Epilepsy Currents
2021, Vol. 21(5) 323–325

DOI: 10.1177/15357597211021020
journals.sagepub.com/home/epi
SAGE

Disentangling the Gordian Knot of Drug-Resistant Epilepsy

Structural Brain Network Abnormalities and the Probability of Seizure Recurrence After Epilepsy Surgery

Sinha N, Wang Y, Moreira da Silva N, et al. *Neurology*. 2021;96(5):e758-e771. doi:10.1212/WNL.0000000000011315

Objective: We assessed preoperative structural brain networks and clinical characteristics of patients with drug-resistant temporal lobe epilepsy (TLE) to identify correlates of postsurgical seizure recurrences. Methods: We examined data from 51 patients with TLE who underwent anterior temporal lobe resection (ATLR) and 29 healthy controls. For each patient, using the preoperative structural, diffusion, and postoperative structural magnetic resonance imaging, we generated 2 networks: presurgery network and surgically spared network. Standardizing these networks with respect to controls, we determined the number of abnormal nodes before surgery and expected to be spared by surgery. We incorporated these 2 abnormality measures and 13 commonly acquired clinical data from each patient into a robust machine learning framework to estimate patient-specific chances of seizures persisting after surgery. Results: Patients with more abnormal nodes had a lower chance of complete seizure freedom at 1 year, and, even if seizure-free at 1 year, were more likely to relapse within 5 years. The number of abnormal nodes was greater and their locations more widespread in the surgically spared networks of patients with poor outcome than in patients with good outcome. We achieved an area under the curve of 0.84 $\pm$ 0.06 and specificity of 0.89 $\pm$ 0.09 in predicting unsuccessful seizure outcomes (International League Against Epilepsy [ILAE] 3-5) as opposed to complete seizure freedom (ILAE 1) at 1 year. Moreover, the model-predicted likelihood of seizure relapse was significantly correlated with the grade of surgical outcome at year 1 and associated with relapses up to 5 years after surgery. Conclusion: Node abnormality offers a personalized, noninvasive marker that can be combined with clinical data to better estimate the chances of seizure freedom at 1 year and subsequent relapse up to 5 years after ATLR. Classification of evidence: This study provides class II evidence that node abnormality predicts postsurgical seizure recurrence.

Commentary

Animal data as well as histopathological, radiological, and electrophysiological human data converge that epilepsy constitutes a neural network disorder.[1] Implicit to this concept is that a set of tightly interwoven cortical and subcortical brain structures are responsible for the phenotypical expression of seizures and their peri-ictal repercussions.[2] That notion gave rise to a whole research field in epilepsy that of "connectomics," aiming to decipher the intricacies of networks frequently as complicated as the Gordian Knot in Asia Minor, a conundrum of several knots all so firmly entwined that it was impossible to see how they were fastened.[3] As a result, unraveling these connections bears the promise of conquering a surgical cure for epilepsy, in the same way that disentangling the Gordian Knot, once held the promise of ruling the whole Asia itself.[3]

The study of Sinha et al[4] utilizes computational analysis of presurgical structural and diffusion-weighted magnetic resonance imaging (MRI) as well as postsurgical structural MRI data of patients who underwent anterior temporal lobectomy (ATL) for drug-resistant temporal lobe epilepsy (TLE) compared to healthy controls in order to chart the presurgical epilepsy network and its postsurgical remnant. The authors conclude that patients with higher burden of abnormal nodes in the surgically spared network had both lower chances of achieving seizure freedom in one year and lower chances of maintaining seizure freedom over a 5-year period. Moreover, by incorporating clinical data to their network analysis through sophisticated machine learning techniques, the authors create a prediction model that can reliably forecast the likelihood of both seizure freedom and seizure relapse postoperatively. Interestingly, the remaining load of abnormal nodes postsurgically is shown to be more predictive of those 2 outcomes of interest compared to the entire presurgical network and to the evaluated clinical features.

Following prior studies that also attempted preoperative mapping of an epileptic network through structural and functional imaging and assessed its remainders postoperatively,[5,6]

this investigation is noteworthy since it attempts to integrate clinical parameters to network analysis with the intent to eventually accomplish a "virtual resection" tool for clinical practice. The premise of such a strategy is to incorporate the surgical approach into the prediction model and assess "what is/will be left behind." Although this reasoning is ostensible, it may not always hold true. For example, despite the potential of secondary epileptogenesis, targeted approaches of hypothalamic hamartomas can "run down" more widespread epileptic networks,[7] while extensive resections of epileptic networks can still fail due to remodeling of the initial network or emergence of secondary epileptogenic zones.[6] As such, addressing the majority of the abnormal nodes of an epileptic network may not always be neither necessary nor sufficient to result in a surgical cure. Focusing specifically in lesional mesial TLE, an epilepsy type closer to the current investigation, more confined destructive surgeries such as selective amygdalohippocampectomy,[8] stereotactic laser amygdalohippocampotomy,[9] or stereotactic radiosurgery[10] hold substantial chances of seizure freedom in carefully selected individuals, despite their admittedly lower rates compared to more generous temporal lobe resections.

Beyond this theoretical debate, there are several other aspects that merit discussion. The use of healthy controls provides a solid means for comparison to identify and estimate the abnormal nodes in patients with mesial TLE, but it may be worthwhile investigating the use of patients with drug-responsive mesial TLE as controls to better understand what drives pharmacoresistance and which network characteristics are really important to surgically address. Certain clinical variables that play a cardinal role in surgical decision-making such as clinical semiology, interictal and ictal neurophysiologic data, other imaging modalities (eg, positron emission tomography or single photon emission computed tomography), and neuropsychological evaluations were not incorporated in the prediction model. Most importantly, the study population did not undergo intracranial monitoring to confirm their suspected localization. Despite the fact that this is not common practice for a cohort like this with high rates of mesial temporal sclerosis, it might have an independent impact on the prediction model, particularly for nonlesional temporal or extratemporal cases. The issue of collinearity between some of the baseline clinical characteristics that differed between the "surgical successes" and the "surgical failures" or "relapses" (eg, older age at disease onset, higher burden of anti-seizure medications [ASMs]) is hard to disambiguate from the computationally derived node abnormality load, as both may suggest an overlapping tendency toward intractability. Analysis of "relapses" was performed only for those patients who achieved seizure freedom for at least one year postoperatively, though early relapses may have different etiological connotations from late relapses.[4] Other postoperative clinical parameters such as ASMs withdrawal could have further modified the observed outcomes. Finally, as acknowledged by the authors, the post-surgical analysis is based on presurgical imaging data. This may not necessarily reflect any postoperative modifications in the original epileptic network that could act as a cause of surgical failure or seizure recurrence.[6]

These limitations notwithstanding, the current study is a commendable endeavor to decrypt the mysteries of drug-resistant epilepsy and create noninvasive *network* biomarkers that look beyond the traditional horizons of an epilepsy *focus* approach. As such, it can help both with the understanding of disease neurobiology and for diagnostic, treatment, and prognostication purposes. In the future, the research community should expand the integrative investigation of similar clinically, neurophysiologically, and radiologically based computational prediction tools to advise on the impact of resective and disconnective surgeries beyond ATL, to predict the effect of minimally invasive surgeries such as radiofrequency thermocoagulation, laser ablation, or radiosurgery, to provide prognostic information on the use of pharmacological and neuromodulation techniques, and to extend the scope of inquiry beyond mere seizure outcomes, incorporating network analysis to assess the cognitive and affective sequelae of epilepsy and its management. Extensive validation and widespread accessibility of such tools would render them invaluable to clinical practice.

In 333 BC, Alexander the Great invaded Gordium and allegedly cut its knot prior to forming his formidable empire, as the oracle once predicted.[3] Understanding the complexity of and subsequently finding the cure for drug-resistant epilepsy may take more than a "sword's stroke," but advances like these move us closer to the target.

By Ioannis Karakis

ORCID iD

Ioannis Karakis https://orcid.org/0000-0001-5122-7211

References

1. Bernhardt BC, Bonilha L, Gross DW. Network analysis for a network disorder: the emerging role of graph theory in the study of epilepsy. *Epilepsy Behav*. 2015;50:162-170. doi:10.1016/j.yebeh.2015.06.005
2. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia*. 2002;43(3):219-227. doi:10.1046/j.1528-1157.2002.26901.x
3. Rufus QC. In: Humphreys W, ed. *Selections from the History of Alexander the Great*. Ginn & Co; 1896.
4. Sinha N, Wang Y, Moreira da Silva N, et al. Structural brain network abnormalities and the probability of seizure recurrence after epilepsy surgery. *Neurology*. 2021;96(5):e758-e771. doi:10.1212/WNL.0000000000011315
5. Bonilha L, Helpern JA, Sainju R, et al. Presurgical connectome and postsurgical seizure control in temporal lobe epilepsy. *Neurology*. 2013;81(19):1704-1710. doi:10.1212/01.wnl.0000435306.95271.5 f
6. da Silva NM, Forsyth R, McEvoy A, et al. Network reorganisation following anterior temporal lobe resection and relation with post-surgery seizure relapse: a longitudinal study. *Neuroimage Clin*. 2020;27. doi:10.1016/j.nicl.2020.102320

7. Scholly J, Staack AM, Kahane P, et al. Hypothalamic hamartoma: epileptogenesis beyond the lesion? *Epilepsia*. 2017;58(suppl 2): 32-40. doi:10.1111/epi.13755
8. Josephson CB, Dykeman J, Fiest KM, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. *Neurology*. 2013;80(18):1669-1676. doi:10.1212/WNL.0b013e3182904f82
9. Gross RE, Stern MA, Willie JT, et al. Stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Ann Neurol*. 2018;83(3):575-587. doi:10.1002/ana.25180
10. McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: systematic review and international stereotactic radiosurgery society (ISRS) practice guideline. *Epilepsy Res*. 2017; 137:123-131. doi:10.1016/j.eplepsyres.2017.08.016