Prediction and Prevention of Verbal Memory Decline After Temporal Lobectomy

A Functional Magnetic Resonance Imaging Study Mapping the Episodic Memory Encoding Network in Temporal Lobe Epilepsy.


Functional magnetic resonance imaging has demonstrated reorganization of memory encoding networks within the temporal lobe in temporal lobe epilepsy, but little is known of the extra-temporal networks in these patients. We investigated the temporal and extra-temporal reorganization of memory encoding networks in refractory temporal lobe epilepsy and the neural correlates of successful subsequent memory formation. We studied 44 patients with unilateral temporal lobe epilepsy and hippocampal sclerosis (24 left) and 26 healthy control subjects. All participants performed a functional magnetic resonance imaging memory encoding paradigm of faces and words with subsequent out-of-scanner recognition assessments. A blocked analysis was used to investigate activations during encoding and neural correlates of subsequent memory were investigated using an event-related analysis. Event-related activations were then correlated with out-of-scanner verbal and visual memory scores. During word encoding, control subjects activated the left prefrontal cortex and left hippocampus whereas patients with left hippocampal sclerosis showed significant additional right temporal and extra-temporal activations. Control subjects displayed subsequent verbal memory effects within left parahippocampal gyrus, left orbitofrontal cortex and fusiform gyrus whereas patients with left hippocampal sclerosis activated only right posterior hippocampus, parahippocampus and fusiform gyrus. Correlational analysis showed that patients with left hippocampal sclerosis with better verbal memory additionally activated left orbitofrontal cortex, anterior cingulate cortex and left posterior hippocampus. During face encoding, control subjects showed right lateralized prefrontal cortex and bilateral hippocampal activations. Patients with right hippocampal sclerosis showed increased temporal activations within the superior temporal gyri bilaterally and no increased extra-temporal areas of activation compared with control subjects. Control subjects showed subsequent visual memory effects within right amygdala, hippocampus, fusiform gyrus and orbitofrontal cortex. Patients with right hippocampal sclerosis showed subsequent visual memory effects within right posterior hippocampus, parahippocampal and fusiform gyri, and predominantly left hemisphere extra-temporal activations within the insula and orbitofrontal cortex. Correlational analysis showed that patients with right hippocampal sclerosis with better visual memory activated the amygdala bilaterally, right anterior parahippocampal gyrus and left insula. Right sided extra-temporal areas of reorganization observed in patients with left hippocampal sclerosis during word encoding and bilateral lateral temporal reorganization in patients with right hippocampal sclerosis during face encoding were not associated with subsequent memory formation. Reorganization within the medial temporal lobe, however, is an efficient process. The orbitofrontal cortex is critical to subsequent memory formation in control subjects and patients. Activations within anterior cingulum and insula correlated with better verbal and visual subsequent memory in patients with left and right hippocampal sclerosis, respectively, representing effective extra-temporal recruitment.

Memory Reorganization Following Anterior Temporal Lobe Resection: A Longitudinal Functional MRI Study.


Anterior temporal lobe resection controls seizures in 50–60% of patients with intractable temporal lobe epilepsy but may impair memory function, typically verbal memory following left, and visual memory following right anterior
temporal lobe resection. Functional reorganization can occur within the ipsilateral and contralateral hemispheres. We investigated the reorganization of memory function in patients with temporal lobe epilepsy before and after left or right anterior temporal lobe resection and the efficiency of postoperative memory networks. We studied 46 patients with unilateral medial temporal lobe epilepsy (25/26 left hippocampal sclerosis, 16/20 right hippocampal sclerosis) before and after anterior temporal lobe resection on a 3 T General Electric magnetic resonance imaging scanner. All subjects had neuropsychological testing and performed a functional magnetic resonance imaging memory encoding paradigm for words, pictures and faces, testing verbal and visual memory in a single scanning session, preoperatively and again 4 months after surgery. Event-related analysis revealed that patients with left temporal lobe epilepsy had greater activation in the left posterior medial temporal lobe when successfully encoding words postoperatively than preoperatively. Greater preoperative activation in the ipsilateral posterior medial temporal lobe for encoding words correlated with better verbal memory outcome after left anterior temporal lobe resection. In contrast, greater postoperative than preoperative activation in the ipsilateral posterior medial temporal lobe correlated with worse postoperative verbal memory performance. These postoperative effects were not observed for visual memory function after right anterior temporal lobe resection. Our findings provide evidence for effective preoperative reorganization of verbal memory function to the ipsilateral posterior medial temporal lobe due to the underlying disease, suggesting that it is the capacity of the posterior remnant of the ipsilateral hippocampus rather than the functional reserve of the contralateral hippocampus that is important for maintaining verbal memory function after anterior temporal lobectomy. Early postoperative reorganization to ipsilateral posterior or contralateral medial temporal lobe structures does not underpin better performance. Additionally our results suggest that visual memory function in right temporal lobe epilepsy is affected differently by right anterior temporal lobe resection than verbal memory in left temporal lobe epilepsy.

**Commentary**

Resective surgery is currently the treatment of choice for intractable temporal lobe epilepsy (TLE), achieving long-term seizure freedom in up to 50 to 60 percent of patients, even without a clear MRI lesion (1). This seizure control may come at the expense of various functional deficits, including an upper quadrant visual field cut, naming difficulties, and a side-dependent memory impairment, with verbal memory at highest risk following dominant mesial temporal resections and visual memory with nondominant temporal lobe surgery. In fact, “significant” memory decline occurs in 30 to 60 percent of patients after dominant anterior temporal lobectomy (2), and in 33 to 50 percent after left selective amygdalohippocampectomy (3). It is therefore essential to develop and validate tools to accurately predict both the occurrence and severity of postoperative memory change to better inform the presurgical counseling and decision making. At another, deeper level, it behooves the epilepsy community to identify reliable strategies that may prevent or reduce this risk—not solely predict it. Knowledge gained from the two articles chosen for this commentary advances both domains: The prediction and prevention of memory decline following epilepsy surgery.

The first article by Sidhu et al. joins a growing body of literature in evolving our appreciation of memory as a “network function” while simultaneously highlighting the critical role of the mesial temporal structures. In a study of 44 patients with unilateral mesial TLE due to hippocampal sclerosis, the authors found extensive bilateral extratemporal and lateral temporal reorganization of fMRI activation during memory encoding. However, better memory function was mainly dependent on reorganization within the medial temporal lobe itself (particularly in the posterior hippocampus), with additional key activation of the orbitofrontal cortex, anterior cingulum, and insula. The second paper by Bonelli et al. further reinforces the importance of this medial temporal reorganization by showing that a robust preoperative activation of the left posterior hippocampus during word encoding can reliably predict better verbal memory outcomes after temporal lobectomy. So, what do these findings mean in relation to our two domains of interest: prediction and prevention of postoperative memory decline?

The question of memory outcome prediction is indeed worth considering because traditional predictors such as preoperative memory performance on neuropsychological testing, age at epilepsy onset, and even WADA testing are insufficient to provide a comprehensive assessment of surgical memory risk (2). fMRI naturally emerges then as a noninvasive additional investigative method. Theoretically, a tool that measures memory function should help assess memory reserve and organization. The issue is that practically, many intracacies need to be addressed before a memory predictive fMRI becomes widely accepted as a clinically useful tool.

First, the ideal “memory measuring” protocol needs to be defined. Studies that used scene-encoding tasks activating the mesial temporal lobes bilaterally—possibly masking deficits due to a unilateral dysfunction (4, 5)—were less predictive of postoperative verbal memory decline than those using more specific paradigms, such as word list learning, story recall, and delayed recall, as was done in the manuscript at hand by Bonelli et al. and others (6, 7). Besides the activation paradigms, fMRI findings vary depending on several technical definitions, including the delineation of the seed region within the mesial temporal structures, MRI acquisition parameters, and comparative control population (8). These multiple
parameters may account for variable results in the current literature, and underscore our second point: the “ideal” memory fMRI protocol—once determined—needs to be reproducible and validated in the clinical setting. One challenge includes the transition between “group data” and “group analyses” to clinically meaningful information at the individual patient level. If we consider the current findings by Bonelli et al., for example, it makes intuitive sense that patients whose verbal memory function “lives” in the anterior hippocampus—typically resected in TLE surgery due to hippocampal sclerosis—would be at higher risk for memory decline than patients whose verbal memory “lives” in the typically spared posterior hippocampus and tail: The challenge is that for an individual patient considering a temporal lobectomy and needing to assess his or her risk for memory decline with surgery, a verbal memory paradigm will likely activate the whole hippocampus—anterior and posterior to varying degrees, and an estimation of this particular patient’s risk in relation to the degree and pattern of his or her hippocampal activation will be helpful. Lastly, given current evidence that a language lateralizing fMRI may provide the dual advantage of assessing both language and verbal memory risks with temporal lobe resections (2), it would be interesting to determine the additional predictive contribution of a “memory fMRI.”

Beyond predicting a postoperative memory decline, the significance of critical work presented in the manuscripts at hand extends to indicating potential preventative measures. One such obvious measure proposed here and elsewhere is to limit the extent of hippocampal resection whenever possible. This again makes excellent intuitive sense, as the goal of any epilepsy surgery, by definition, is to remove the smallest amount of brain tissue required to achieve seizure freedom. Several challenging questions remain: First, the tail and posterior hippocampus are already often spared in a “standard temporal lobectomy”; in fact, sparing them in patients with “inefficient” preoperative reorganization of verbal memory (i.e., one relying more on anterior hippocampus) would not necessarily be expected to improve memory outcomes. Conversely, it is difficult to predict what the residual verbal memory function would actually be if the anterior hippocampus is “spared” but effectively disconnected because the remaining sclerosis and epileptic hippocampus needed to be removed. Second, it remains to be seen how the fMRI episodic memory maps generated in cohorts with hippocampal sclerosis translate to patients with nonlesional TLE, who are actually at the highest risk of verbal memory decline after surgery. The last untapped opportunity for prevention resides in a better understanding of the mechanisms underlying various patterns of presurgical memory reorganization in patients with epilepsy. Data presented here by Sidhu et al. and by other investigators (8) suggest that there are multiple potential patterns of altered resting functional connectivity and task-driven fMRI activation in patients with otherwise clinically similar mesial TLE, albeit with some patterns being more efficient than others and correlating with better baseline and postoperative memory function. Multiple factors may account for this variability, including variability in learning strategies during development (9) or genetic predisposition (10). It is unclear whether preoperative dysfunctional networks can be modified prior to surgery to optimize a patient’s chance of a successful outcome.

While several questions remain, thoughtful work such as the studies highlighted here help in moving us closer to answers.

by Lara E. Jehi, MD

References

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