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Preoperative Prediction of Verbal Episodic Memory Outcome Using fMRI

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fMRI; memory; epilepsy; temporal lobectomy

Uses for Functional Imaging of Memory Systems

Interest in functional imaging of memory systems stems from two clinical problems. The first of these is localization of seizure foci in temporal lobe epilepsy (TLE). TLE often arises from the medial temporal lobe (MTL) (4,31,134), and structural and functional abnormalities in the MTL can provide important evidence regarding seizure localization. Asymmetric sclerosis and volume loss in TLE can be detected with good sensitivity and specificity using structural MRI (20,23,58,135). Positron emission tomography (PET) may reveal interictal MTL hypometabolism and associated hypoperfusion in patients with TLE (86,123,139). The memory portion of the Wada test, which assesses episodic encoding during unilateral cerebral anesthesia, can detect asymmetric dysfunction of the MTL, which can be used to infer the laterality of a seizure focus (1,61,81,85,102). One potential application of fMRI, therefore, is to provide evidence about seizure focus laterality by measuring asymmetry of activation in the MTL. In addition to assisting in seizure focus identification, asymmetry of activation might be useful for predicting seizure outcome after anterior temporal lobe (ATL) surgery. When functional asymmetry consistent with the side of seizure focus is demonstrated on PET or on the Wada memory test, for example, seizure control is better than when no asymmetry or reversed asymmetry is observed (75,84,86,102,124,139). Although several fMRI studies suggest that MTL activation asymmetry may be correlated with side of seizure focus and seizure outcome in TLE (46,60,66,108), sample sizes in these studies have been small, and no studies have yet examined whether fMRI contributes additional predictive value beyond ictal EEG, ictal semiology, and structural MRI.

The present chapter focuses on an equally important neurosurgical problem for which functional imaging may have a role. Temporal lobe epilepsy surgery typically involves removal of much of the anterior MTL, including portions of the hippocampus and parahippocampus, which are known to be critical for encoding and retrieval of long-term episodic memories (127). Verbal episodic memory decline after left ATL resection is a consistent finding in group studies and is observed in 30-60% of such patients

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(7,16,18,25,^{27,44,52,55,70,77,79},83,89,115,130). In contrast, non-verbal memory decline after right ATL resection is less consistently observed in both groups and individuals (16,77,79,130). One main focus of the preoperative evaluation in ATL surgery candidates is, therefore, to estimate risk of verbal memory decline, particularly in patients undergoing left ATL resection.

The Wada memory test was originally developed for the purpose of predicting global amnesia after ATL resection (93), though its reliability for this purpose has often been questioned (73,76,80,82,88,95,119). Studies of its ability to predict relative verbal memory decline have been inconsistent, with several suggesting good predictive value (11,27,70,83,115) and others showing little or none, particularly when used in combination with non-invasive tests (16,24,69,74,79,130). Other presurgical tests of MTL functional or anatomical asymmetry are modestly predictive of memory outcome, including structural MRI of the hippocampus (29,79,130,131,141) and inter-ictal PET (48). Preoperative neuropsychological testing also has predictive value, in that patients with good memory abilities prior to surgery are more likely to decline than patients with poor preoperative memory (7,8,16,25,^{34,44,52,55,59,79,130}). Given the availability of these other known predictors, the value of fMRI depends not only on its ability to predict memory outcome in isolation, but also on its ability to contribute additional predictive value beyond other noninvasive measures.

A key point often neglected in discussion of these topics is that the goals of seizure focus lateralization and memory outcome prediction call for fundamentally different methodological considerations. In the case of seizure focus lateralization, the ideal fMRI procedure is probably one that activates the MTL symmetrically in healthy people, thus allowing optimal detection of deviation from normal symmetry in either direction. In contrast, prediction of verbal memory outcome requires an fMRI procedure that specifically identifies verbal memory processes. Because many stimuli are encoded into memory in both verbal and nonverbal forms, MTL activation resulting from such stimuli cannot be assumed to represent verbal memory processes. Stimuli that are dually encoded, such as pictures, might be ideal for producing bilateral MTL activation and thus for detecting seizure focus lateralization, while these same activation patterns, because they represent a mix of verbal and nonverbal processes, may predict little or nothing about verbal memory outcome.

Varieties of Memory

Memory refers to the ability to store and retrieve information. The human brain performs four essentially different kinds of memory processes, distinguished by the type of information stored and the length of time over which storage persists. At one end of the spectrum is *procedural memory*, which refers to knowing how to do motor and sensory tasks. Common examples include walking, eating, throwing a ball, tying a tie, riding a bike. The information stored involves complex sensory-motor sequences that are largely outside conscious awareness and cannot be described in detail. Another notable example of procedural memory is talking, which involves very complex sequences of tongue, lip, vocal cord, and diaphragm movements of which perfectly fluent speakers are largely unaware. *Semantic memory* refers to knowing facts about the world, such as the color of a banana, the capital of France, or the meaning of a word. Semantic memory allows us to recognize and name objects, produce and comprehend sentences, form opinions, and plan the future. Like procedural memory, information in semantic memory typically persists over an entire lifetime, though loss of semantic memory is a characteristic feature of some forms of dementia. At the other end of the spectrum, *short-term memory* refers to the ability to hold information in consciousness for seconds or a few minutes, usually by active mental recitation. Short-term memory allows us to hold in mind otherwise meaningless sequences

like telephone numbers long enough to complete a task for which they are needed. The transient nature of short-term memory is illustrated by the fact that distraction of attention typically causes the information to rapidly fade, and by the common use of semantic memory in the form of “mnemonic devices” to allow longer maintenance of otherwise meaningless sequences.

The focus of the present review is *episodic memory*, which refers to the ability to update and maintain a conscious record of personal experiences. Episodic memory can include both verbal and non-verbal information, such as the content of recent conversations, names of new friends, personally experienced events and their order of occurrence, or the location of one's car in a parking lot. Information in episodic memory can persist for hours, days, or years depending on factors such as the meaningfulness or emotional significance of the event and the frequency with which the event is recalled. Episodic memory was first linked conclusively with the MTL after cases of severe episodic memory loss, labeled amnesia, were reported from temporal lobe damage involving the MTL bilaterally (92,118). Such patients are unable to form new memories of events or learn new verbal information (anterograde amnesia), and may also lose partial memory of events experienced prior to the MTL damage (retrograde amnesia). In contrast, knowledge about objects and previously learned facts about the world are spared, as are motor skills and the ability to hold information through active recitation, indicating relative preservation of semantic, procedural, and short-term memory.

A Little Bit of Theory

Episodic memory plays a vital role in everyday life. The purpose of having an ongoing, constantly updated record of personal events is so that we can accomplish the basic tasks of survival. Without such a record, we would be unable to keep track of our current needs, the steps already taken to meet these needs, or the plans for meeting them. We could not keep track of imminent threats or new information about potential threats. We could not maintain a record of common experience that forms the basis for human discourse.

Given these vital functions of episodic memory, it should not be surprising that the episodic memory system has evolved a method for preferentially storing events that are meaningful and of personal significance. A typical meaningful event (say, a conversation about an upcoming trip) includes processing of sensory information (e.g., speech sounds), retrieval of semantic information (e.g., word meanings, factual knowledge), cognitive responses (e.g., conversational exchanges), and emotional responses (e.g., excitement, pleasure). Thus, a meaningful event typically elicits a complex, sequential cascade of neural activations throughout the cortex that are specific to the event. Research suggests that the essential role of the hippocampus is to bind these sensory, semantic, executive, and affective responses into unique, indexable event configurations (28,90,96). Recall of the event is accompanied by a partial recreation of the spatial-temporal sequence of neural activity that occurred during the original event. Events that are more meaningful to the individual (emotionally or intellectually) elicit more widespread semantic, executive, and affective processing, and are thus more easily recalled (32). This simple principle accounts for a wide range of phenomena observed in experimental studies of verbal episodic memory, such as the greater ease of learning lists of words compared to nonsense words, familiar relative to unfamiliar words, semantically encoded compared to phonologically encoded words, concrete compared to abstract words, semantically related compared to unrelated words, and stories compared to sequences of unrelated sentences (32,37,67,98,⁹⁹,103,121,122,142).

Two interesting and important aspects of episodic memory are often overlooked despite their particular relevance to imaging studies. The first is the ongoing, continuous nature of

this process. We remember events without specifically trying to, and without instruction beforehand to do so. Except for periods during sleep, we do not have long gaps in our recent memory record. If the evolutionary purpose of episodic memory is to maintain a record of events, it makes sense that the “recorder keeps running” whenever we are awake. A complementary point is that events recorded in episodic memory need not be physical events occurring in the external world. Mental events, too, can induce extensive semantic processing, executive responses, and emotional responses. Lying in an MRI scanner during periods of “rest” in an fMRI study, it is not hard to imagine a patient thinking about the experience and how it feels, or composing a list of things to do when the study is over. After the study, it would be surprising indeed if the patient could not recall how the experience felt or the to-do list she composed. Her ability to do so indicates that these mental events are every bit as “encoded” into episodic memory as are external physical events.

FMRI of the Medial Temporal Lobe

MTL activation during memory encoding and retrieval tasks has been a subject of intense research with fMRI (for reviews, see (42,57,100,113,116,117,136)). Hippocampal activation has been demonstrated using a variety of task paradigms (e.g., (13,15,30,33,^{38,39,47,51,53,64,65,87,97,101,107,120,125,128,137,140,144})), although fMRI of this region is not without technical challenges. The hippocampal formation is small relative to typical voxel sizes used in fMRI. Within-voxel averaging of signals from active and inactive structures may thus impair detection of hippocampal activity. Loss of MRI signal in the medial ATL due to macroscopic field inhomogeneity can affect the amygdala and occasionally the anterior hippocampus (30,40,94). Finally, the baseline condition employed in subtraction analyses is of critical importance. Hippocampal encoding processes continue beyond the duration of external stimuli (2), and human imaging evidence suggests that the hippocampus is relatively activated in the “resting” state (3,14,87,128). Stark & Squire (128), for example, showed that the hippocampus and parahippocampus both show higher BOLD signals during “rest” than during active perceptual discrimination tasks. Activation of these MTL regions during encoding of pictures was detected using the perceptual discrimination tasks as a baseline, but not when “rest” was used as a baseline.

MTL fMRI paradigms generally employ one of three approaches. The first of these involves a contrast between encoding novel and repeated stimuli, based on earlier electrophysiological studies showing that the hippocampus responds more strongly to novel than to repeated stimuli (49,71,78,112). The encoding task might involve explicit memorization for later retrieval testing or a decision task designed to produce implicit encoding. Such novelty contrasts mainly activate the posterior parahippocampus and adjacent fusiform gyrus, with involvement of the posterior hippocampus in some but not all studies (13,40,43,56,68,129,132). The second approach involves manipulating the degree of associative/semantic processing that occurs during encoding. As noted above, hippocampal encoding is thought to involve the creation of configural representations that tie together sensory, semantic, affective, and other codes activated by an event (28,90,96). External events that are meaningful and activate semantic and emotional associations engage the hippocampus more robustly and are thus more effectively recorded (32). Thus many fMRI studies have demonstrated hippocampal activation using contrasts between a stimulus or task that engages associative/semantic processing (e.g., a word or picture) and a stimulus or task that engages only sensory processing (e.g., a nonword or unrecognizable visual form) (5,13,15,33,^{53,54,64,65,87,97,120,125,138,144}). Finally, a third approach uses subsequent recognition performance as a direct index of MTL activity during encoding. Items encoded during the fMRI scan are sorted according to whether they were later remembered, and a contrast is made between successfully and unsuccessfully encoded items. These studies consistently show greater MTL activation during subsequently remembered compared to

subsequently forgotten stimuli, though the precise MTL regions showing this effect have varied considerably (19,21,30,33,^{39,68,97,106},107,133,138,140).

Finally, the lateralization of MTL activation detected by fMRI depends on the type of stimulus material encoded. MTL activation is left-lateralized for word stimuli, symmetric for scene stimuli, and generally right-lateralized for face stimuli (13,15,18,35,^{45,63},87,97,104,109).

Medial Temporal Lobe FMRI as a Predictor of Verbal Memory Outcome

The relationship between preoperative MTL activation and memory outcome after ATL surgery has been explored in a number of studies (Table 1). Rabin et al. (108) examined 23 patients undergoing ATL resection (10 left, 13 right) using a scene-encoding task that activates the posterior MTL bilaterally (35). Patients were tested for delayed recognition of the same pictures immediately after scanning. Delayed picture recognition was then tested again after surgery, and the change on this recognition task was used as the primary memory outcome variable. About half of the patients in both surgery groups declined on this measure. Preoperative fMRI activation lateralization toward the side of surgery was correlated with decline, as was the extent of activation on the side of surgery. These results were the first to demonstrate a relationship between preoperative fMRI activation asymmetry and outcome, yet they are of limited relevance to the problem of predicting verbal memory outcome. In the left ATL patients studied by Rabin et al., neither Wada memory nor fMRI activation asymmetry predicted verbal memory decline as measured by standard verbal memory tests.

Richardson, Powell, and colleagues studied correlations between hippocampal activation and verbal memory outcome in three small studies (105,110,111). Patients performed a semantic decision task with words during the fMRI scan and then took a recognition test after scanning. Words that were subsequently recognized were contrasted with words that were judged to be familiar but not recognized. The aim of these studies was to ascertain whether activation or activation asymmetry in any region of the MTL was related to outcome, rather than to predict outcome *per se*. Rather than defining an *a priori* ROI, the authors searched the MTL image space for any voxels where activation, or activation asymmetry, was correlated with memory change scores. The results, though somewhat inconsistent across the studies, suggested that preoperative fMRI activation maps contain information related to memory outcome. It is important to note, however, that the ROIs in these studies were defined post hoc using a group analysis and have varied in location across studies. It is not clear how this method of extracting activation values could be applied to a newly encountered patient.

Frings et al. studied the relationship between preoperative hippocampal activation asymmetry and verbal memory outcome in a small sample of patients undergoing left or right ATL resection (41). The fMRI protocol used a task in which patients viewed a virtual-reality environment containing colored geometric shapes and either memorized the location of these objects or performed a recognition decision following memorization. These “memory tasks” were contrasted with a control task in which patients saw two versions of a geometric object and indicated which one was larger. This fMRI contrast had been shown previously to activate posterior MTL regions (mainly posterior parahippocampus) bilaterally. A lateralization index was computed using the entire hippocampus as the ROI. Verbal memory change was marginally correlated (1-tailed $p = .077$) with preoperative LI in the left ATL surgery group, but not in the right surgery group. A significant correlation (1-tailed $p < .05$) was obtained when the groups were combined, indicating greater verbal memory decline with increasing lateralization of activation toward the side of surgery.

Köylü et al. examined correlations between preoperative MTL activation and verbal memory performance before and after ATL surgery (72). Average fMRI activation produced by a semantic decision - tone decision contrast was measured in left and right MTL ROIs including the hippocampus and parahippocampus. The authors observed correlations between MTL activation and both preoperative and postoperative verbal memory. In the left ATL surgery group, postoperative memory was positively correlated with preoperative activation in the right MTL. Unfortunately, the analyses examined only pre- and postoperative scores in isolation and not pre- to postoperative change, which is the primary issue of clinical interest.

Binder et al. (17) measured hippocampal activation asymmetry in 30 left and 37 right ATL surgery patients using a scene encoding task. An anterior hippocampal ROI was defined using a probabilistic atlas in standard stereotaxic space. When contrasted with a perceptual matching task, this paradigm activates the anterior hippocampus bilaterally (13). Activation asymmetry was correlated with side of seizure focus ($p = .004$) and with Wada memory testing performed in the same patients ($p = .009$). This activation asymmetry, however, did not predict verbal memory outcome.

In the most significant study on this topic to date, Bonelli et al. (18) examined verbal and nonverbal memory outcome in 29 patients undergoing left ATL surgery. The fMRI paradigm used the subsequent recognition contrast with words and faces developed by Powell et al. (104,105). The authors operationally defined ROIs in each individual as the location where activation asymmetry was highest. An “asymmetry image” was created in each individual by contrasting activation levels in mirror-symmetric voxels in the left and right temporal lobe. A small sphere around the voxel with the highest asymmetry value was used as the ROI. Two such ROIs were created in each patient, one in the anterior MTL and one in the posterior MTL. The main finding was a strong correlation ($R^2 = 0.23$, $p = .008$) between anterior MTL ROI asymmetry during word encoding and verbal memory change scores, such that the greater the asymmetry toward the left, the greater the decline in verbal memory. Interestingly, there was a significant correlation ($R^2 = 0.14$, $p = .04$) in the opposite direction for the posterior MTL ROI, such that greater asymmetry toward the left was associated with *less* verbal memory decline. Given that the posterior hippocampus is typically spared in ATL resections, the authors interpret the latter finding as evidence that intrahemispheric recruitment of the posterior left hippocampus in left TLE is important for preservation of verbal memory processes.

These studies are informative in several ways. Three studies (17,41,108) used scene encoding tasks that activate the MTL bilaterally on fMRI, a pattern that suggests activation of both verbal and nonverbal memory encoding systems. Prediction of verbal memory outcome using these paradigms appears to be weak at best. In contrast, the verbal memory fMRI paradigms used by Richardson, Powell, Bonelli et al. provide better predictive information regarding verbal memory outcome. These results provide further support for the long-standing concept of material-specific encoding in the episodic memory system. The results of Bonelli et al., though based on a relatively small sample, are particularly promising and should be confirmed prospectively in a larger group of patients.

Language Lateralization as a Predictor of Verbal Memory Outcome

Binder et al. studied the relationship between preoperative language lateralization and verbal memory outcome (16). The premise underlying this approach is that the verbal episodic memory encoding system is likely to be co-lateralized with language. More generally, the authors proposed that the type of material encoded by the left or right MTL depends on the type of information it receives from the ipsilateral neocortex. According to this model, the

language lateralization should be a reliable indicator of verbal memory lateralization and thus should predict verbal memory outcome.

The study included 60 patients who underwent left ATL resection and a control group of 63 right ATL resection patients. The fMRI paradigm used a contrast between an auditory semantic decision task and a nonlinguistic tone decision task (Figure 1). Verbal memory was measured preoperatively and 6 months after surgery using the Selective Reminding Test, a word-list learning and delayed recall test (22). Testing also included several measures of nonverbal learning and memory. Language LIs were computed from the fMRI data using a large region of interest covering the lateral two-thirds of each hemisphere (126). All patients also underwent preoperative Wada language and memory testing.

The left ATL surgery group showed substantial changes in verbal memory, with an average raw score decline of 43% on word list learning and 45% on delayed recall of the word list. Of the individual patients, 33% declined significantly on the learning measure and 55% on the delayed recall measure. In contrast, the right ATL surgery group improved slightly on both measures. Neither group showed significant changes on any nonverbal memory tests. The strongest predictor of verbal memory change in the left surgery group was the preoperative score ($r = .662$ for list learning, $r = .654$ for delayed recall). The next strongest predictor was fMRI language LI ($r = .432$ for list learning, $r = .316$ for delayed recall). Wada memory asymmetry was only marginally predictive ($r = .331$ for list learning, $r = .135$ for delayed recall).

In applying these results to real clinical situations, the main questions to resolve are: which tests make a significant independent contribution to predicting outcome, and how should results from these tests be optimally combined? Binder et al. addressed these questions in a series of stepwise multiple regression analyses. The first variables entered in all analyses were preoperative test performance and age at onset of epilepsy, since these variables can be obtained at relatively little cost and at no risk to the patient. Next, the fMRI language LI was added, followed by simultaneous addition of both the Wada memory and Wada language asymmetry scores. The rationale for adding fMRI in the second step is that fMRI is non-invasive and carries less risk than the Wada test. The two Wada scores were added together in the final step because these measures are typically obtained together.

Preoperative score and age at onset of epilepsy together accounted for 49% of the variance in list learning outcome and 54% of the variance in delayed recall outcome. The fMRI LI explained an additional 10% of the variance in list learning outcome ($p = .001$) and 7% of the variance in delayed recall outcome ($p = .003$). Addition of the Wada language and memory data did not improve the predictive power in either case. Used together in a multivariate regression formula, the preoperative score, age at onset, and fMRI LI showed 90% sensitivity and 80% specificity for predicting significant decline on list learning, and 81% sensitivity and 100% specificity for predicting decline on delayed recall.

These results are interesting for several reasons. Most intriguing is the finding that *language* lateralization, whether measured by fMRI or the Wada test, is a better predictor of verbal *memory* outcome than Wada memory testing. The explanation for this apparent paradox rests on two hypotheses. One, mentioned above, is that verbal memory encoding processes tend to co-lateralize with language processes. The second hypothesis is that many tests of memory lateralization do not specifically assess verbal memory encoding. Visual stimuli such as objects and pictures can be dually encoded as both names and visual objects. Wada memory procedures that use such stimuli (including the Wada test used by Binder et al.) therefore do not provide a measure of verbal memory lateralization, but rather a measure of overall memory lateralization that includes both verbal and nonverbal encoding processes.

Thus, verbal memory lateralization is more tightly linked with language lateralization than with Wada memory asymmetry. Of greatest concern are patients who show marked declines in verbal memory postoperatively despite preoperative Wada testing showing lateralization of memory to the right side (16). The explanation for these cases is simple: overall memory as measured by the Wada was lateralized to the right, but *verbal* memory remained on the left, a fact that cannot be determined by object memory testing.

Further confirmation of a link between language lateralization and verbal memory outcome comes from the recent study by Bonelli et al. (18), who reported a correlation of $r = .331$ between fMRI language LI and verbal memory change in 29 left ATL surgery patients. Language LI was measured in a frontal ROI using a word generation task contrasted with rest. As noted above, the authors also examined activation asymmetry in the MTL during word encoding, which produced a stronger correlation with verbal memory outcome ($r = .480$) than the frontal language LI. Preoperative scores, duration of epilepsy, and left hippocampal volume were all uncorrelated with outcome. In a multivariate regression analysis, MTL activation asymmetry was the only significant predictor, with all other variables, including language LI, failing to contribute additional predictive power. In a final analysis, however, the authors report that the specificity of an outcome prediction “algorithm” improved from 41% to 86%, and the positive predictive value increased from 35% to 70%, by adding language lateralization and preoperative memory data, suggesting substantial additional predictive value from these variables.

Summary and Conclusions

Two recent studies provide the first strong evidence that preoperative fMRI is clinically useful for predicting verbal memory outcome in left ATL surgery. The larger study used preoperative language dominance to predict verbal memory outcome (16), while the second study used MTL activation asymmetry during word encoding (18). Both methods predicted about 20% of the variance in outcome when used alone, and both added independent predictive power when combined with other noninvasive measures. The language LI approach of Binder et al. is based on activation over a very large ROI, thus the LI might be more stable and reproducible than an LI based on a small MTL ROI, and less susceptible to signal dropout that can affect the MTL. From an economical standpoint, the language LI can also be used to predict naming outcome in left ATL surgery (114), thus this approach addresses two clinical questions with a single protocol. The advantage of the MTL approach is that it could in theory have higher predictive value, since it lateralizes verbal encoding processes directly rather than indirectly. Results of the MTL approach are still based on a relatively small sample of patients and need to be confirmed in future studies. Future studies should also compare the MTL and language LI approaches in larger samples.

The goal of the studies reviewed here has been to develop methods for quantitative prediction of cognitive risk from ATL surgery. The quantitative nature of these predictions represents something of a paradigm shift, in that traditional predictive models using the Wada test tended to be implemented as a dichotomous “pass or fail” judgment. In addition to examining the role of fMRI, recent studies have increasingly used multivariate models to optimize predictions and to compute predicted change scores (Figure 1). These quantitative predictions provide a much more realistic picture of the actual outcomes, which are not dichotomous, but vary smoothly along a continuum. Ultimately, of course, the decision whether to undergo surgery is a categorical one, but the categorical nature of the decision does not obviate the need for precision regarding the factors that enter into the decision. A patient disabled by frequent seizures may be willing to tolerate a substantial memory decline for seizure control, whereas a patient who depends on such cognitive abilities for her livelihood may be willing to risk a small decline but not a large one.

The availability of fMRI for predicting memory outcome raises further questions about the role of Wada testing in the presurgical epilepsy evaluation (9,12). fMRI is a safe, noninvasive test that improves prediction accuracy relative to other noninvasive measures. In the study by Binder et al., Wada memory asymmetry was a relatively weak predictor of memory outcome and did not improve prediction accuracy relative to available noninvasive tests, confirming several previous studies that also examined multivariate prediction models (24,69,74,79,130). These results call into question the routine use of the Wada test for predicting material-specific verbal memory outcome, particularly if a validated fMRI test is available. Some practitioners use the Wada test to assess risk for global amnesia, which may occur after bilateral MTL damage (36,50,93,118). According to this theory, anesthetization of the to-be-resected MTL is necessary to discover whether the contralateral hemisphere is healthy enough to support memory on its own. Empirical observations, however, provide little support for such an approach. Cases of global amnesia following unilateral temporal lobe resection -- especially modern, well-documented cases -- appear to be rare in the extreme (6,62,73,82,95,119). Furthermore, there is ample evidence that contralateral hemisphere "memory failure" on the Wada test suffers from poor test-retest reliability and does not reliably predict amnesia (10,73,76,80,⁸²,88,95,119,143). Given the availability of fMRI for predicting material-specific verbal memory outcome, perhaps use of the Wada test should be reserved only for those patients at greatest risk for global amnesia, i.e. patients undergoing unilateral ATL resection who have structural or functional evidence of damage to the contralateral MTL. Because it is noninvasive and requires fewer personnel, fMRI is also likely to be substantially less costly than the Wada test (91).

An important caveat to keep in mind is that fMRI is a complex test of higher brain function, which will produce high-quality results only if high-quality methods are used. Unlike a structural imaging study, the patient is required to perform a specific mental task or tasks during fMRI, must understand fully what to do, and must be monitored for compliance during the study. The task conditions must be designed to reliably and specifically identify the mental processes of interest, based on modern scientific evidence about these processes rather than on folk psychology or 19th century neurology. These challenges can best be met through close involvement of cognitive scientists in the design of task protocols and by direct involvement of clinicians with expertise in cognitive testing to provide patient instruction and performance assessment during scanning.

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Figure 1.

Predicted vs. observed individual memory change scores in 60 left ATL surgery patients on tests of word list learning and delayed recall. Predicted list learning change scores were computed from the formula: $17.67 - 0.704(\text{Preoperative Score}) - 0.280(\text{Age at Onset}) - 12.19(\text{fMRI LI})$. Predicted delayed recall change scores were computed from the formula: $3.76 - 0.688(\text{Preoperative Score}) - 0.093(\text{Age at Onset}) - 2.14(\text{fMRI LI})$. (Adapted from (16))

Table 1

FMRI studies of verbal memory outcome prediction in ATL surgery.

Author	Year	N	FMRI Contrast	Memory Measure	Summary
Rabin et al.	2004	10 L 13 R	Indoor/outdoor decision on visual scenes vs. Passive viewing of scrambled scenes	Recognition of scenes encoded during fMRI; standardized verbal memory tests	MTL laterality index (LI) predicts change in scene memory in both surgery groups, but not change in verbal memory.
Richardson et al.	2004	10 L	Subsequently Recognized vs. Familiar but not recognized words encoded during a semantic decision task	Word list learning and story recall (Adult Memory and Information Processing Battery)	Activation asymmetry in part of the hippocampus is correlated with memory outcome.
Richardson et al.	2006	12 L	Same as Richardson et al. (2004)	Same as Richardson et al. (2004)	Unilateral activation in both left and right hippocampus is correlated with memory outcome.
Binder et al.	2008	60 L	Semantic decision on auditory words vs. Sensory decision on tones	Word list learning and delayed recall (Selective Reminding Test)	Language LI predicts verbal memory outcome, adds value beyond other predictors.
Frings et al.	2008	9 L 10 R	Memorizing and recognizing object locations vs. Comparing size of two objects	Word list learning (Verbal Learning- & Merckhaefigkeitest)	Hippocampal LI predicts verbal memory outcome, mainly in left group.
Köylü et al.	2008	14 L 12 R	Semantic decision on auditory words vs. Sensory decision on tones	Word list learning and delayed recall (Münchner Gedächtnistest)	MTL activation correlates with pre- and postoperative memory
Powell et al.	2008	7 L 8 R	Subsequently Recognized vs. Forgotten words and faces encoded during a semantic decision task	Word list learning and visual design learning	Unilateral activation in dominant-side hippocampus is correlated with memory outcome in dominant resection.
Binder et al.	2010	30 L 37 R	Indoor/outdoor decision on visual scenes vs. Perceptual matching of scrambled scenes	Word list learning and delayed recall (Selective Reminding Test)	Hippocampal LI for scenes does not predict verbal memory outcome.
Bonelli et al.	2010	29 L 25 R	Same paradigm as in Powell (2008) for MTL activation. Verbal fluency task for frontal lobe language LI.	Same as Powell et al. (2008)	Anterior and posterior MTL LIs from the word encoding condition predict verbal memory outcome. Language LI predicts verbal memory outcome, but less strongly than MTL LIs.