How to Image Memory in Epilepsy

Memory *f*MRI in Left Hippocampal Sclerosis: Optimizing the Approach to Predicting Postsurgical Memory

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BACKGROUND: An optimal technique for clinical memory *f*MRI is not established. Previous studies suggest activity in right parahippocampal gyrus and right hippocampus shows the strongest difference between left hippocampal sclerosis (HS) patients and normal control subjects and that the difference in activity between left and right hippocampus predicts postoperative memory change.

METHODS: The authors studied 30 patients with mesial temporal lobe epilepsy (mTLE) and left HS, 12 of whom subsequently underwent surgery, and 13 normal control subjects. The patients who had surgery underwent neuropsychometric evaluation pre- and postoperatively. All subjects underwent a verbal memory encoding event-related *f*MRI study. Activation maps were assessed visually. Subsequently, the brain regions involved in the memory task were revealed by group averaging; these regions were used to determine regions of interest (ROIs) for subsequent analysis. By use of stepwise discriminant function and stepwise multiple regression, the ROIs that optimally discriminated between patients and normal control subjects and that optimally predicted postoperative verbal memory outcome were determined.

RESULTS: Visual inspection of individual patient activation statistic maps revealed noisy data that did not afford visual interpretation. Stepwise discriminant function revealed the difference between left and right hippocampal activity best discriminated between patients and normal control subjects. Stepwise multiple regression revealed left hippocampal activity was the strongest predictor of postoperative verbal memory outcome; greater left hippocampal activity predicted a greater postoperative decline in memory.

CONCLUSIONS: Patients with left hippocampal sclerosis (HS) differ from normal control subjects in the distribution of memory-encoding activity between left and right hippocampus. Functional adequacy of left hippocampus best predicts postoperative memory outcome in left HS.

Functional MRI of Memory in the Hippocampus: Laterality Indices May Be More Meaningful if Calculated from Whole Voxel Distributions

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Lateralization of memory by functional MRI (*f*MRI) may be helpful for surgical planning related to the medial temporal lobe (MTL). Most *f*MRI memory studies have calculated lateralization indices (LI) in the MTL from suprathreshold voxels only, but the selection of threshold remains highly arbitrary. We hypothesized that LIs could be reliably extracted from the distribution of voxels encompassing all positive *T* statistical values, each weighted by their own statistical significance. We also hypothesized that patient LIs that are two or more standard deviations (SD) away from the control group mean LI may be more clinically relevant than LIs that are not compared to control group. Thirteen healthy subjects had memory *f*MRI, and five epilepsy patients had both *f*MRI and the intracarotid amobarbital procedure (IAP). The *f*MRI task consisted of encoding patterns, scenes, and words. We found that normal subjects' LIs extracted from whole weighted statistical distributions tended to lateralize to the left for words, to the right for patterns, and intermediately for scenes, consistent with previous research. Weighted LIs were less variable than those calculated from suprathreshold voxels only. Using this approach, all patients had *f*MRI memory lateralizations consistent with IAP results. The weighted LIs provided a more clear-cut distinction of patients from the normal group (in terms of SDs from the group mean) than the suprathreshold voxel count approach. Our results suggest that using weighted distributions can be a useful strategy for assessing memory lateralization by *f*MRI in the MTL.

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COMMENTARY

The preoperative evaluation for epilepsy surgery requires not only localization of the epileptic focus but also localization of dysfunction. Understanding the differential topography of functional and dysfunctional cerebral regions is critical to prediction and avoidance of postoperative neuropsychological deficits. Functional data also provide added information for prediction of postoperative seizure outcome. For over 50 years, the intracarotid amobarbital procedure (i.e., Wada test) has been an integral component of the preoperative evaluation used to lateralize language and memory function (1). Advantages of the Wada test include long-term experience and the fact that it simulates the effects of surgery by inactivation of regions that are to be included in the planned resection. Disadvantages of the Wada test include confounds of sedation and other adverse behavioral responses, poor spatiotemporal resolution, questionable reproducibility, and most importantly, the risk entailed by the invasive procedure. Furthermore, the Wada test is not standardized and results vary across different versions used by various medical centers.

Functional MRI (fMRI) is poised to replace the Wada test for both lateralization of language and memory. Advantages of fMRI include its greater spatial resolution and noninvasive nature, which offers the potential for repeated testing. Disadvantages include rather limited postoperative outcome data and insufficient evidence that results are equivalent across different protocols or that they are reproducible during test–retest within an individual patient. An additional disadvantage is that, unlike the Wada test, fMRI reveals activation differences across tasks or time epochs, rather than showing the effects of inactivation, which mirror surgical resection. Thus, fMRI-activated blood oxygen level-dependent (BOLD) regions may not be critical for the specified function tested, whereas regions that are not activated in the BOLD image may be necessary. Correlation with postoperative outcomes will be critical.

Lateralization of language by fMRI appears to be reliable across various behavioral protocols, reproducible, and is strongly related to Wada language lateralization. In addition, it appears that simple lateralization of language by fMRI is reproducible, although this finding is less clear for localization of language. Furthermore, it is unclear which behavioral paradigms are best to use to activate specific language circuits and how these local activations related to postoperative outcome data warrant further study.

The mesial temporal lobes are critical for formation of new episodic memories, have the lowest seizure thresholds, and frequently are included in resections for epilepsy surgery since they are the most common location of focal epilepsy. Thus, fMRI should be able to evaluate these regions if it is to be applied to epilepsy surgery. Several factors have contributed to the delay in development of fMRI memory imaging of the mesial temporal lobes. The lobes are thought to be continuously active, leading to small differences in activation during control versus memory task conditions. This problem is confounded by other factors that interfere with fMRI signals, such as susceptibility artifacts in the mesial temporal lobes, individual variability in the sources of noise (e.g., pulsatile brain movement, vascular distribution, vascular reactivity), and individual differences in distribution of neural activity to perform the same task. Furthermore, there is a lack of consistency in behavioral paradigms, imaging acquisition techniques, and processing protocols. Two recent studies provide insight into how to optimize fMRI applications for imaging of memory systems.

In the first study, Richardson et al. employed a verbal fMRI task that required subjects to discriminate between words that were representative of "living" versus "nonliving" items. Subsequently, subjects underwent a surprise recognition task outside the MRI scanner. Images of T statistics comparing recognized versus familiar words were calculated for each subject and then normalized using Z transform. The contrast between recognized versus familiar words was used rather than recognized versus novel words in order to reduce the behavioral differences across subjects. The investigators analyzed classifications based on visual inspection of activation maps and compared them to a statistical approach. The statistical approach involved stepwise discriminant function to determine the regions of interest (ROIs) that best differentiate healthy controls from epilepsy patients with left hippocampal sclerosis; then, stepwise multiple regression was used to determine the ROIs that optimally predicted postoperative verbal memory outcome, following left temporal lobectomy. Visual inspection was ineffective. In contrast, the statistical approach was effective for predicting postoperative verbal memory outcome, which was best predicted by preoperative left hippocampal activation. Given that the image produced by fMRI is a statistical image, perhaps it is not surprising that statistical analysis of the activations could be superior to visual analysis of the statistical topographic map.

Richardson et al. also addressed the issue of functional adequacy as compared with functional reserve. They concluded that functional adequacy was the best determinant of verbal memory outcome, since left hippocampal activation was the strongest predictor of postoperative verbal memory outcome in their patients with left mesial temporal lobe epilepsy and hippocampal sclerosis. These findings are consistent with two prior fMRI studies (2,3) as well as with Wada memory results (4). Nevertheless, the functional reserve of the contralateral mesial temporal lobe is important, as it is predictive of the risk for severe amnesia. The functional adequacy of the ipsilateral mesial temporal lobe provides the best preoperative estimate of lesser, but potentially clinically significant, declines in modality-specific memory loss. The original role of the Wada memory test was

to determine the risk for amnesia, although later it was applied to predict clinically significant declines in recent memory, short of amnesia. Modern structural imaging techniques have largely supplanted the role of functional techniques in estimating the risk of severe amnesia, as contralateral hippocampal sclerosis or other structural abnormalities would strongly imply risk for amnesia.

In a second study examining methods to improve fMRI of memory systems, Branco et al. investigated a new technique to calculate lateralization indices (LIs). They note that most fMRI studies rely on analysis of suprathreshold voxels based on *T* statistical values but that the selection of threshold remains very arbitrary and differences in thresholds can have dramatic effects on the fMRI results. To address this problem, the investigators first extracted the distribution of all voxels with positive *T* statistical values weighted by their own statistical significance then calculated the LIs. The behavioral task required subjects to classify stimuli into one of two categories using stimuli, which were words (concrete/abstract), scenes (indoor/outdoor) or patterns (regular/irregular). After fMRI scanning, subjects underwent a recognition memory test. Weighted LIs from ROI analysis were less variable than those calculated from suprathreshold voxels only. Furthermore, the LIs from weighted fMRI activations were consistent with LIs derived from Wada memory tests.

The studies by Richardson et al. and Branco et al. advance the understanding of imaging memory systems in patients with epilepsy; however, additional issues need to be addressed. The ultimate validation of preoperative fMRI is the relationship the activations have to postoperative memory outcome for an individual patient. To date, the results are very promising, but there have been only three studies, comprising a total of 49 temporal lobe epilepsy patients, that have compared specific fMRI procedures to postoperative memory changes (2,5, Richardson et al.). Clearly, larger patient population with postoperative outcomes are required, and novel fMRI protocols ultimately should be validated against postoperative memory outcomes. Since other techniques that assess mesial temporal lobe function (e.g., Wada, PET) have been shown to predict postoperative seizure outcome, similar analyses should be conducted for fMRI data. The fMRI techniques vary considerably across centers. Systematic investigations are needed to further optimize fMRI assessment of memory systems and to explore the variance created by different behavioral paradigms, image sequencing techniques, image analyses, and statistical processing methods. Test–retest reliability for individual patients should be determined. Patient performance has to be monitored during fMRI tasks, which has not always been the case. Since one cross-sectional study suggested that antiepileptic drugs may reduce fMRI activations in the mesial temporal lobes (6), systematic investigations of drug effects are needed to determine how such effects might alter the fMRI results. Finally, applicability of fMRI for patients at lower ages and with lower IQ should be delineated.

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