Network Changes after Epilepsy Surgery: It's Time to Reconnect

Network-Targeted Approach and Postoperative Resting-State Functional Magnetic Resonance Imaging Are Associated With Seizure Outcome

Boerwinkle VL, Cediel EG, Mirea L, et al. *Ann Neurol.* 2019;86(3):344-356.

Objective: Postoperative resting-state functional magnetic resonance imaging (MRI) in children with intractable epilepsy has not been quantified in relation to seizure outcome. Therefore, its value as a biomarker for epileptogenic pathology is not well understood. Methods: In a sample of children with intractable epilepsy who underwent prospective resting-state seizure onset zone (SOZ)-targeted epilepsy surgery, postoperative resting-state functional MRI (rs-fMRI) was performed 6 to 12 months later. Graded normalization of the postoperative resting-state SOZ was compared to seizure outcomes, patient, surgery, and anatomical MRI characteristics. Results: A total of 64 cases were evaluated. Network-targeted surgery, followed by postoperative rs-fMRI normalization was significantly ($P < .001$) correlated with seizure reduction, with a Spearman rank correlation coefficient of 0.83. Of 39 cases with postoperative rs-fMRI SOZ normalization, 38 (97%) became completely seizure free. In contrast, of the 25 cases without complete rs-fMRI SOZ normalization, only 3 (5%) became seizure free. The accuracy of rs-fMRI as a biomarker predicting seizure freedom is 94%, with 96% sensitivity and 93% specificity. Interpretation: Among seizure localization techniques in pediatric epilepsy, network-targeted surgery, followed by postoperative rs-fMRI normalization, has high correlation with seizure freedom. This study shows that rs-fMRI SOZ can be used as a biomarker for the epileptogenic zone, and postoperative rs-fMRI normalization is a biomarker for SOZ quiescence.

Commentary

Focal epilepsy is now recognized as a brain network disorder, where network changes extend beyond the epileptogenic zone.[1] Neuroimaging and electrophysiology studies of network connectivity in focal epilepsy have rapidly increased over the past 2 decades, with several investigations examining surgical patients and how preoperative connectivity patterns relate to postoperative seizure outcome. However, only in the last couple of years have studies examining network changes after epilepsy surgery begun to emerge.

This resting-state functional magnetic resonance imaging (fMRI) study by Boerwinkle and colleagues is the largest to date to include serial functional connectivity measurements before and after surgery, and it is one of the few investigations of this type focused on the pediatric patient population. The study builds upon prior work by the group in which independent component analysis (ICA) is used to identify both normal and expected functional networks (eg, sensorimotor, language), as well as abnormal resting-state networks that are likely related to the epileptogenic zone.[2] The definition of these networks after ICA is based on several criteria such as fMRI spatial patterns, symmetry, and frequency. In the most recent

work, the final designation was then made by blinded reviewers. Of note, the authors report that epileptogenic networks often demonstrate higher frequency signal oscillations than healthy areas, and therefore they incorporated this criterion into the network definition. Delineation of these epileptogenic networks then helped guide the authors' surgical targeting, which is unique, as most centers performing presurgical connectivity analysis have not integrated those methods into clinical decision-making. Functional imaging and analyses were then repeated 6 to 12 months after surgery, and investigators determined whether epileptogenic networks had "normalized," which essentially meant the network was no longer detected by ICA. Also noted were cases in which networks were still detected, but the spatiotemporal features were less prominent.

Overall, the network-targeted surgical approach in this study resulted in seizure freedom in 64% of cases. The cohort includes a small number of patients treated with neuromodulation or disconnection alone. The investigators reported normalization of the epileptogenic networks after surgery in 61% of cases, but a sizable minority was still detected. There was a robust relationship between epileptogenic network

normalization and seizure freedom after surgery, with an overall accuracy of 84% when utilizing these resting-state analysis methods as a potential biomarker for outcome. The authors conclude that their network-targeted approach may aid presurgical planning, and that postoperative normalization of epileptogenic functional networks may help predict long-term seizure freedom.

As fMRI network analysis after epilepsy surgery is an emerging field, there are few prior investigations to compare to the present report. One small study of children undergoing epilepsy surgery did note some disruptions in low frequency fMRI signal fluctuations that improved after surgery.[3] In adult temporal lobe epilepsy (TLE), one early study suggested that certain network perturbations seen in this disorder do not improve after resection.[4] Another investigation showed that some functional connections, in particular involving contralateral hippocampus, may move further away from control values.[5] However, there is also preliminary evidence that functional connectivity of certain arousal networks, which are also perturbed in TLE, may recover closer to control values in patients with favorable postoperative seizure outcomes.[6] Nevertheless, the effects of surgery on functional networks remain unexplored in most epilepsy disorders, and postoperative network changes have not yet been related to neurocognitive outcomes, to my knowledge.

In general, studies which do show improvements in certain network connections after successful epilepsy surgery may elicit a "chicken or egg" question. Does surgery result in normalization of the altered networks, which then allows seizure freedom? Or does postoperative seizure cessation itself allow networks to normalize? In the investigation by Boerwinkle and colleagues, given that surgery removed large portions of the predefined epileptogenic networks in many patients, it is likely that the resection itself makes the network less detectable with postoperative ICA. However, it is also possible that seizure freedom may contribute to favorable network changes. Interestingly, some resting-state fMRI studies of adults with TLE have noted relationships between seizure frequency and connectivity abnormalities in limbic networks,[7,8] but this has not been explored in detail in postoperative patients.

In future studies, the relationship between network properties and seizure outcome may be better defined using serial connectivity measurements after surgery, in which the evolution of network changes can be tracked, and the potential effect of late seizure recurrence on connectivity can also be ascertained. Final limitations worth mentioning in the study by Boerwinkle and colleagues include the absence of a healthy control group, which may better help define network abnormalities, and the use of conscious sedation, which may influence fMRI signals and correlations. Nevertheless, the highlighted study represents an important early milestone in understanding how brain networks are altered with epilepsy surgery, and how these changes relate to long-term seizure outcome. This young field is likely to grow rapidly in the next few years.

By Dario J. Englot ⓘ

ORCID iD

Dario J. Englot ⓘ https://orcid.org/0000-0001-8373-690X

References

1. Zijlmans M, Zweiphenning W, Van Klink N. Changing concepts in presurgical assessment for epilepsy surgery. *Nat Rev Neurol*. 2019; 15(19):595-606.
2. Boerwinkle VL, Mohanty D, Foldes ST, et al. Correlating resting-state functional magnetic resonance imaging connectivity by independent component analysis-based epileptogenic zones with intracranial electroencephalogram localized seizure onset zones and surgical outcomes in prospective pediatric intractable epilepsy study. *Brain connect*. 2017;7(7):424-442.
3. Li Y, Tan Z, Wang J, et al. Alterations in spontaneous brain activity and functional network reorganization following surgery in children with medically refractory epilepsy: a resting-state functional magnetic resonance imaging study. *Front neurol*. 2017;8:374.
4. Maccotta L, Lopez MA, Adeyemo B, et al. Postoperative seizure freedom does not normalize altered connectivity in temporal lobe epilepsy. *Epilepsia*. 2017;58(11):1842-1851.
5. Morgan VL, Rogers BP, Gonzalez HFJ, Goodale SE, Englot DJ. Characterization of postsurgical functional connectivity changes in temporal lobe epilepsy [published online]. *J neurosurg*. 2019:1-11. doi: 10.3171/2019.3.JNS19350.
6. Gonzalez HFJ, Chakravorti S, Goodale SE, et al. Thalamic arousal network disturbances in temporal lobe epilepsy and improvement after surgery. *J Neurol Neurosurg Psychiat*. 2019;90(10):1109-1116.
7. Park CH, Choi YS, Kim HJ, et al. Interactive effects of seizure frequency and lateralization on intratemporal effective connectivity in temporal lobe epilepsy. *Epilepsia*. 2018;59(1):215-225.
8. Jo HJ, Kenney-Jung DL, Balzekas I, et al. Relationship between seizure frequency and functional abnormalities in limbic network of medial temporal lobe epilepsy. *Front neurol*. 2019;10:488.