



fMRI to Predict Naming Decline: Can We Improve the Grade From a C to an A?

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Prediction of Naming Outcome With fMRI Language Lateralization in Left Temporal Epilepsy Surgery

Gross WL, Helfand AI, Swanson SJ, Conant LL, Humphries CJ, Raghavan M, Mueller WM, Busch RM, Allen L, Anderson CT, Carlson CE, Lowe MJ, Langfitt JT, Tivarus ME, Drane DL, Loring DW, Jacobs M, Morgan VL, Allendorfer JB, Szaflarski JP, Bonilha L, Bookheimer S, Grabowski T, Vannest J, Binder JR; FMRI in Anterior Temporal Epilepsy Surgery (FATES) Study. *Neurology*. 2022;98(23):e2337-e2346. doi:10.1212/WNL.0000000000200552. PMID: 35410903; PMCID: PMC9202528.

Background and Objectives: Naming decline after left temporal lobe epilepsy (TLE) surgery is common and difficult to predict. Preoperative language fMRI may predict naming decline, but this application is still lacking evidence. We performed a large multicenter cohort study of the effectiveness of fMRI in predicting naming deficits after left TLE surgery. **Methods:** At 10 US epilepsy centers, 81 patients with left TLE were prospectively recruited and given the Boston Naming Test (BNT) before and ≈ 7 months after anterior temporal lobectomy. An fMRI language laterality index (LI) was measured with an auditory semantic decision-tone decision task contrast. Correlations and a multiple regression model were built with a priori chosen predictors. **Results:** Naming decline occurred in 56% of patients and correlated with fMRI LI ($r = -0.41$, $p < 0.001$), age at epilepsy onset ($r = -0.30$, $p = 0.006$), age at surgery ($r = -0.23$, $p = 0.039$), and years of education ($r = 0.24$, $p = 0.032$). Preoperative BNT score and duration of epilepsy were not correlated with naming decline. The regression model explained 31% of the variance, with fMRI contributing 14%, with a 96% sensitivity, and 44% specificity for predicting meaningful naming decline. Cross-validation resulted in an average prediction error of 6 points. **Discussion:** An fMRI-based regression model predicted naming outcome after left TLE surgery in a large, prospective multicenter sample, with fMRI as the strongest predictor. These results provide evidence supporting the use of preoperative language fMRI to predict language outcome in patients undergoing left TLE surgery.

Commentary

The goal of epilepsy surgery is complete seizure freedom. Unfortunately, in patients undergoing a left temporal resection, 41% can experience a decline in naming¹ which can have a negative impact on their quality of life.² We have been trying to predict those at risk of decline for decades and initially relied on the invasive intracarotid sodium amobarbital procedure (IAP) also known as the Wada test. Over time, surgical centers started shifting away from their reliance on the IAP and started to rely on noninvasive functional magnetic resonance imaging (fMRI) paradigms.³ Despite its common use, the evidence for the predictive value of fMRI has been limited. In fact, the 2017 AAN Guideline Development, Dissemination, and Implementation Subcommittee studied the use of fMRI for the

presurgical evaluation of persons with epilepsy and graded the evidence as only a “C” for predicting postsurgical language outcomes, that is, of possible benefit.⁴

The current study⁵ represents the efforts of 10 surgical epilepsy centers in characterizing the utility of fMRI in the prediction of naming decline after epilepsy surgery. The cohort was recruited over 7 years and consisted of 81 patients undergoing some form of anterior temporal resection (70% underwent a standard lobectomy). The primary outcome was the change in the 60-item Boston naming test (BNT) score assessed

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at baseline and an average of 7 months postoperatively. The fMRI consisted of a semantic decision-tone decision paradigm from which lateralization indices (LIs) were derived. Regions of interest to calculate the LIs were extracted from the activation maps of 80 healthy volunteers and their mirror images in the right hemisphere. To identify the predictive utility of fMRI, the authors first analyzed the correlation between fMRI and known predictors of naming decline and then ended with a multivariate model which included age at onset, age at surgery, and education. The model only predicted 13% of the variance, this improved to 27% with the addition of the fMRI LI in the model. Given the significance of the findings, the authors conclude that there is now enough evidence to support the use of fMRI to predict naming decline in patients undergoing left temporal lobe resections.

It is refreshing to see good evidence establishing the utility of a test that is very commonly used. Evidence for the utility of fMRI started coming out in the early 2000s, and it's taken us this long to establish strong evidence for its use. The epilepsy community should immediately rally to set up well-designed studies as soon as a tool becomes incorporated into routine clinical practice to inform surgical decision-making and avoid irreversible adverse outcomes. We continued to rely on the IAP prior to fMRI, but never clearly established its predictive value. The study also emphasizes the importance of thinking about language lateralization as a continuum rather than a dichotomous variable and that there is a spectrum of language lateralization present suggesting variable risks and variable potential for postoperative language reorganization.

How do we explain the 73% variance which was unaccounted for in the model? Possibilities include the state of the language network preoperatively, this can be evaluated using functional connectivity,⁶ the extent of pathology already present (how sick is the temporal lobe prior to the surgery), in addition to the extent of the surgical resection with more posterior resections leading to greater declines.⁷ Curiously other predictors identified in the literature were not found to be significant in the study such as sex.⁸

Can these findings be widely adopted? The answer is complicated because of the lack of standardized fMRI paradigms. The paradigm used in the study was favored for several reasons including the fact that it was validated with IAP findings. The American Society for Functional Neuroradiology, for example, recommended the use of paradigms involving at least 6 tasks (sentence completion, silent word generation, rhyming, antonym generation, passive story listening, and object naming) with the goal of standardizing presurgical language assessments.⁹ For the findings of the current study to be reproducible, the same protocol, same regions of interest, and same thresholds must be applied.


Are these findings too late? We are already shying away from standard left temporal lobectomies because of the cognitive concerns, and instead are relying on less invasive procedures such as laser interstitial thermal therapy (LITT) or neuromodulation. However, our LITT cases can also experience a decline and in some cases can have seizure recurrence and may ultimately need a more aggressive lobectomy. On the

other hand, responsive nerve stimulation may sometimes identify a well-lateralized seizure pattern leading to surgery.¹⁰ As result, it would be important to perform preoperatively language mapping with fMRI because of these possibilities as well as to assess the risk of verbal memory decline.

Is the primary outcome the most ideal? The BNT is the best naming assessment tool we have given that it is incorporated in standard neuropsychological batteries, includes common and uncommon objects, and can be analyzed across multiple centers. Clinically meaningful decline was determined by reliable change indices scores, and in this study was found to be a decline of 4.4 on the BNT. One could argue whether you can truly label someone as not declining if their score dropped by 4 versus someone as declining if their score dropped by 5. Ultimately, this was probably the best strategy at hand to analyze the data. It would have been ideal if subjective data were also available. Fortunately, a large analysis of BNT data in epilepsy patients showed a good correlation between the severity of language complaints and severity of decline in BNT with mild declines defined as a drop by 5 to 10 points, and severe declines defined as ≥ 11 .¹¹ Automated speech analysis¹² is another method of analyzing language deficits and might be another outcome of interest in future studies focusing on postoperative language changes.


In the future, we will need updated guidelines to incorporate the current evidence, but we should also start planning for studies to guide our more limited resections. We also need to establish the ideal resting state and task-based fMRI protocols that can be performed in one setting and provide the highest yield predictive data. While doing so, we should keep aiming for an "A."

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