Prediction of Postsurgical Neuropsychological Outcome: Increasing Options

Presurgery Resting-State Local Graph-Theory Measures Predict Neurocognitive Outcomes After Brain Surgery in Temporal Lobe Epilepsy.

Doucet GE, Rider R, Taylor N, Skidmore C, Sharan A, Sperling M, Tracy JI. *Epilepsia* 2015;21:517–526.

OBJECTIVE: This study determined the ability of resting-state functional connectivity (rsFC) graph-theory measures to predict neurocognitive status postsurgery in patients with temporal lobe epilepsy (TLE) who underwent anterior temporal lobectomy (ATL). **METHODS:** A presurgical resting-state functional magnetic resonance imaging (fMRI) condition was collected in 16 left and 16 right TLE patients who underwent ATL. In addition, patients received neuropsychological testing pre- and postsurgery in verbal and nonverbal episodic memory, language, working memory, and attention domains. Regarding the functional data, we investigated three graph-theory properties (local efficiency, distance, and participation), measuring segregation, integration and centrality, respectively. These measures were only computed in regions of functional relevance to the ictal pathology, or the cognitive domain. Linear regression analyses were computed to predict the change in each neurocognitive domain. **RESULTS:** Our analyses revealed that cognitive outcome was successfully predicted with at least 68 percent of the variance explained in each model, for both TLE groups. The only model not significantly predictive involved nonverbal episodic memory outcome in right TLE. Measures involving the healthy hippocampus were the most common among the predictors, suggesting that enhanced integration of this structure with the rest of the brain may improve cognitive outcomes. Regardless of TLE group, left inferior frontal regions were the best predictors of language outcome. Working memory outcome was predicted mostly by right-sided regions, in both groups. Overall, the results indicated our integration measure was the most predictive of neurocognitive outcome. In contrast, our segregation measure was the least predictive. **SIGNIFICANCE:** This study provides evidence that presurgery rsFC measures may help determine neurocognitive outcomes following ATL. The results have implications for refining our understanding of compensatory reorganization and predicting cognitive outcome after ATL. The results are encouraging with regard to the clinical relevance of using graph-theory measures in presurgical algorithms in the setting of TLE.

Commentary

Clinicians are obligated to inform patients considering surgical treatment for medically refractory epilepsy about the possible benefits and risks of the procedure. In the case of anterior temporal lobe lobectomy (ATL) for treatment of medically refractory epilepsy, a benefit is that the probability of seizure freedom after 1 year ranges from 50 to 85 percent (1). In terms of risks, cognitive decline is observed in a significant number of patients. More specifically, results of a meta-analysis indicate memory decline in 44 percent of patients undergoing resection of the dominant left hemisphere and in 20 percent of those undergoing right side resection (2). Findings from the same analysis revealed a decline in naming abilities in 34 percent of patients and a far less frequent change observed for

other neuropsychological domains, including attention and executive functions.

Over the past 20 years, our ability to predict neuropsychological outcome from ATL has rested on two competing models, both of which were initially outlined in a classic article by Chelune (3). In the functional adequacy model, the assumption is that postsurgical outcome can be predicted on the basis of the integrity of the brain structures to be resected. Patients exhibiting functional deficits associated with zone of resection are predicted to exhibit good postsurgical outcome, and those with intact structures are predicted to develop a functional decline. In contrast, the functional reserve model assumes that the level of functioning observed after surgery is predicted by the integrity of brain regions contralateral to the side of the resection, which are expected to support cognitive functions once structures on the other side are removed.

To date, most empirical findings have supported the functional adequacy model based on its ability to identify patients who might be prone developing memory decline after ATL. This was confirmed initially through results from studies

demonstrating that patients exhibiting patterns of presurgical memory impairment consistent with the side of the focus to be resected, identified through neuropsychological testing or the Wada test (3), were less likely to exhibit postsurgical decline. The model has been extended further through results of neuroimaging studies using structural MRI and functional MRI (fMRI) demonstrating more structural pathology or less functional activity in the area to be resected (4). Information obtained from these studies are now used routinely when counseling patients about the prospect of developing memory decline after ATL.

In an age when increasing attention is turning to ameliorating or preventing postsurgical cognitive decline, it turns out that the functional adequacy model has limits in its ability to predict the cognitive and neural mechanisms that will be used in adapting to the effects of ATL. In many ways, the functional reserve model, with its emphasis on the functioning of brain regions not directly affected by the surgery, has the potential of being much more suited for this purpose. Consistent with this model, a number of brain imaging studies using advanced MRI (5) and fMRI (6) techniques are now turning to the topic of identifying brain networks existing before surgery that are potentially more resistant to the development of cognitive decline after ATL. The ultimate goal would be the use of this information to guide efforts at minimizing postsurgical neuropsychological impairment while also providing the means for designing a tailored approach for development of cognitive rehabilitative strategies that is implemented before and after surgery (7).

The recent study by Doucet et al. describes a novel approach to predicting neuropsychological status after ATL through analysis of resting-state fMRI data with graph-theory measures obtained before surgery. The authors provide a good case for using resting-state fMRI, which can be obtained within a 5-minute acquisition period in contrast to traditional task-based fMRI methods, which are difficult, uncomfortable, and lengthy and produce data that are ambiguous for predicting cognitive risk. While resting-state fMRI methodology has been used to study how epilepsy affects brain activity, there have been no prior studies analyzing its utility in predicting postsurgical outcome.

The authors provide a detailed and readable description of graph-theory and the advantages of using this method of analyzing fMRI data to investigate resting-state functional connectivity (rsFC). The major advantage to this technology is that one is able to investigate different aspects of network organization, including local efficiency, distance, and participation, all of which are explained as measures of the degree of activity of a specific brain region in relation to activity of other regions within its vicinity and beyond. The results of a stepwise linear analysis indicated that these graph-theory measures accounted for 68 percent of the variance in predicting postsurgical neuropsychological outcome in a wide range of cognitive domains, which was greater than the level of prediction provided by standard variables.

The major finding from this study was that graph-theory measures of rsFC associated with the healthy contralateral hippocampus provide the best predictors of postsurgical neuropsychological performance, which offers rather strong support

for the model of functional reserve. The distance measure was the most predictive of neuropsychological outcome with implications that a greater integration of the contralateral hippocampus with the rest of brain leads to better functional outcome. The study also demonstrated the role of extratemporal brain regions, including the inferior frontal cortex, in predicting postsurgical outcome of a wide range of cognitive functions.

It is interesting to note that the only model that failed prediction was nonverbal memory functioning in patients with right temporal lobe epilepsy, which replicates some of the negative findings in previous examinations of patients undergoing ATL of the nondominant hemisphere, which were explained by limitations in assessment methods and/or shortcomings of the general material-specific model of memory (8, 9).

The authors argue that their graph-theory measures of rsFC capture unique properties of brain functioning that are relevant to the pathology of temporal lobe epilepsy and subsequent cognitive recovery. While the findings demand replication and extension in studies with more patients, they open the doors for additional studies using resting-state fMRI methodology and graph-theory analysis to investigate how postsurgical functioning can be maximized after ATL. Results from this and similar studies have the potential of providing the field with an option of extending our ability to counsel patients on their prospects for adapting positively to the effects of ATL rather than focusing on the probability of a subsequent functional decline.

by William Barr, PhD

References

1. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol* 2008;7:525–537.
2. Sherman EM, Wiebe S, Fay-McClymont TB, Tellez-Zenteno J, Metcalfe A, Hernandez-Ronquillo L, Hader WJ, Jetté N. Neuropsychological outcomes after epilepsy surgery: Systematic review and pooled estimates. *Epilepsia* 2011;52:857–869.
3. Chelune GJ. Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Arch Clin Neuropsychol* 1995;10:413–432.
4. Dulay MF, Busch RM. Prediction of neuropsychological outcome after resection of temporal and extratemporal seizure foci. *Neurosurg Focus* 2012;32:E4.
5. Yogarajah M, Focke NK, Bonelli SB, Thompson P, Vollmar C, McEvoy AW, Alexander DC, Symms MR, Koepp MJ, Duncan JS. The structural plasticity of white matter networks following anterior temporal lobe resection. *Brain* 2010;133(Pt 8):2348–2364.
6. Bonnici HM, Sidhu M, Chadwick MJ, Duncan JS, Maguire EA. Assessing hippocampal functional reserve in temporal lobe epilepsy: A multi-voxel pattern analysis of fMRI data. *Epilepsy Res* 2013;105:140–149.
7. Mazur-Mosiewicz A, Carlson HL, Hartwick C, Dykeman J, Lenders T, Brooks BL, Wiebe S. Effectiveness of cognitive rehabilitation following epilepsy surgery: Current state of knowledge. *Epilepsia* 2015;56:735–744.
8. Barr WB. Examining the right temporal lobe's role in nonverbal memory. *Brain Cogn* 1997;35:26–41.
9. Saling MM. Verbal memory in mesial temporal lobe epilepsy: Beyond material specificity. *Brain* 2009;132(Pt 3):570–582.