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fMRI Language Activation—If You See It Don't Resect It…

fMRI Prediction of Naming Change After Adult Temporal Lobe Epilepsy Surgery: Activation Matters.

You X, Zachery AN, Fanto EJ, et al. *Epilepsia*. 2019. doi:10.1111/epi.14656. [Epub ahead of print] PMID: 30740666.

Objective: We aimed to predict language deficits after epilepsy surgery. In addition to evaluating surgical factors examined previously, we determined the impact of the extent of functional magnetic resonance imaging (fMRI) activation that was resected on naming ability. Method: Thirty-five adults (mean age: 37.5 ± 10.9 years, 13 males) with temporal lobe epilepsy completed a preoperative fMRI auditory description decision task, which reliably activates frontal and temporal language networks. Patients underwent temporal lobe resections (20 left resection). The Boston Naming Test (BNT) was used to determine language functioning before and after surgery. Language dominance was determined for Broca and Wernicke area (WA) by calculating a laterality index following statistical parametric mapping processing. We used an innovative method to generate anatomic resection masks automatically from pre- and postoperative magnetic resonance imaging tissue map comparison. This mask provided the following: (a) resection volume, (b) overlap between resection and preoperative activation, and (c) overlap between resection and WA. We examined postoperative language change predictors using stepwise linear regression. Predictors included parameters described above as well as age at seizure onset (ASO), preoperative BNT score, and resection side and its relationship to language dominance. Results: Seven of 35 adults had significant naming decline (6 dominant-side resections). The final regression model predicted 38% of the naming score change variance (adjusted $r^2 = 0.28$, $P = .012$). The percentage of top 10% fMRI activation resected ($P = .017$) was the most significant contributor. Other factors in the model included WA LI, ASO, volume of WA resected, and WA LI absolute value (extent of laterality). Significance: Resection of fMRI activation during a word-definition decision task is an important factor for postoperative change in naming ability, along with other previously reported predictors. Currently, many centers establish language dominance using fMRI. Our results suggest that the amount of the top 10% of language fMRI activation in the intended resection area provides additional predictive power and should be considered when planning surgical resection.

In 2017, the American Academy of Neurology published a practice guideline summary that addressed the use of fMRI in the presurgical evaluation of patients with epilepsy.[1] The authors of the guideline put forth several level B and C recommendations regarding the use of fMRI in place of intracarotid amobarbital procedure (IAP) for lateralization of language and/or memory functions and for prediction of postsurgical language and verbal memory outcomes. However, the guideline also identified several gaps concerning the use of fMRI in this setting and made several recommendations regarding future research. One of the unknowns identified by the guideline, similar to other reports, was the prediction of whether the resection of fMRI signals identified with the fMRI tasks is associated with negative postsurgical cognitive outcomes. The study by You et al is the first attempt to address this question in patients undergoing temporal lobectomy (or equivalent) for the treatment of temporal lobe epilepsy (TLE).

In this retrospective study, You et al analyzed data from 35 adults who underwent surgical resection for the treatment of TLE. Important is that prior to resection all patients received a well-researched and documented form of semantic fMRI task called Auditory Description Decision Task (ADDT)[2] and Boston Naming Test (BNT); all participants also received postresection BNT, but the time from resection to postresection testing was variable, potentially allowing biases related to the duration of postresection recovery. They used reliable change index to determine the clinical significance of the pre-to-post changes in BNT. However, the most important aspect of the study is the novel approach to handling the fMRI data. Instead of using the workhorses of neuroimage data analyses such as region of interest or group analyses, the authors addressed the shortcoming of previous studies by utilizing individual data for individual predictions. Hence, this approach not only eliminated the need for group analyses but also supplanted them with something much more individualized that takes into account individual fMRI activation levels in an unbiased way. On the surface, this approach appears to be contrary to the well-publicized critique of using individual thresholds for analyzing fMRI data (see, eg, "Now you see it, now you don't: statistical considerations in fMRI" by Loring et al).[3] However, You et al utilized a modified version of a previously developed clever approach to individual fMRI data analyses called "activation mapping as percentage of local excitation."[4] In the original version of the method, the author developed an approach to creating blood oxygenation level–dependent (BOLD) signal maps by assessing (and providing) their spatial and signal magnitude stability and reproducibility. That is, by utilizing statistics, this author was able to show that certain areas of BOLD signal activation will have high repeatability within the subject while the overall signal distribution may be very variable between scans, scanners, and trial duration and that the repeatability of the signal depends on its peak value derived from the overall activation pattern.[4] In the new/updated rendition of the method, You et al used the individualized thresholds comprising of 10% of the peak activation for each subject to create individualized spatial activation pattern that they later applied to the resection map from postresection MRI. In this manner, they were able to visualize the percentage of the brain area involved in ADDT that was resected and the percentage of the resected ADDT signal. While this approach is novel in its application to epilepsy and presurgical evaluation, another novel aspect of the study is that You et al focused on "Wernicke area" activation rather than on the overall activation pattern related to their task. While language processes are governed by a widely distributed network,[5] damage to each of the networks' nodes (eg, via surgical resection) can result in negative outcomes. In other words, damage (eg, via resection) to the dominant frontal region may result in different deficit than damage to the dominant temporal region, but these resections may have overall similar effect on the language network.[6]

As a result of their approach, they were able to show 2 important findings—one being that the postresection performance on BNT depended on the volume of the voxels activated with ADDT that were resected ($P < 0.0001$) and second being that the percentage of the resected language voxels correlated with postresection performance on BNT (trend toward significance at $P = 0.065$). These results were not corrected for multiple comparisons and need to be verified in larger prospective studies in which the surgical team is unaware of the results of fMRI (not the case here). However, they are the first (and large) step toward showing that the individualized fMRI results may predict postresection outcomes and, thus, influence surgical decision-making in the epilepsy surgery evaluation. Hence, this study adds to and enhances the previously published guideline by slowly plugging the gaps in knowledge that currently prevent fMRI from being used as the only language and memory localization/lateralization and postresection outcome prediction tool in the presurgical evaluation of epilepsy patients.

We need to further discuss one other result of the study—the outcome prediction and the contribution of several measures to the outcome. All in all, in the model developed by You et al, fMRI was the most significant contributor to the postresection naming score change. In many ways, the result of the study by You et al mirrors the results of another fMRI study that showed that a different semantic decision fMRI task is better at predicting verbal memory outcome than IAP and that this task adds substantial power to the postresection outcome prediction.[7] However, where the present study falls short is at the comparison between fMRI and IAP—while these authors utilized IAP in selected cases, they do not describe the degree of agreement between these 2 measures or whether one versus the other contribute more to the postresection prediction of outcomes. This is something that will need to be accomplished before we finally put IAP to rest.

So, are we ready to replace IAP with fMRI? This question has been lingering in our minds since the editorial in *Neurology* almost 20 years ago—"Is it time to replace the Wada test?"[8] The answer to this question is not that simple. We need more studies that replicate the results of You et al's study and that take us a step further and show which one is better at predicting cognitive outcomes after surgery—IAP versus fMRI. However, we also need to answer another important question that has been bugging epileptologists for years. If we have fMRI tasks and analytical approaches that reliably localize eloquent cortex on the individual level, can we altogether replace IAP and direct cortical mapping that also has been shown to be variable in its application and not very predictive of outcomes but is still done every day in the surgical evaluation of the epilepsy (and not only) patient?[9]

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