From Nodes to Networks: Can Virtual Resections Predict Neurosurgical Outcomes in Focal Epilepsy?

Epilepsy is one of the most common neurological disorders, affecting more than 68 million people worldwide. Up to a third of patients have seizures that are refractory to trials of multiple medications and may suffer in terms of cognition, productivity, quality of life, and mortality. For those with focal epilepsy, where seizures are believed to originate from a localizable brain region, surgery is an important treatment option. However, identification of the epileptogenic zone can be challenging, particularly in cases of nonlesional, neocortical epilepsy. Electroencephalography (EEG) interpretation still relies primarily on visual inspection of spontaneous seizures. Various data mining efforts have evaluated seizure onset patterns, high frequency oscillations, and interictal (nonseizure) spiking activity to better delineate areas for resection, but objective, quantified methods have not yet proven reliable enough for widespread adoption. More recently, attention has turned to defining epileptogenic networks to more fully capture complex seizure dynamics and the distribution of epileptic activity.1

In their recent study published in Brain, Sinha et al2 investigated the ability of a computation model using baseline (interictal) functional connectivity to predict the epileptogenic potential of cortical areas and postoperative seizure outcomes. They used publicly available subdural strip and grid intracranial monitoring data provided by IEEG portal (https://www.ieeg.org) from 16 patients with pharmaco-resistant epilepsy treated at Massachusetts General Hospital and Mayo Clinic. The work was a collaborative effort between researchers at Nanyang Technological University, Newcastle University, University College London, and Harvard Medical School and was supported by funds from the Ministry of Education of Singapore, the Engineering and Physical Sciences Research Council of the United Kingdom, and the National Institute Neurological Disorders and Stroke in the United States.

To build their model, the authors first constructed a baseline functional network for each patient using interictal EEG recordings. Using a graph representation of the implied network, they treated every electrode in a subdural grid or strip as a node and computed the connectivity between every pair of nodes as a correlation of the 2 signals in limited frequency bands. They then investigated how this baseline network structure, or connectivity matrix, relates to the likelihood of seizure activity in each node. They constructed a mathematical model to predict the transition from the resting (nonseizure) state to the seizure state. Previous work elucidated the different initial conditions that predict onset of seizure activity in each node.3

This stochastic process focused on how multiple measures of noise input to each node affect escape time, or how quickly the node transitions to the seizure state. In the current study, Sinha et al2 incorporated patient-specific functional connectivity into their predictive model. They found that measures of network connectivity, specifically node strength and clustering coefficient, were the best predictors of seizures in their model.

The model’s predictions of seizure likelihood were sometimes, but not always, in agreement with the clinically identified seizure onset zone and subsequent resections. To validate their method, the researchers simulated how removal of nodes in the network (ie, virtual resections) would affect the connectivity matrix of the remaining nodes, average escape time, and thus seizure likelihood. They simulated the actual resections and compared their predicted outcomes to the clinical outcomes.Figure demonstrates 2 examples. Patient P1 had a clinically determined resection that removed nodes with high-simulated seizure likelihood in patient 2 removed nodes with lower seizure likelihood and resulted in a poor outcome. In 16 patients, the predicted outcomes were found to be the same as the clinical outcome for most patients (81.3%), with 87.5% sensitivity and 75% specificity.

This and other recent studies4-6 demonstrate the potential of models based on individual neurophysiology patterns to predict surgical outcomes and test virtual
resections. If further validated, such simulations could aid surgical planning. Multiple simulations could be tested to identify the ideal resection, a minimum beneficial resection, or, if the seizure focus involves eloquent cortex, an alternative resection. The authors also used their model to recommend additional resections in the patients in whom they predicted poor outcomes, though these were not actually tested.

The model developed by Sinha et al is unique for its dependence on a narrow frequency band and relatively brief random segment of baseline interictal activity. It excluded EEG elements traditionally associated with seizure susceptibility, such as high frequency oscillations and seizure onset patterns. Clinically, this would be a useful additional method of localization, particularly given that it can sometimes be difficult or time consuming to capture a sufficient number of seizures during a monitoring stay. It is also possible that more complex models including other known clinical, radiographic, and EEG predictors of surgical response, would further improve accuracy. Higher resolution recording modalities, 3-dimensional cortical and subcortical stereoelectroencephalography (SEEG) networks, and source localization techniques combining EEG and Magnetoencephalography (MEG) may also further inform future models.

The results are preliminary and there are several limitations. The clinical outcome validation study was done in a small number of patients and limited by the previously chosen resections. The reliability was also lower than some other published models, including one based solely on magnetic resonance imaging-derived structural brain morphology. EEG-based measures of correlation are known to vary with physiological circumstances not captured by the model.

However, the findings are likely to further future investigations into the relationship between network functional connectivity and seizure susceptibility and inform future computational model based approaches to the surgical treatment of pharmaco-resistant focal epilepsy.

**REFERENCES**


**Brett E. Youngerman, MD**  
**Guy M. McKhann, II, MD**  
**Department of Neurological Surgery**  
**Columbia University Medical Center**  
**New York, New York**

**Sustained Benefit of Endovascular Therapy in Acute Ischemic Stroke**

Endovascular thrombectomy for large vessel intracranial occlusion has been established beyond doubt as standard of care in select patients with acute ischemic stroke. 1 Several sentinel randomized trials were published in 2015 and were responsible for demonstrating the benefit of endovascular mechanical thrombectomy in improving outcomes as measured by modified Rankin scores (mRS) and reducing mortality. 2 These studies examined mRS scores at 90 d postintervention and found positive results with mechanical thrombectomy. While this conveyed short-term advantage for the properly selected endovascular stroke patient, sustained benefit has not been well documented in controlled trials.

The investigators for the MR CLEAN study 3 adopted an extended study design beyond the original study in which they sought to follow enrolled patients for 2 yr. The primary outcome was mRS at 2 yr and secondary outcomes were mortality and quality of life (QOL). Of the 500 patients in the original study, 391 patients had 2-yr outcome data. One hundred ninety-four were in the intervention group and 197 in the “conventional” group (who did not undergo endovascular therapy). The results of the study indicated that endovascular treated patients had statistically better odds (ratio of 1.68 and P = .007) of favorable mRS outcome at 2 yr. They also had higher QOL scores (P = .006). 4

It should be noted that the study highlights some nuances that challenge a simplistic interpretation of commonly applied assessment scales. Lower rates of mRS 0 or 1 were seen at 2 yr in comparison to 90-d scores in the original study. The interpretation was that challenges with daily activities tend to be magnified outside of rehab settings, that are typical of patients studied early in their poststroke course. This implies that the administration and documentation of mRS scores is subject to vagaries and is not infallible. Better stroke outcome measures are necessary in the broader sense of stroke trials.

Interestingly, subgroup analyses according to NIHSS (National Institutes of Health Stroke Scale) score, age, occlusion of the internal carotid artery terminus, additional extracranial internal carotid artery obstruction, time from stroke onset to randomization and the Alberta Stroke Program Early CT score did not show any relation to intervention. This may not be consistent with routine clinical experience. A plausible explanation would be the inconsistency of measurement and quantification of ischemic penumbra tissue and the need for robust, user-friendly techniques to achieve the same. The rate of major vascular events in either treatment...