Understanding Memory Systems in TLE: Networks, Nodes, and Hubs

Memory fMRI Predicts Verbal Memory Decline After Anterior Temporal Lobe Resection.

Sidhu MK, Stretton J, Winston GP, Symms M, Thompson PJ, Koepp MJ, Duncan JS. *Neurology* 2015; 84:1512–1519.

OBJECTIVE: To develop a clinically applicable memory functional MRI (fMRI) method of predicting postsurgical memory outcome in individual patients. **METHODS:** In this prospective cohort study, 50 patients with temporal lobe epilepsy (23 left) and 26 controls underwent an fMRI memory encoding paradigm of words with a subsequent out-of-scanner recognition assessment. Neuropsychological assessment was performed preoperatively and 4 months after anterior temporal lobe resection, and at equal time intervals in controls. An event-related analysis was used to explore brain activations for words remembered and change in verbal memory scores 4 months after surgery was correlated with preoperative activations. Individual lateralization indices were calculated within a medial temporal and frontal region and compared with other clinical parameters (hippocampal volume, preoperative verbal memory, age at onset of epilepsy, and language lateralization) as a predictor of verbal memory outcome. **RESULTS:** In left temporal lobe epilepsy patients, left frontal and anterior medial temporal activations correlated significantly with greater verbal memory decline, while bilateral posterior hippocampal activation correlated with less verbal memory decline postoperatively. In a multivariate regression model, left lateralized memory lateralization index (≥ 0.5) within a medial temporal and frontal mask was the best predictor of verbal memory outcome after surgery in the dominant hemisphere in individual patients. Neither clinical nor functional MRI parameters predicted verbal memory decline after nondominant temporal lobe resection. **CONCLUSION:** We propose a clinically applicable memory fMRI paradigm to predict postoperative verbal memory decline after surgery in the language-dominant hemisphere in individual patients.

Commentary

In a very unsystematic literature search for the years 2014–2016, Google Scholar listed more than 17,000 citations related to the topic of epilepsy and neural networks. This albeit roughly approximated number highlights the tremendous interest, growth, and emerging advances in the field's efforts toward better understanding how traditionally conceptualized local neural processes are more richly comprehended as a network of intricately interconnected brain systems involved in seizure propagation (1, 2).

While much work has been done disentangling our understanding of seizure propagation patterns/networks, there has also been increasing attention garnered toward appreciating the complexity of network models as related to cognitive function in epilepsy, in particular temporal lobe epilepsy (TLE), via sophisticated neuroimaging, electrophysiological measurement, and statistical methodologies (3). Several studies employing these technological advances have demonstrated reorganization and compensatory brain activation patterns occurring in the face of neurologic injury

and disease. While this is certainly not unique to the field of epilepsy (4), the historical influence of our understanding of memory systems using epilepsy populations has been of particular importance.

Since the introduction of surgery for treatment of TLE, the overarching goal has been to render persons seizure free, thereby allowing for an opportunity at improved quality of life with concomitant focus toward minimizing adverse outcome events. One of the major areas related to this topic has been predicting cognitive change after surgery (either positive or negative).

Highlighting these recent advances toward applying sophisticated neural network models to understanding cognitive networks and changes after surgery is a recent series of published studies by Sidhu and colleagues highlighted by their 2015 *Neurology* publication cited above (5, 6, 7). This research group has made efforts toward understanding local and distal brain network changes in memory encoding processes in TLE and the subsequent impact of those changes on post-surgery memory. They have described fMRI-based activation changes within ipsilateral, contralateral, and extratemporal brain regions in relation to memory encoding processes. They have found extratemporal changes occurring in persons with left hippocampal sclerosis (HS), as well as persons with right HS. These changes were conceptually described as reflecting

reorganization/compensatory effects of the brain when faced with pathological processes (5).

In a follow-up study by this group, Sidhu et al. (6) further developed their network model by examining relationships among clinical/medical factors potentially impacting those earlier identified memory encoding networks. They examined a well-characterized sample of 53 persons with TLE and hippocampal sclerosis. Three important clinical variables were examined (age at seizure onset, seizure duration, and seizure frequency) as possible influences to the reorganized memory network. Both fMRI-based word encoding and facial encoding tasks were used. A number of interesting findings were described, including a shift toward posterior hippocampal activation in the presence of earlier age at epilepsy onset, positive relationships between mesial temporal lobe memory formation and shorter duration of epilepsy and lower seizure frequencies. TLE with longer disease durations and higher seizure frequency rates was associated with extratemporal lobe activations. These extratemporal activation patterns were found to be associated with poorer memory performances.

Last year, Sidhu et al (2015) extended their research series to explore how preoperative memory network changes can impact postoperative memory outcome. An editorial comment by Trenerry and Meador (8) accompanying that study publication encouragingly commented on the expansion and appreciation for the richness and complexity of network changes in TLE and that methods such as those presented by the study's authors help to facilitate efforts for clinical prediction of cognitive surgery outcome and ultimately lead to improved patient quality of life.

This newly published study by Sidhu, et al. (2015) included clinically well-characterized samples of persons with either left or right TLE all undergoing anterior temporal lobectomy and most of whom had achieved seizure freedom at a 4-month postoperative assessment. As in their prior study (6), a concrete noun fMRI paradigm was presented. A recognition score was obtained for each encoding component. The authors calculated a lateralization index (LI) from the preoperative fMRI memory encoding activation results. The LI included measurements of both mesial temporal (i.e., including amygdala, hippocampus) and frontal activations from left and right hemispheres.

Regression analyses revealed that the memory LI showing left activation greater than right activation of mesial and frontal lobes achieved positive predictive power of 70% in predicting verbal memory decline. However, neither fMRI nor clinical variables (i.e., age at onset of epilepsy) predicted memory outcome in right-sided TLE. Interestingly, they also reviewed individual patient-level data in cases where the LI was not associated with memory decline contrary to prediction. While fMRI protocols such as that presented are quite promising, these authors also acknowledged that other factors remain involved in postoperative outcome as exemplified by these highlighted individual cases.

In another recently published study (7), the same authors extended their investigation of postoperative network changes in persons with TLE and found extended 12-month postoperative compensatory changes in memory encoding operations, which occurred in the contralateral hippocampus.

Studies such as those from this research group's series highlight the exciting developments in our understanding of the rich dynamic properties of cognitive neural networks and how they affect outcomes after epilepsy surgery.

It is also worth noting that in this study all the included patients with epilepsy had hippocampal sclerosis. While this was a relatively homogeneous population to examine their study hypotheses, other patient groups are also frequently assessed in epilepsy clinics for possible surgical intervention (i.e., persons with nonlesional TLE, dual pathology, or developmental cortical malformations). Continued efforts will be important in examining these broader populations of commonly encountered candidates for epilepsy surgery, as it pertains to forms of compensatory and reorganizational neural network and effects on cognitive functions.

Within the context of better understanding cognitive neural networks in epilepsy, other investigatory questions for future study have arisen and are being investigated. Questions such as these: How might new technology developments (i.e., responsive neurostimulation, deep brain stimulation) affect cognitive neural networks and potentially affect cognitive risks within the context of improving chances for seizure reduction or elimination? How might identifiable compensatory/ reorganizational network processes inform postsurgery cognitive rehabilitation efforts? Research could expand beyond neural network effects on memory systems and include other potential effects on other cognitive/behavioral domains, such as executive function, language, behavior/psychiatric systems, and social cognition. Studies exploring these types of broader cognitive systems are being conducted and are exploring the multitude of brain network systems (e.g., default mode network, dorsal attention network, limbic network) (9). For example, one recent study demonstrated that fMRI activation network patterns in adolescents and young adults with autism predicted behavioral/adaptive outcomes (10).

Also, as Sidhu et al. pointed out, most studies to date present group-level analysis when describing the neural network's relationship to cognitive outcome. However, there is a need for algorithm development incorporating network models that can be used at the individual patient level to provide post-surgery cognitive outcome prediction.

by Roy Martin, PhD

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