of the ipsilateral uncinate could classify patients from controls with a sensitivity of 98%; importantly, by co-registering the preoperative fibre maps to postoperative surgical lacuna maps, we observed that the extent of uncinate resection was significantly greater in patients who were rendered seizure-free, suggesting that a smaller resection of the uncinate may represent insufficient disconnection of an anterior temporal epileptogenic network. These results may have the potential to be developed into imaging prognostic markers of postoperative outcome and provide new insights for why some patients with temporal lobe epilepsy continue to experience postoperative seizures.

Commentary

It is a major understatement to say that MRI has revolutionized our approach to the evaluation and diagnosis of patients with epilepsy. Our patients are fortunate to live in times when techniques like pneumoencephalography have long been replaced by MRI and its derivatives, including magnetic resonance spectroscopy (MRS) or diffusion tensor imaging (DTI), and that these techniques can be used to predict epilepsy course and/or outcome of epilepsy surgery. It is clear that high-quality imaging provides important information that is invaluable to patients with new-onset and chronic epilepsy alike (1). Modern imaging techniques, frequently supplemented by methods that are sophisticated and difficult to replicate without lengthy training in mathematics and statistics data processing methods, provide new or additional information that may inform us about epilepsy pathophysiology and/or change the approach to evaluating the patient or predicting the outcome An example of this is the study by Keller that used DTI to examine how this technique contributed to epilepsy surgery outcome prediction.

There is a growing body of studies in which the investigators have applied DTI alone or in combination with other techniques to evaluate patients with focal and generalized epilepsies, including temporal lobe epilepsy (TLE). As a technique, DTI provides information regarding the intrinsic properties of the white matter and its architecture as well as

Epilepsy Currents, Vol. 17, No. 3 (May/June) 2017 pp. 155–156

structural connectivity by noninvasively measuring the diffusion of water molecules. Typically used in DTI, scalar indices such as fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) are implemented to characterize the integrity of the white matter. While FA provides a measure of water diffusion in a voxel, AD and RD provide information regarding the movement of water along the length of and perpendicular to axons; MD is a measure of average diffusion. These measures rely on the assumption that the motion of water molecules within a voxel is unrestricted and follows Gaussian distribution and that the DTI signal decays monoexponentially (2). Because these assumption may not be entirely correct in biological systems, new methods of diffusion data collection and analysis have been developed to address these and other concerns (e.g., diffusion kurtosis, high angular resolution diffusion imaging, neurite orientation dispersion and density imaging) (1). In the study by Keller et al., the authors used one of the newer and more advanced methods of DTI data analysis—automated fiber quantification (AFQ) — to comprehensively analyze the tissue characteristics along the white matter bundles in the temporal lobes. The choice of AFQ was dictated by the fact that this technique allows medical professionals to consider regional intra-tract integrity rather than average characteristic along the entire white matter tract. These authors were able to show that all patients included in the study, independent of the outcome of the anterior temporal lobectomy, had significant differences in AFQ compared with healthy controls. Further, only patients with persistent postresection seizures showed significant AFQ abnormalities in the *ipsilateral* fornix that were outside the resection area; additional abnormalities in patients who did not achieve seizure freedom after resection were observed in the *contralateral* hippocampus. Further, they showed that the presence of uncinate fasciculus abnormalities ipsilateral to the resection classified the site of seizure onset in 98% of the patients. Overall, these findings are interesting and add to our understanding of the pathophysiology of TLE and of epilepsy surgery failures. While up-to-date DTI has been used in the presurgical evaluation of patients with epilepsy to delineate the white matter tracts that need to be avoided during the surgical procedure, for example, to avoid or decrease the chance of postresection visual field cuts (3), it remains unclear whether knowledge of medial temporal lobe connectivity adds to the current armamentarium of presurgical testing.

What this study does is adds to the growing body of literature that focuses on the application of connectomics to the presurgical evaluation of patients with TLE. But beyond that, what else? Seizures are thought to start in gray matter structures and then spread within and outside those structures via connection (i.e., *connectomics*), including white matter tracts. Thus, it is not surprising to find focal abnormities in the white matter connections that originate in the gray matter structures that generate or are involved in seizures. But, it is not clear why the presence (or absence) of abnormalities in these tracts would be predictive of response to a surgical intervention since it is not the white matter tracts but rather the gray matter structures that they connect to that generate seizures. This study also does not address or answer the question of which was first—seizures with secondary injury in the white matter tracts or vice versa—and the finding of *contralateral* DTI abnormalities remains unexplained, although the authors put forth hypotheses trying to explain it. A nice and meaningful contribution would have been performing postresection DTI to evaluate whether these contralateral abnormalities persisted or whether they resolved after surgery—akin to the contralateral metabolic abnormalities demonstrated with MRS that have resolved after resection (4).

The question also remains as to how these findings apply to patients who undergo standard anterior temporal lobe resection or laser ablation versus amygdalo-hippocampectomy, which was the standard approach in this study. The extent of surgical resection is different in these three procedures, and hence, the results may not be applicable to patients who undergo surgical management of TLE in the United States, where most, if not all, patients undergo either standard temporal lobe resection with resection margin 4 to 6 cm posterior to the temporal tip or, more recently, laser ablation (5, 6). Finally, how do these findings apply to individual patients and do they have any additive value in the presurgical evaluation of patients with TLE? The TLE evaluation is fairly standardized, and while newcomers are welcome, their utility needs to be tested prospectively, using a randomized approach, and compared against the standard workhorses of presurgical evaluation, including clinical semiology, EEG, neuropsychological testing, PET, and structural MRI. Thus, this study while very interesting, only adds to the list of potentially useful techniques in this setting but does not necessarily provide an answer as to whether we should use AFQ in every patient with TLE to predict seizure outcomes. But this study provides additional and important insights into the pathophysiology of TLE and establishes a potential springboard for the development of a trial that would test its contributions to the process.

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