Published in final edited form as:
Epilepsy Behav. 2011 February ; 20(2): 214–222. doi:10.1016/j.yebeh.2010.08.004.

FMRI Is a Valid Noninvasive Alternative to Wada Testing

Jeffrey R. Binder, MD

Abstract

Partial removal of the anterior temporal lobe (ATL) is a highly effective surgical treatment for intractable temporal lobe epilepsy, yet roughly half of patients who undergo left ATL resection show decline in language or verbal memory function postoperatively. Two recent studies demonstrate that preoperative fMRI can predict postoperative naming and verbal memory changes in such patients. Most importantly, fMRI significantly improves the accuracy of prediction relative to other noninvasive measures used alone. Addition of language and memory lateralization data from the intracarotid amobarbital (Wada) test did not improve prediction accuracy in these studies. Thus, fMRI provides patients and practitioners with a safe, non-invasive, and well-validated tool for making better-informed decisions regarding elective surgery based on a quantitative assessment of cognitive risk.

Keywords

fMRI; epilepsy; Wada test; language; speech; temporal lobe

Introduction

The first reports of human functional brain mapping using MRI scanners appeared 20 years ago [1,2]. Functional magnetic resonance imaging (fMRI) in its most common form, using endogenous blood oxygen-level-dependent (BOLD) contrast, is now practiced routinely at most medical centers. Despite extensive research and clinical experience, uncertainty persists over the use of fMRI in the presurgical evaluation for epilepsy. This article reviews evidence supporting the use of fMRI for predicting postoperative language and verbal memory deficits in patients undergoing elective anterior temporal lobe (ATL) surgery. This clinical setting continues to be the most common indication for the intracarotid amobarbital (Wada) test. Recent studies suggest that fMRI provides a valid noninvasive alternative to the Wada test for most patients.

Although the focus of this review is on lateralization of language and verbal memory functions, it should be noted that fMRI also provides detailed activation maps that can in some cases be used to guide surgical resections. For example, fMRI can localize primary and secondary motor areas, even in some patients whose brain anatomy has been profoundly distorted by developmental anomalies or mass lesions [3-8]. Together with diffusion tensor imaging (DTI) localization of corticospinal white matter pathways, these maps can be valuable in helping surgeons maximize a resection zone while avoiding critical motor areas

Corresponding Author: Dr. Jeffrey R. Binder, Department of Neurology, Medical College of Wisconsin, 9200 W. Wisconsin Ave., Milwaukee, Wisconsin 53226 USA, jbinder@mcw.edu, Phone: 414-456-4662, Fax: 414-456-6562.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

[9]. Similarly, fMRI can localize primary auditory, somatosensory, and visual cortex. In the case of visual cortex, the fMRI experiment can be designed to generate a retinotopic map showing the precise cortical representation of each region in the visual field [10,11], allowing the surgeon to know with reasonable certainty what pattern of visual field loss will result from resection of a particular cortical zone. The utility of these sensory and motor activation maps, however, rests on well-established lesiondeficit relationships. The discovery of retinotopic maps, for example, was based on decades of careful observation in patients with focal occipital lesions [12], thus there is no doubt about the effects that can be expected from focal damage to these regions.

Compared to these relatively straightforward relationships, the relationships between focal lesions and specific language deficits are complex and incompletely understood. The traditional emphasis on Broca and Wernicke areas has given way in recent decades to a much more complex picture of the language system, with recognition that both production and comprehension of language involve widely distributed brain networks, including many regions outside the traditional Broca and Wernicke zones [13-21]. In addition, evidence suggests that the exact location of language areas varies from person to person [22,23], perhaps accounting for some of the wide variation in aphasia outcome after focal lesions [24]. Given this uncertainty and the highly distributed nature of language processes, important concerns have been raised about the meaning of activation foci identified by fMRI language experiments. Unlike with primary motor and sensory areas, the effect of removing an fMRI-defined “language area” is simply not known. Some areas identified by fMRI could participate in language functions but play a nonessential role. Because language tasks engage a variety of general cognitive processes, such as attention and working memory, some of the areas “activated” in an fMRI language study may represent these general cognitive processes rather than the language components of interest. Adding to the uncertainty surrounding fMRI language maps is the fact that there are many different task paradigms available, which produce markedly different patterns of activation (see [25-28] for examples of comparisons between paradigms). Thus, a brain area declared “not active” using one paradigm might very well turn out to be “active” using another. These legitimate concerns about the specificity and sensitivity of fMRI-defined language maps currently limit the usefulness of such maps for detailed surgical planning. Those who would use fMRI language maps in this way run two risks: sparing of “active” regions that are actually not critical for language, resulting in sub-optimal seizure control; and resection of critical language zones that are “not active” merely due to insensitivity of the particular fMRI protocol employed, resulting in post-operative language deficits. Only through carefully designed and systematic studies – in which resections are performed blind to the fMRI data, standardized procedures are used for assessing outcome, and quantitative measures are made of the anatomical and functional lesion – will the usefulness of fMRI language maps for planning surgical resections be determined.

Although in the author's opinion fMRI language maps should not yet be routinely used for planning resection boundaries, fMRI already has a clearly established role to play as an alternative to the Wada test. Temporal lobectomy is highly effective for seizure control [29-31], yet roughly half of patients undergoing dominant ATL resection experience postoperative language [32-37] or verbal memory decline [38-46]. The traditional role of the Wada test is to estimate the risk of decline by determining the patient's hemispheric dominance for language and memory. Risk assessment provides the patient and physician with additional information that can be useful in deciding whether to proceed with treatment in elective situations. This information can also be used to select high-risk patients for more invasive procedures such as electrical stimulation mapping.

Use of FMRI for Predicting Naming Outcome

Measuring Language Lateralization

The Wada test was originally developed to assess the risk of language decline in patients undergoing brain surgery [47], based on the assumption that operating on the language-dominant hemisphere entailed increased risk. Though the Wada test has been in use for over 50 years, until recently the relationship between Wada language asymmetry and postoperative language outcome had never been quantified. The historical reasons for this curious knowledge gap relate to the traditional view of language lateralization as dichotomous (left or right) or trichotomous (left, right, or bilateral). Under this schema, it was obvious that operating on a non-dominant hemisphere would be safer than operating on a language-dominant hemisphere. Several aspects of this formulation have changed in recent decades. First, language lateralization has come to be seen as a continuously graded rather than an all-or-none phenomenon, with relative degrees of dominance rather than distinct categories [48-54]. Thus, while the majority (~75%) of patients who undergo left hemisphere surgery for epilepsy are left-hemisphere dominant for language, there is variation within this group in terms of the degree of left dominance. This variability raises the question of whether graded degrees of language dominance are reflected in graded levels of risk. Second, quantitative neuropsychological evaluation for postoperative language deficits has become a more standard practice, resulting in a shift of the clinical focus away from prediction of severe aphasia (which is very rare after standard left ATL resection) and toward prediction of more moderate degrees of language decline.

Use of fMRI for predicting language outcome in epilepsy surgery is therefore motivated by two critical assumptions. First, it is assumed that patients show varying degrees of language (mainly naming) deficit after surgery, and that it is desirable to know before surgery what degree of decline can be expected. Second, it is assumed that the degree of decline will be related to the degree of language lateralization toward the surgical hemisphere. The goal of fMRI in this context is thus to provide a reliable and valid measure of language lateralization. Many fMRI language activation paradigms have been described, differing in the type of language stimuli, stimulus modality, language task, control stimuli, and control task used, raising the question of which of these paradigms, if any, is optimal. Though different paradigms have seldom been compared quantitatively, it is clear that they can produce very different, in some cases entirely non-overlapping, activation patterns. This variation is related primarily to the cognitive, sensory, and motor processes engaged by the tasks, and the degree to which the language and control conditions differ in engaging these specific processes [55].

Several simple criteria can be applied in assessing the usefulness of fMRI language paradigms. First, the pattern of activation obtained in healthy, right-handed adults should be lateralized to the left hemisphere, as almost all such individuals are left-hemisphere dominant for language [50,56]. Second, the activation should be robust, i.e., it should be reliably obtained across individuals and in the same general brain regions. Third, there should be concordance between language lateralization measured with the fMRI paradigm and lateralization measured with other techniques, such as the Wada test, in the same individuals. Finally, it may be desirable that the paradigm produce activation in particular target brain regions. In the case of ATL surgery, for example, activation asymmetry in the temporal lobe might be more predictive of outcome than activation in the frontal lobe, thus a paradigm that activates the temporal lobe would have advantages over one that does not.

Lateralization of fMRI activation is typically expressed numerically in the form of a laterality index (LI). The first such LI was based on a simple count of the voxels that survived thresholding in each hemisphere [49]. The formula (L - R)/(L + R), where L and R refer to the voxel counts in each hemisphere, yields a number that varies from +1 when all activated voxels are on the left side to -1 when all activated voxels are the right. LI values obtained with this method vary as a function of the threshold used for defining activated voxels, thus several authors have explored alternative asymmetry measures that do not require thresholding [27,53,54,57-59]. No consensus regarding the optimal method for calculating activation asymmetry has yet emerged from these studies.

Figure 1 illustrates the critical importance of task selection in language fMRI studies. The figure shows average activation maps obtained while 26 right-handed subjects listened to spoken words and performed a semantic decision task [14,28]. In the top panel, BOLD signal during this task is compared to a "resting" baseline. The activated regions are largely bilateral, including bilateral auditory, working memory, general executive, and attention networks. In the middle panel of the figure, the semantic decision task is compared to a nonlinguistic auditory control task. In this case the activated regions are strongly left-lateralized and include several left temporal, parietal, and prefrontal regions (indicated by blue arrows) that were not observed when the resting baseline was used. These data illustrate in dramatic fashion how activation patterns depend on the choice of control condition. In the second paradigm, the use of an active nonlinguistic control task "subtracts out" bilateral activation in early auditory, general executive, and attention networks, leaving activation in left-lateralized language networks. These results also demonstrate that many high-level language processing regions are active during the "resting" state and can only be observed when an active nonlinguistic control condition is employed [28,60-64]. Graphs in the lower portion of Figure 1 show average activation volumes and laterality indexes for each task contrast, again illustrating the dramatic differences that can occur simply by changing the choice of control condition.

Many fMRI language paradigms have been compared to Wada language testing [25,26,49,53,58,65-80]. These studies generally report high concordance rates, typically in the 80-90% range (for reviews, see [81,82]). In assessing concordance, patients are usually assigned to categories such as "left dominant", "right dominant", or "mixed" on each test. The proportion of concordant cases depends strongly on how these arbitrary categories are defined.

Predicting Outcome

With so many studies focusing on fMRI-Wada correlations, it is easy to forget that the actual aim of measuring language lateralization prior to brain surgery is prediction of language outcome. An fMRI procedure that reliably identifies patients at risk for postoperative naming deficits would be a valuable clinical tool, especially if the fMRI results added information over and above other available tests. Previous studies have identified demographic and behavioral variables that may predict outcome. For example, left ATL patients who develop seizures at an earlier age generally have a lower risk for postoperative language decline [34,83,84], presumably because earlier age at onset is associated with a higher probability of language shift to the right hemisphere [50]. Better preoperative naming performance is associated with a higher risk for decline [32]. It has long been assumed that Wada language testing is predictive of language outcome, though the actual evidence on this issue is limited to a few case reports [33,47].

Sabsevitz et al. [37] studied 24 consecutively encountered patients undergoing left ATL resection. The fMRI paradigm used a contrast between an auditory semantic decision task and a nonlinguistic tone decision task (see Figure 1). A previous study had shown that asymmetry of activation with this task paradigm is correlated with language lateralization on the Wada test [49]. For the Sabsevitz et al. study, separate LIs were computed for the whole hemisphere, frontal lobe, temporal lobe, and angular gyrus. All patients also underwent

Wada testing and preoperative assessment of confrontation naming using the 60-item Boston Naming Test (BNT). The BNT was administered again at 6 months after surgery, and a change score was calculated as the difference between postop and preop scores. Surgeries were performed blind to the fMRI data but were tailored using intraoperative electrical stimulation mapping.

Compared to a control group of 32 right ATL patients, the left ATL group declined postoperatively on the BNT ($p < .001$), with an average change score of -9. Within the left ATL group there was considerable variability, with 13 patients (54%) showing variable degrees of decline relative to the control group. The temporal lobe fMRI LI was the strongest predictor of outcome (r = -.64, $p < .001$), indicating that language lateralization toward the left (surgical) temporal lobe was related to poorer naming outcome, whereas lateralization toward the right temporal lobe was associated with little or no decline. This fMRI measure showed 100% sensitivity, 73% specificity, and a positive predictive value of 81% in predicting significant decline. By comparison, the Wada language LI showed a somewhat weaker correlation with outcome (r = -.50, $p < .05$), 92% sensitivity, 43% specificity, and a positive predictive value of 67%. Notably, the frontal lobe fMRI LI was also less predictive (r = -.47, $p < .05$), suggesting that an optimal LI is one that indexes lateralization in the surgical resection area.

Sabsevitz et al. also created multivariate models to determine the contribution of fMRI relative to other noninvasive predictors. Both age at epilepsy onset (r = -.35, $p = .09$) and preoperative performance (r = -.39, $p = .06$) showed strong trends toward a correlation with outcome, and together these variables accounted for 27% of the variance in outcome. Adding the temporal lobe fMRI LI to this model accounted for an additional 23% of the variance, indicating a significant increase in predictive power ($p < .01$). Addition of the Wada language asymmetry score did not improve the model (1% increase in explained variance, $p > .1$).

These results show how preoperative fMRI can be used to stratify patients in terms of risk for language decline in the setting of left ATL resection, allowing patients and physicians to more accurately weigh the risks and benefits of the surgery. It is crucial to note, however, that these results hold only for the particular methods used in the study and may not generalize to other fMRI protocols, analysis methods, patient populations, or surgical procedures. Future studies should not only confirm these results using larger patient samples, but also test whether other fMRI protocols in current widespread use have similar predictive capability.

Use of FMRI for Predicting Verbal Memory Outcome

Verbal memory decline after left ATL resection is a consistent finding in group studies and is observed in 30-60% of such patients [38-46,85-90]. A main focus of the preoperative evaluation in ATL surgery candidates is, therefore, to estimate the risk of verbal memory decline in patients undergoing left ATL resection. The Wada memory test was originally developed for the purpose of predicting global amnesia after ATL resection [91]. Studies of its ability to predict material-specific verbal memory decline have been inconsistent, with several suggesting good predictive value [41,87-89,92] and others showing little or none, particularly when used in combination with non-invasive tests [42,45,46,93-95]. Some authors have questioned the general validity and reliability of Wada memory results [96-102]. Others have emphasized the sensitivity of the test to certain details of the stimulus presentation, procedures used for recall, and other methodological factors [103-106].

As with any invasive test, a major concern with the Wada test is whether it adds information beyond that available from noninvasive measures. Structural MRI of the hippocampus is modestly predictive of memory outcome [42,45,107-109] as is inter-ictal positron emission tomography [110]. Preoperative neuropsychological testing is one of the strongest predictors of outcome, in that patients with good memory abilities prior to surgery are more likely to decline than patients with poor preoperative memory [39,42-46,85,86,111-113]. Age at onset of epilepsy is also predictive, with decline more likely in those with later age at onset [43,86,111,114]. Recent research has investigated whether fMRI might provide additional predictive information.

Medial Temporal Lobe FMRI as a Predictor of Verbal Memory Outcome

Medial temporal lobe (MTL) activation during memory encoding and retrieval tasks has been a subject of intense research with fMRI (for reviews, see [115-121]). 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 [122-124]. Finally, the baseline state employed in subtraction analyses is probably of critical importance. Human imaging evidence suggests that the hippocampus is relatively activated in the “resting” state [61,125,126]. Stark & Squire [61], 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.

Several fMRI studies have examined the relationship between preoperative medial temporal lobe (MTL) activation and memory outcome after ATL surgery (Table 1). Rabin et al. [127] studied 23 patients undergoing ATL resection (10 left, 13 right) using a scene-encoding task that activates the posterior MTL bilaterally [128]. 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 and colleagues studied correlations between hippocampal activation and verbal memory outcome in three small studies [129-131]. 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. In the first of these studies [129], the authors observed a focus in the anterior hippocampus where *asymmetry* of activation (i.e., left -right) predicted verbal memory outcome on a standardized word list learning test after left ATL resection. Greater activation in this region on the left side relative to the right side predicted greater decline. The second study by the same authors, however, showed correlations between outcome and hippocampal activation on either side [130]. That is, greater activation unilaterally on the left or the right was associated with poorer outcome. The correlation between verbal memory decline after *left* ATL resection and activation in the *right* hippocampus is difficult to explain, as patients with greater activation in the right hippocampus preoperatively would be expected to have a better outcome, not a worse outcome [132]. This finding was not replicated in the third study [131], which reported a correlation between left hippocampus

NIH-PA Author Manuscript

NIH-PA Author Manuscript

activation and poor outcome but no correlation between right hippocampus activation and outcome. A methodological limitation in all of these studies is that they are based on fMRI activation values extracted from a small region of interest defined by searching the volume for voxels that show a correlation with outcome across a group of patients. As the coordinates of these correlated voxels have varied across the studies, it is not clear how this method of extracting activation values would 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 [133]. 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 region of interest. 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 when preoperative hippocampal activation was lateralized more toward the side of surgery.

Köylü et al. examined correlations between preoperative MTL activation and verbal memory performance before and after ATL surgery [134]. Average fMRI activation produced by a semantic decision - tone decision contrast was measured in left and right MTL regions of interest 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.

Finally, Binder et al. [135] measured hippocampal activation asymmetry in 30 left and 37 right ATL surgery patients using a scene-encoding task. When contrasted with a perceptual matching task, this paradigm activates the anterior hippocampus bilaterally [136]. 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.

Although preliminary, these studies are informative in several ways. Three studies [127,133,135] used complex 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 seems to be weak at best. In contrast, the verbal memory fMRI paradigms used by Richardson et al. provide better predictive information regarding verbal memory outcome, at least when the analysis is confined to a specific region of the hippocampus. The persistent difficulty in applying the latter approach, however, is identifying *a priori* the small set of voxels that will be predictive in a given individual patient.

Language Lateralization as a Predictor of Verbal Memory Outcome

Binder et al. studied the relationship between preoperative language lateralization and verbal memory outcome [46]. 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 preferentially encoded by the left or right MTL depends on the type of information it receives from the ipsilateral neocortex. According to this model, the MTL in the language-dominant hemisphere is more critical for supporting verbal episodic memory, and language lateralization should be a reliable indicator of verbal memory lateralization.

The study included 60 patients who underwent left ATL resection and a control group of 63 patients who underwent right ATL resection. 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 retention test [137]. Other neuropsychological testing included the story recall and visual reproduction subtests from Wechsler Memory Scale [138]. Language LIs were computed from the fMRI data using a large region of interest covering the lateral two-thirds of each hemisphere [50]. All patients also underwent preoperative Wada language and object 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 in this group, 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. Preoperative measures that predicted verbal memory decline in the left surgery group included the preoperative score, the fMRI language LI, the Wada language asymmetry score, the age at onset of epilepsy, and the Wada memory asymmetry score (Table 2, Figure 2).

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. The rationale for including these variables first is that they can be obtained with relatively little expense 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 accounted for 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 significantly improve the predictive power of either model (R^2 change for List Learning = .025, R^2 change for Delayed Recall = .017, both $p > .1$). When patients were categorized as showing decline or no decline based on a negative change score 1.5 standard deviations or more from the mean change score in the right ATL surgery group, the List Learning outcome model showed sensitivity of 90% and specificity of 80% for predicting decline on List Learning. The Delayed Recall outcome model showed sensitivity of 81% and specificity of 100% 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. That is, visual stimuli such as objects and pictures can be dually encoded using both verbal and visual codes. 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. Together, these two hypotheses suggest that language asymmetry may be a better indicator of verbal memory lateralization than Wada memory asymmetry (Figure 3). In particular, some patients with left temporal seizures show right-lateralized memory on the Wada test due to a strong nonverbal memory component in the right hemisphere, but are nevertheless at high risk for verbal memory decline because their *verbal* memory remains strongly lateralized to the left (Figure 3B).

These data also have direct implications for clinical practice. First, they confirm the utility of fMRI for predicting verbal memory outcome in patients undergoing left ATL resection. The fMRI language LI is a safe, noninvasive measure that improves prediction accuracy relative to other noninvasive measures. The finding that Wada memory lateralization is not a strong predictor of verbal memory outcome and adds no predictive value beyond these noninvasive measures confirms several previous studies that also examined multivariate prediction models [42,45,93-95]. Although Binder et al. found that Wada language asymmetry is a stronger predictor of verbal memory outcome than Wada memory lateralization, even the addition of both Wada tests together did not contribute additional predictive power after inclusion of available noninvasive data (including fMRI). These results call into question the routine use of the Wada test for predicting material-specific verbal memory outcome, particularly if a validated fMRI measure of language lateralization is available. Some practitioners value the Wada test as an indicator of risk for severe "global" amnesia, such as is known to occur after bilateral MTL damage [91,139-141]. 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 [96,97,99,100,142,143]. 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 [96-102]. 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 [144].

Conclusions

Recent studies demonstrate that preoperative fMRI can be used to predict postoperative naming and verbal memory changes in patients undergoing left ATL resection. Most importantly, two studies showed that fMRI significantly improves prediction accuracy when combined with other noninvasive measures, and that Wada testing does not add significant additional predictive power [37,46]. Thus, fMRI provides patients and practitioners with a tool for making better-informed decisions based on a quantitative assessment of cognitive risk. 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. The alternative approach followed in many recent studies involves the development of multivariate models that compute predicted change scores (Figure 4). 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 decline in naming or verbal memory, 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.

In practice, implementation of fMRI methods for predicting outcome in epilepsy surgery will depend on the availability of a validated fMRI protocol and involvement of clinicians with the necessary clinical expertise. Fast T2*-weighted imaging capabilities necessary for fMRI are a standard feature on currently marketed clinical MRI systems, and fMRI is now available in some form at most medical centers. Implementation of fMRI protocols requires only installation of relatively low-cost audiovisual stimulation and response monitoring systems. Of course, fMRI is not suitable for all epilepsy patients. The largest outcome studies cited above [37,46] included all patients with full-scale IQ >70, but those with more severe cognitive impairments may not be able to comply with task requirements. Wada testing will continue to play a role in determining language dominance in such patients, as well as in younger children who are unable to comply with tasks or to refrain from large movements during scanning. In the author's experience, even many cognitively disabled patients can be scanned successfully when given clear instruction and feedback by a professional with expertise in cognitive assessment. Similarly, the experience at many centers suggests that successful fMRI studies can be conducted in most children over age 10 given adequate instruction, encouragement, and feedback.

Research Highlights

- The probability of naming and verbal memory deficits after anterior temporal lobectomy increases with the degree of language lateralization to the operated hemisphere.
- Preoperative fMRI language lateralization improves the accuracy of outcome prediction relative to other noninvasive indicators alone.
- The addition of Wada language and memory test results does not improve accuracy relative to using fMRI alone.

Acknowledgments

Thanks to Linda Allen, Thomas Hammeke, Wade Mueller, Conrad Nievera, Ed Possing, Manoj Raghavan, David Sabsevitz, Sara Swanson, and other personnel at the Froedtert-MCW Comprehensive Epilepsy Center for assistance with this research, which was also supported by National Institute of Neurological Diseases and Stroke grant R01 NS35929, National Institutes of Health General Clinical Research Center grant M01 RR00058, and the Charles A. Dana Foundation.

References

1. Belliveau JW, Kennedy DN, McKinstry RC, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. Science 1991;254:716–719. [PubMed: 1948051]
2. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping using MRI. Proceedings of the National Academy of Sciences USA 1992;89:5951–5955.

3. Mueller WM, Yetkin FZ, Hammeke TA, Morris GL, Swanson SJ, Reichert K, Cox R, Haughton VM. Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. Neurosurgery 1996;39:515–520. [PubMed: 8875481]
4. Pujol J, Conesa G, Deus J, Loepz-Obarrio L, Isamat F, Capdevila A. Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. Journal of Neurosurgery 1998;88:863–869. [PubMed: 9576255]
5. Achten E, Jackson GD, Cameron JA, Abbott DF, Stella DS, Fabiny G. Presurgical evaluation of the motor hand area with fMRI in patients with tumors and dysplastic lesions. Radiology 1999;210:529–538. [PubMed: 10207440]
6. Håberg A, Kvistad KA, Unsgård G, Haraldseth O. Preoperative blood oxygen level dependent functional magnetic resonance imaging in patients with primary brain tumors: Clinical application and outcome. Neurosurgery 2004;54:902–915. [PubMed: 15046657]
7. Majos A, Tybor K, Stefanczyk L, Goraj B. Cortical mapping by functional magnetic resonance imaging in patients with brain tumors. European Radiology 2005;15:1148–1158. [PubMed: 15627188]
8. De Tiege X, Connelly A, Liegeois F, Harkness W, Clark CA, Chong WK, Gadian DG, Cross JH. Influence of motor functional magnetic resonance imaging on the surgical management of children and adolescents with symptomatic focal epilepsy. Neurosurgery 2009;64:856–864. [PubMed: 19404149]
9. Kamada K, Sawamura Y, Takeuchi F, Kawaguchi H, Kuriki S, Todo T, Morita A, Masutani Y, Aoki S, Kirino T. Functional identification of the primary motor area by corticospinal tractography. Neurosurgery 2005;56:98–109. [PubMed: 15799797]
10. Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RB. Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science 1995;268:889–893. [PubMed: 7754376]
11. DeYoe EA, Carman GJ, Bandettini P, Glickman S, Wieser J, Cox R, Miller D, Neitz J. Mapping striate and extrastriate visual areas in human cerebral cortex. Proceedings of the National Academy of Sciences USA 1996;93:2382–2386.
12. Polyak, SL. The vertebrate visual system. Chicago: University of Chicago Press; 1957.
13. Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR. A neural basis for lexical retrieval. Nature 1996;380:499–505. [PubMed: 8606767]
14. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional MRI. Journal of Neuroscience 1997;17:353–362. [PubMed: 8987760]
15. Grabowski, TJ.; Damasio, AR. Investigating language with functional neuroimaging. In: Toga, AW.; Mazziotta, JC., editors. Brain mapping: The systems. San Diego, CA: Academic Press; 2000. p. 425-461.
16. Démonet JF, Thierry G, Cardebat D. Renewal of the neurophysiology of language: functional neuroimaging. Physiological Reviews 2005;85:49–95. [PubMed: 15618478]
17. Dronkers NF, Wilkins DP, Van Valin RD, Redfern BB, Jaeger JJ. Lesion analysis of the brain areas involved in language comprehension. Cognition 2004;92:145–177. [PubMed: 15037129]
18. Indefrey P, Levelt WJM. The spatial and temporal signatures of word production components. Cognition 2004;92:101–144. [PubMed: 15037128]
19. Awad M, Warren JE, Scott SK, Turkheimer FE, Wise RJS. A common system for the comprehension and production of narrative speech. Journal of Neuroscience 2007;27:11455–11464. [PubMed: 17959788]
20. Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nature Reviews Neuroscience 2007;8:976–987.
21. Binder JR, Desai R, Conant LL, Graves WW. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral Cortex 2009;19:2767–2796. [PubMed: 19329570]
22. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere: An electrical stimulation mapping investigation in 117 patients. Journal of Neurosurgery 1989;71:316–326. [PubMed: 2769383]

23. Seghier ML, Lazeyras F, Pegna AJ, Annoni JM, Zimine I, Mayer E, Michel CM, Khateb A. Variability of fMRI activation during a phonological and semantic language task in healthy subjects. Human Brain Mapping 2004;23:140–155. [PubMed: 15449358]
24. Lazar RM, Antoniello D. Variability in recovery from aphasia. Current Neurology and Neuroscience Reports 2008;8:497–502. [PubMed: 18957187]
25. Benson RR, FitzGerald DB, LeSeuer LL, Kennedy DN, Kwong KK, Buchbinder BR, Davis TL, Weisskoff RM, Talavage TM, Logan WJ, Cosgrove GR, Belliveau JW, Rosen BR. Language dominance determined by whole brain functional MRI in patients with brain lesions. Neurology 1999;52:798–809. [PubMed: 10078731]
26. Lehéricy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, Hertz-Pannier L, LeBihan D, Marsault C, Baulac M. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology 2000;54:1625–1633. [PubMed: 10762504]
27. Jansen A, Menke R, Sommer J, Forster AF, Bruchmann S, Hempleman J, Weber B, Knecht S. The assessment of hemispheric lateralization in functional MRI—Robustness and reproducibility. Neuroimage 2006;33:204–217. [PubMed: 16904913]
28. Binder JR, Swanson SJ, Hammeke TA, Sabsevitz DS. A comparison of five fMRI protocols for mapping speech comprehension systems. Epilepsia 2008;49:1980–1997. [PubMed: 18513352]
29. McIntosh AM, Wilson SJ, Berkovic SF. Seizure outcome after temporal lobectomy: current research practice and findings. Epilepsia 2001;42:1288–1307. [PubMed: 11737164]
30. Jeong SW, Lee SK, Hong KS, Kinm KK, Chung CK, Kim H. Prognostic factors for the surgery for mesial temporal lobe epilepsy: longitudinal analysis. Epilepsia 2005;46:1273–1279. [PubMed: 16060939]
31. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005;128:1188–1198. [PubMed: 15758038]
32. Hermann BP, Wyler AR, Somes G, Clement L. Dysnomia after left anterior temporal lobectomy without functional mapping: frequency and correlates. Neurosurgery 1994;35:52–57. [PubMed: 7936152]
33. Langfitt JT, Rausch R. Word-finding deficits persist after left anterotemporal lobectomy. Archives of Neurology 1996;53:72–76. [PubMed: 8599562]
34. Hermann BP, Perrine K, Chelune GJ, Barr W, Loring DW, Strauss E, Trenerry MR, Westerveld M. Visual confrontation naming following left anterior temporal lobectomy: A comparison of surgical approaches. Neuropsychology 1999;13:3–9. [PubMed: 10067770]
35. Hermann B, Davies K, Foley K, Bell B. Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: a randomized prospective clinical trial. Epilepsia 1999;40:1070–1076. [PubMed: 10448818]
36. Bell BD, Davies KG, Hermann BP, Walters G. Confrontation naming after anterior temporal lobectomy is related to age of acquisition of the object names. Neuropsychologia 2000;38:83–92. [PubMed: 10617293]
37. Sabsevitz DS, Swanson SJ, Hammeke TA, Spanaki MV, Possing ET, Morris GL, Mueller WM, Binder JR. Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. Neurology 2003;60:1788–1792. [PubMed: 12796532]
38. Chelune GJ, Naugle RI, Lüders H, Sedlak J, Awad IA. Individual change after epilepsy surgery: Practice effects and base-rate information. Neuropsychology 1993;7:41–52.
39. Helmstaedter C, Elger CE. Cognitive consequences of two-thirds anterior temporal lobectomy on verbal memory in 144 patients: a three-month follow-up study. Epilepsia 1996;37:171–180. [PubMed: 8635428]
40. Martin RC, Sawrie SM, Roth DL, Giliam FG, Faught E, Morawetz RB, Kuzniecky R. Individual memory change after anterior temporal lobectomy: a base rate analysis using regression-based outcome methodology. Epilepsia 1998;39:1075–1082. [PubMed: 9776328]
41. Sabsevitz DS, Swanson SJ, Morris GL, Mueller WM, Seidenberg M. Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. Epilepsia 2001;42:1408–1415. [PubMed: 11879343]

42. Stroup E, Langfitt JT, Berg M, McDrmott M, Pilcher W, Como P. Predicting verbal memory decline following anterior temporal lobectomy (ATL). Neurology 2003;60:1266–1273. [PubMed: 12707428]
43. Gleissner U, Helmstaedter C, Schramm J, Elger CE. Memory outcome after selective amygdalohippocampectomy in patients with temporal lobe epilepsy: One-year follow-up. Epilepsia 2004;45:960–962. [PubMed: 15270763]
44. Baxendale S, Thompson P, Harkness W, Duncan J. Predicting memory decline following epilepsy surgery: A multivariate approach. Epilepsia 2006;47:1887–1894. [PubMed: 17116029]
45. Lineweaver TT, Morris HH, Naugle RI, Najm IM, Diehl B, Bingaman W. Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. Epilepsia 2006;47:1895–1903. [PubMed: 17116030]
46. Binder JR, Sabsevitz DS, Swanson SJ, Hammeke TA, Raghavan M, Mueller WM. Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. Epilepsia 2008;49:1377–1394. [PubMed: 18435753]
47. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Journal of Neurosurgery 1960;17:266–282.
48. Loring DW, Meador KJ, Lee GP, Murro AM, Smith JR, Flanigin HF, Gallagher BB, King DW. Cerebral language lateralization: Evidence from intracarotid amobarbital testing. Neuropsychologia 1990;28:831–838. [PubMed: 2247209]
49. Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, Frost JA, Rao SM, Haughton VM. Determination of language dominance using functional MRI: A comparison with the Wada test. Neurology 1996;46:978–984. [PubMed: 8780076]
50. Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PSF, Brewer CC, Perry HM, Morris GL, Mueller WM. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain 1999;122:2033–2045. [PubMed: 10545389]
51. Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Flöel A, Ringelstein EB, Henningsen H. Handedness and hemispheric language dominance in healthy humans. Brain 2000;123:2512–2518. [PubMed: 11099452]
52. Knecht S, Floel A, Drager B, Breitenstein C, Sommer J, Henningsen H, Ringelstein EB, Pascual-Leone A. Degree of language lateralization determines susceptibility to unilateral brain lesions. Nature Neuroscience 2002;5:695–699.
53. Chlebus P, Mikl M, Brazdil M, Pazourkova M, Krupa P, Rektor I. fMRI evaluation of hemispheric language dominance using various methods of laterality index calculation. Experimental Brain Research 2007;179:365–374.
54. Seghier ML. Laterality index in functional MRI: methodological issues. Magnetic Resonance Imaging. 2008 in press.
55. Binder, JR. fMRI of language systems. In: Filippi, M., editor. fMRI techniques and protocols. New York: Springer-Humana Press; 2009. p. 323-351.
56. Knecht S, Deppe M, Dräger B, Bobe L, Lohmann H, Ringelstein EB, Henningsen H. Language lateralization in healthy right-handers. Brain 2000;123:74–81. [PubMed: 10611122]
57. Nagata S, Uchimura K, Hirakawa W, Kuratsu J. Method for quantitatively evaluating the lateralization of linguistic function using functional MR imaging. American Journal of Neuroradiology 2001;22:985–991. [PubMed: 11337346]
58. Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 2003;18:423–438. [PubMed: 12595196]
59. Wilke M, Schmithorst VJ. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. Neuroimage 2006;33:522–530. [PubMed: 16938470]
60. Binder JR, Frost JA, Hammeke TA, Bellgowan PSF, Rao SM, Cox RW. Conceptual processing during the conscious resting state: a functional MRI study. Journal of Cognitive Neuroscience 1999;11:80–93. [PubMed: 9950716]
61. Stark CE, Squire LR. When zero is not zero: The problem of ambiguous baseline conditions in fMRI. Proceedings of the National Academy of Sciences USA 2001;98:12760–12766.

62. Price CJ, Devlin JT, Moore CJ, Morton C, Laird AR. Meta-analyses of object naming: effect of baseline. Human Brain Mapping 2005;25:70–82. [PubMed: 15846820]
63. Spitsyna G, Warren JE, Scott SK, Turkheimer FE, Wise RJS. Converging language streams in the human temporal lobe. Journal of Neuroscience 2006;26:7328–7336. [PubMed: 16837579]
64. Visser M, Jefferies E, Lambon Ralph MA. Semantic processing in the anterior temporal lobes: A meta-analysis of the functional neuroimaging literature. Journal of Cognitive Neuroscience 2010;22:1083–1094. [PubMed: 19583477]
65. Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, Gabrieli JDE, Morrell MJ. Functional MRI measurement of language lateralization in Wada-tested patients. Brain 1995;118:1411–1419. [PubMed: 8595473]
66. Bahn MM, Lin W, Silbergeld DL, Miller JW, Kuppusamy K, Cook RJ, Hammer G, Wetzel R, Cross D. Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. American Journal of Radiology 1997;169:575–579.
67. Hertz-Pannier L, Gaillard WD, Mott S, Cuenod CA, Bookheimer S, Weinstein S, Conry J, Papero PH, Schiff SJ, LeBihan D, Theodore WH. Noninvasive assessment of language dominance in children and adolescents with functional MRI: a preliminary study. Neurology 1997;48:1003–1012. [PubMed: 9109891]
68. Worthington C, Vincent DJ, Bryant AE, Roberts DR, Vera CL, Ross DA, George MS. Comparison of functional magnetic resonance imaging for language localization and intracarotid speech amytal testing in presurgical evaluation for intractable epilepsy. Stereotactic and Functional Neurosurgery 1997;69:197–201. [PubMed: 9711754]
69. Yetkin FZ, Swanson S, Fischer M, Akansel G, Morris G, Mueller W, Haughton V. Functional MR of frontal lobe activation: Comparison with Wada language results. American Journal of Neuroradiology 1998;19:1095–1098. [PubMed: 9672017]
70. Carpentier A, Pugh KR, Westerveld M, Studholme C, Skrinjar O, Thompson JL, Spencer DD, Constable RT. Functional MRI of language processing: dependence on input modality and temporal lobe epilepsy. Epilepsia 2001;42:1241–1254. [PubMed: 11737158]
71. Spreer J, Arnold S, Quiske A, Ziyeh S, Altenmüller DM, Herpers M, Kassubek J, Klisch J, Steinhoff BJ, Honegger J, Schulze-Bonhage A, Schumacher M. Determination of hemisphere dominance for language: comparison of frontal and temporal fMRI activation with intracarotid amytal testing. Neuroradiology 2002;44:467–474. [PubMed: 12070719]
72. Rutten GJ, Ramsey N, van Rijen P, Alpherts W, van Veelen C. fMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. Neuroimage 2002;17:447–460. [PubMed: 12482097]
73. Sabbah P, Chassoux F, Leveque C, Landre E, Baudoin-Chial S, Devaux B, Mann M, Godon-Hardy S, Nioche C, Aït-Ameur A, Sarrazin JL, Chodkiewicz JP. Functional MR imaging in assessment of language dominance in epileptic patients. Neuroimage 2003;18:460–467. [PubMed: 12595199]
74. Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf PA, Tuxhorn I, Ebner A. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology 2003;61:699–701. [PubMed: 12963768]
75. Deblaere K, Boon PA, Vandemaele P, Tieleman A, Vonck K, Vingerhoets G, Backes W, Defreyne L, Achten E. MRI language dominance assessment in epilepsy patients at 1.0 T: region of interest analysis and comparison with intracarotid amytal testing. Neuroradiology 2004;46:413–420. [PubMed: 15127167]
76. Gaillard WD, Balsamo L, Xu B, McKinney C, Papero PH, Weinstein S, Conry J, Pearl P, Sachs B, Sato S, Vezina LG, Frattali C, Theodore WH. fMRI language task panel improves determination of language dominance. Neurology 2004;63:1403–1408. [PubMed: 15505156]
77. Benke T, Koylu B, Visani P, Karner E, Brenneis C, Bartha L, Trinka E, Trieb T, Felber S, Bauer G, Chemelli A, Willmes K. Language lateralization in temporal lobe epilepsy: a comparison between fMRI and the Wada Test. Epilepsia 2006;47:1308–1319. [PubMed: 16922875]
78. Szaflarski JP, Holland SK, Jacola LM, Lindsell C, Privitera MD, Szaflarski M. Comprehensive presurgical functional MRI language evaluation in adult patients with epilepsy. Epilepsy and Behavior 2008;12:74–83. [PubMed: 17964221]

79. Arora J, Pugh K, Westerveld M, Spencer S, Spencer DD, Constable RT. Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. Epilepsia 2009;50:2225–2241. [PubMed: 19490042]

80. Suarez RO, Whalen S, Nelson AP, Tie Y, Meadows M, Radmanesh A, Golby AJ. Threshold-independent functional MRI determination of language dominance: A validation study against clinical gold standards. Epilepsy and Behavior 2009;16:288–297. [PubMed: 19733509]

81. Binder, JR.; Raghavan, M. Functional MRI in epilepsy. In: D'Esposito, ME., editor. Functional MRI: Applications in neurology and psychiatry: Informa Healthcare. 2006. p. 81-114.

82. Swanson SJ, Sabsevitz DS, Hammeke TA, Binder JR. Functional magnetic resonance imaging of language in epilepsy. Neuropsychology Review 2007;17:491–504. [PubMed: 18058239]

83. Stafiniak P, Saykin AJ, Sperling MR, Kester DB, Robinson LJ, O'Connor MJ, Gur RC. Acute naming deficits following dominant temporal lobectomy: prediction by age at first risk for seizures. Neurology 1990;40:1509–1512. [PubMed: 2215940]

84. Saykin AJ, Stafiniak P, Robinson LJ, Flannery K, Gur R, O'Connor MJ, Sperling MR. Language before and after temporal lobectomy: specificity of acute changes and relation to early risk factors. Epilepsia 1995;36

85. Chelune GJ, Naugle RI, Lüders H, Awad IA. Prediction of cognitive change as a function of preoperative ability level among temporal lobectomy patients at six months follow-up. Neurology 1991;41:399–404. [PubMed: 2006008]

86. Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Relationship of age at onset, chronologic age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia 1995;36:137–145. [PubMed: 7821270]

87. Kneebone AC, Chelune GJ, Dinner DS, Naugle RI, Awad IA. Intracarotid amobarbital procedure as a predictor of material-specific memory change after anterior temporal lobectomy. Epilepsia 1995;36:857–865. [PubMed: 7649125]

88. Loring DW, Meador KJ, Lee GP, King DW, Nichols ME, Park YD, Murro AM, Gallagher BB, Smith JR. Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. Neurology 1995;45:1329–1333. [PubMed: 7617192]

89. Chiaravalloti ND, Glosser G. Material-specific memory changes after anterior temporal lobectomy as predicted by the intracarotid amobarbital test. Epilepsia 2001;42:902–911. [PubMed: 11488891]

90. Lee TMC, Yip JTH, Jones-Gotman M. Memory deficits after resection of left or right anterior temporal lobe in humans: A meta-analytic review. Epilepsia 2002;43:283–291. [PubMed: 11906514]

91. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium amytal. Transactions of the American Neurologic Association 1962;87:224–226.

92. Bell BD, Davies KG, Haltiner AM, Walters GL. Intracarotid amobarbital procedure and prediction of postoperative memory in patients with left temporal lobe epilepsy and hippocampal sclerosis. Epilepsia 2000;41:992–997. [PubMed: 10961626]

93. Chelune, GJ.; Najm, IM. Risk factors associated with postsurgical decrements in memory. In: Luders, HO.; Comair, Y., editors. Epilepsy surgery. 2nd. Philadelphia: Lippincott; 2000. p. 497-504.

94. Lacruz ME, Alarcon G, Akanuma N, Lum FC, Kissani N, Koutroumanidis M, Adachi N, Binnie CD, Polkey CE, Morris RG. Neuropsychological effects associated with temporal lobectomy and amygdalohippocampectomy depending on Wada test failure. Journal of Neurology, Neurosurgery and Psychiatry 2004;75:600–607.

95. Kirsch HE, Walker JA, Winstanley FS, Hendrickson R, Wong ST, Barbaro NM, Laxer KD, Garcia PA. Limitations of Wada memory asymmetry as a predictor of outcomes after temporal lobectomy. Neurology 2005;65:676–680. [PubMed: 16157898]

96. Novelly RA, Williamson PD. Incidence of false-positive memory impairment in the intracarotid Amytal procedure. Epilepsia 1989;30:711.

97. Loring DW, Lee GP, Meador KJ, Flanigin HF, Figueroa RE, Martin RC. The intracarotid amobarbital procedure as a predictor of memory failure following unilateral temporal lobectomy. Neurology 1990;40:605–610. [PubMed: 2320233]

98. Lee GP, Loring DW, Smith JR, Flanigin HF. Intraoperative hippocampal cooling and Wada memory testing in the evaluation of amnesia risk following anterior temporal lobectomy. Archives of Neurology 1995;52:857–861. [PubMed: 7661721]
99. Kubu CS, Girvin JP, McLachlan RS, Pavol M, Harnadek MC. Does the intracarotid amobarbital procedure predict global amnesia after temporal lobectomy? Epilepsia 2000;41:1321–1329. [PubMed: 11051129]
100. Simkins-Bullock J. Beyond speech lateralization: a review of the variability, reliability, and validity of the intracarotid amobarbital procedure and its nonlanguage uses in epilepsy surgery candidates. Neuropsychology Review 2000;10:41–74. [PubMed: 10839312]
101. Martin RC, Grote CL. Does the Wada test predict memory decline following epilepsy surgery. Epilepsy and Behavior 2002;3:4–15.
102. Loddenkemper T, Morris HH, Lineweaver TT, Kellinghaus C. Repeated intracarotid amobarbital tests. Epilepsia 2007;48:553–558. [PubMed: 17319921]
103. Loring DW, Meador KJ, Lee GP, King DW, Gallagher BB, Murro AM, Smith JR. Stimulus timing effects on Wada memory testing. Archives of Neurology 1994;51:806–810. [PubMed: 8042929]
104. Loring DW, Hermann BP, Perrine K, Plenger PM, Lee GP, Nichols ME, Meador KJ. Memory for real objects is superior to line drawing recognition in discrimination of lateralized temporal lobe impairment during the Wada test. Journal of the International Neuropsychological Society 1995;1:134.
105. Carpenter K, Oxbury JM, Oxbury S, Wright GD. Memory for objects presented after intracarotid sodium amytal: a sensitive clinical neuropsychological indicator of temporal lobe pathology. Seizure 1996;5:103–108. [PubMed: 8795124]
106. Alpherts WC, Vermeulen J, van Veelen CW. The Wada test: prediction of focus lateralization by asymmetric and symmetric recall. Epilepsy Research 2000;39:239–249. [PubMed: 10771250]
107. Trenerry MR, Jack CRJ, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, Marsh WR, Kelly PJ, Meyer FB. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 1993;43:1800–1805. [PubMed: 8414035]
108. Wendel JD, Trenerry MR, Xu YC, Sencakova D, Cascino GD, Britton JW, Lagerlund TD, Shin C, So EL, Sharbrough FW, Jack CR. The relationship between quantitative T2 relaxometry and memory in nonlesional temporal lobe epilepsy. Epilepsia 2001;42:863–869. [PubMed: 11488885]
109. Cohen-Gadol AA, Westerveld M, Alvarez-Carilles J, Spencer DD. Intracarotid amytal memory test and hippocampal magnetic resonance imaging volumetry: validity of the Wada test as an indicator of hippocampal integrity among candidates for epilepsy surgery. Journal of Neurosurgery 2004;101:926–931. [PubMed: 15597752]
110. Griffith HR, Perlman SB, Woodard AR, Rutecki PA, Jones JC, Ramirez LF, DeLaPena R, Seidenberg M, Hermann BP. Preoperative FDG-PET temporal lobe hypometabolism and verbal memory after temporal lobectomy. Neurology 2000;54:1161–1165. [PubMed: 10720291]
111. Jokeit H, Ebner A, Holthausen H, Markowitsch HJ, Moch A, Pannek H, Schulz R, Tuxhorn I. Individual prediction of change in delayed recall of prose passages after left-sided anterior temporal lobectomy. Neurology 1997;49:481–487. [PubMed: 9270581]
112. Davies KG, Bell BD, Bush AJ, Wyler AR. Prediction of verbal memory loss in individuals after anterior temporal lobectomy. Epilepsia 1998;39:820–828. [PubMed: 9701371]
113. Baxendale S, Thompson P, Harkness W, Duncan J. The role of the intracarotid amobarbital procedure in predicting verbal memory decline after temporal lobe resection. Epilepsia 2007;48:546–552. [PubMed: 17346250]
114. Saykin AJ, Gur RC, Sussman NM, Gur RE, O'Connor MJ. Memory before and after temporal lobectomy: effects of laterality and age of onset. Brain and Cognition 1989;9:191–200. [PubMed: 2923710]
115. Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 1999;9:7–24. [PubMed: 10088896]

116. Gabrieli, JDE. Functional imaging of episodic memory. In: Cabeza, R.; Kingstone, A., editors. Handbook of Functional Neuroimaging of Cognition. Cambridge, MA: MIT Press; 2001. p. 253-291.
117. Paller KA, Wagner AD. Observing the transformation of experience into memory. Trends in Cognitive Sciences 2002;6:93–102. [PubMed: 15866193]
118. Rugg MD, Otten LJ, Henson RNA. The neural basis of episodic memory: evidence from functional neuroimaging. Philosophical Transactions of the Royal Society of London, Series B 2002;357:1097–1110. [PubMed: 12217177]
119. Hwang DY, Golby AJ. The brain basis for episodic memory: insights from functional MRI, intracranial EEG, and patients with epilepsy. Epilepsy and Behavior 2006;8:115–126. [PubMed: 16278097]
120. Schacter DL, Addis DR. The cognitive neuroscience of constructive memory: remembering the past and imagining the future. Philosophical Transactions of the Royal Society of London: Series B 2007;362:773–786. [PubMed: 17395575]
121. Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia 2008;46:1787–1799. [PubMed: 18343462]
122. Constable RT, Carpentier A, Pugh K, Westerveld M, Oszunar Y, Spencer DD. Investigation of the hippocampal formation using a randomized event-related paradigm and z-shimmed functional MRI. Neuroimage 2000;12:55–62. [PubMed: 10875902]
123. Fransson P, Merboldt KD, Ingvar M, Petersson KM, Frahm J. Functional MRI with reduced susceptibility artifact: high-resolution mapping of episodic memory encoding. Neuroreport 2001;12:1415–20. [PubMed: 11388421]
124. Morawetz C, Holz P, Lange C, Baudewig J, Weniger G, Irle E, Dechent P. Improved functional mapping of the human amygdala using a standard functional magnetic resonance imaging sequence with simple modifications. Magnetic Resonance Imaging 2008;26:45–53. [PubMed: 17574366]
125. Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Boles Ponto LL, Hichwa RD. Remembering the past: Two facets of episodic memory explored with positron emission tomography. American Journal of Psychiatry 1995;152:1576–1585. [PubMed: 7485619]
126. Martin A. Automatic activation of the medial temporal lobe during encoding: Lateralized influences of meaning and novelty. Hippocampus 1999;9:62–70. [PubMed: 10088901]
127. Rabin ML, Narayan VM, Kimberg DY, Casasanto DJ, Glosser G, Tracy JI, French JA, Sperling MR, Detre JA. Functional MRI predicts post-surgical memory following temporal lobectomy. Brain 2004;127:2286–2298. [PubMed: 15329352]
128. Detre JA, Maccotta L, King D, Alsop DC, D'Esposito M, Zarahn E, Aguirre GK, Glosser G, French JA. Functional MRI lateralization of memory in temporal lobe epilepsy. Neurology 1998;50:926–932. [PubMed: 9566374]
129. Richardson MP, Strange BA, Thompson PJ, Baxendale SA, Duncan JS, Dolan RJ. Pre-operative verbal memory fMRI predicts post-operative memory decline after left anterior temporal lobe resection. Brain 2004;127:2419–2426. [PubMed: 15459025]
130. Richardson MP, Strange BA, Duncan JS, Dolan RJ. Memory fMRI in left hippocampal sclerosis. Optimizing the approach to predicting postsurgical memory. Neurology 2006;66:699–705. [PubMed: 16534106]
131. Powell HWR, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, Koepp MJ. Preoperative fMRI predicts memory decline following anterior temporal lobe resection. Journal of Neurology, Neurosurgery and Psychiatry 2008;79:686–693.
132. Chelune GC. Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. Archives of Clinical Neuropsychology 1995;10:413–432. [PubMed: 14588901]
133. Frings L, Wagner K, Halsband U, Schwarzwald R, Zentner J, Schulze-Bonhage A. Lateralization of hippocampal activation differs between left and right temporal lobe epilepsy patients and correlates with postsurgical verbal learning decrement. Epilepsy Research 2008;78:161–170. [PubMed: 18180141]

134. Koylu B, Walser G, Ischebeck A, Ortler M, Benke T. Functional imaging of semantic memory predicts postoperative episodic memory functions in chronic temporal lobe epilepsy. Brain Research 2008;1223:73–81. [PubMed: 18599025]

135. Binder JR, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, Mueller WM. A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: Language lateralization vs. hippocampal activation asymmetry. Epilepsia 2010;51:618–626. [PubMed: 19817807]

136. Binder JR, Bellgowan PSF, Hammeke TA, Possing ET, Frost JA. A comparison of two fMRI protocols for eliciting hippocampal activation. Epilepsia 2005;46:1061–1070. [PubMed: 16026558]

137. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24:1019–1025. [PubMed: 4473151]

138. Wechsler, D. Wechsler Memory Scale - Third Edition. WMS-III Administration and Scoring Manual. San Antonio, TX: Psychological Corporation; 1997.

139. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery and Psychiatry 1957;20:11–21.

140. Guerreiro CAM, Jones-Gotman M, Andermann F, Cendes F. Severe amnesia in epilepsy: Causes, anatomopsychological considerations, and treatment. Epilepsy and Behavior 2001;2:224–246. [PubMed: 12609367]

141. Di Gennaro G, Grammaldo LG, Quarato PP, Esposito V, Mascia A, Sparano A, Meldolesi GN, Picardi A. Severe amnesia following bilateral medial temporal lobe damage occurring on two distinct occasions. Neurological Sciences 2006;27:129–133. [PubMed: 16816912]

142. Baxendale S. Amnesia in temporal lobectomy patients: historical perspective and review. Seizure 1998;7:15–24. [PubMed: 9548221]

143. Kapur N, Prevett M. Unexpected amnesia: are there lessons to be learned from cases of amnesia following unilateral temporal lobe surgery? Brain 2003;126:2573–2585. [PubMed: 12958081]

144. Medina LS, Aguirre E, Bernal B, Altman NR. Functional MR imaging versus Wada test for evaluation of language lateralization: Cost analysis. Radiology 2004;230:49–54. [PubMed: 14695386]

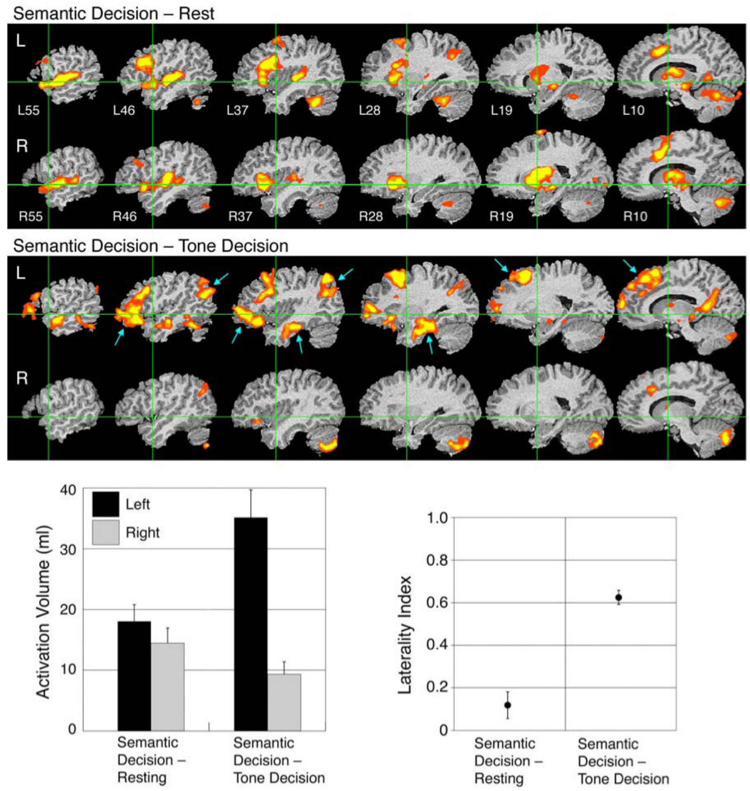

Figure 1.

fMRI data from 26 healthy volunteers performing two language mapping paradigms. The activation maps are displayed as serial sagittal sections through the brain at 9-mm intervals. X-axis locations for each slice are given in the top panel. Both maps are thresholded at a whole-brain corrected $p < 0.05$ using voxel-wise $p < 0.0001$ and cluster extent > 200 mm^3. The three steps in each color continuum represent voxel-wise p thresholds of 10^{-4}, 10^{-5}, and 10^{-6}. Top: Semantic Decision relative to Resting. Middle: Semantic Decision relative to Tone Decision. Blue arrows in the middle image indicate left hemisphere language areas that are active during the resting state and thus visible only when an active nonlinguistic task is used as the baseline. The graph at bottom left shows the mean volume of activation in left and right hemispheres for each task contrast. The graph at bottom right shows the mean LI for each task contrast. Error bars represent standard error. (Adapted from [28])

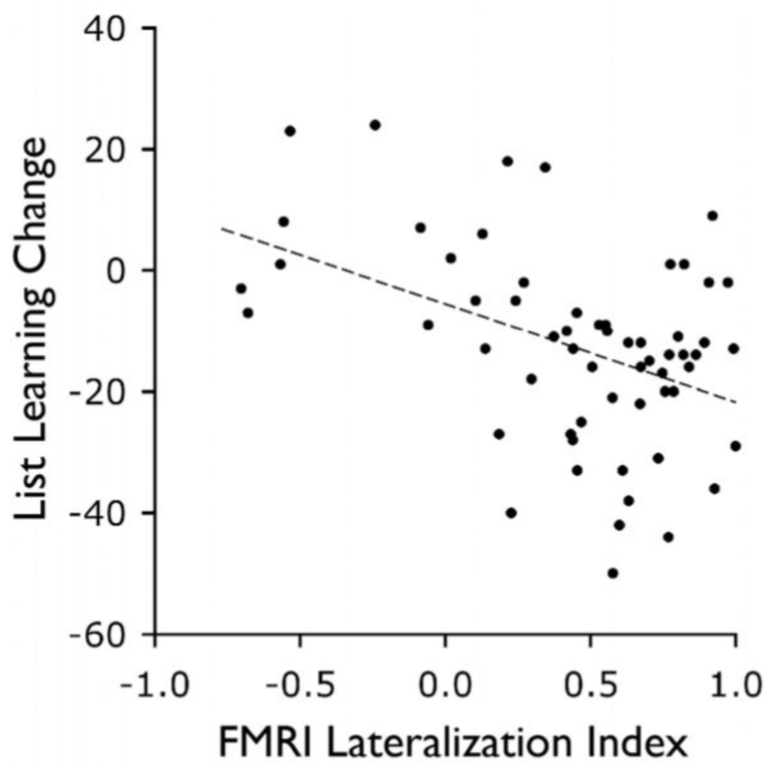

Figure 2.
Relationship between fMRI lateralization indexes and individual change scores on a word-list learning verbal memory test (Continuous Long-Term Recall from the Selective Reminding Test) in 60 left ATL surgery patients ($r = -.432$, $p < .001$). (Adapted from [46])

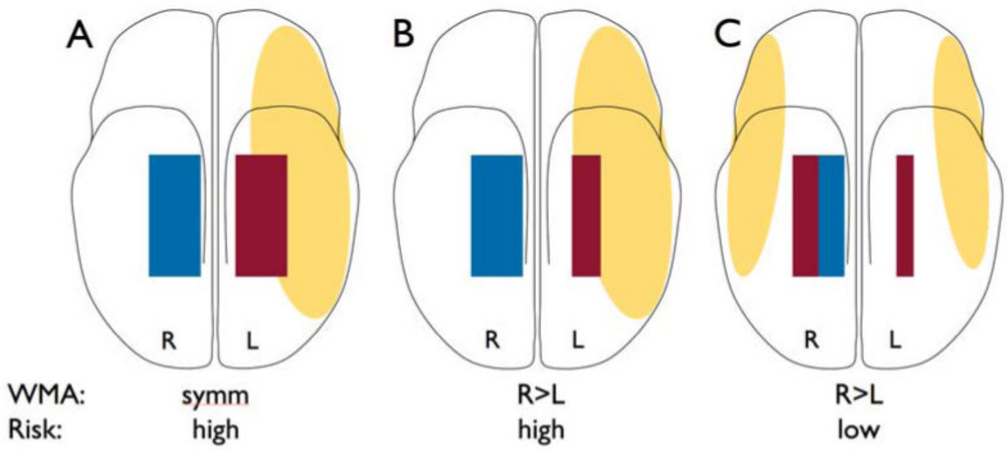

Figure 3.

Schematic diagram of a hypothetical model of memory and language representation in temporal lobe epilepsy (TLE). The yellow ovals represent language systems, red rectangles represent verbal episodic memory encoding systems in the MTL, and green rectangles represent non-verbal episodic memory encoding systems in the MTL. (A) Typical state in healthy subjects and patients with late-onset epilepsy. Language and verbal memory processes are strongly left-lateralized, placing the patient at high risk for verbal memory decline. (B) Chronic left TLE without shift. The left MTL is dysfunctional, causing Wada memory lateralization to the right, but verbal memory has not shifted, leaving the patient at high risk for verbal memory decline. (C) Chronic left TLE with shift. Both language and verbal memory functions have shifted partially to the right, lowering the risk for verbal memory decline. Note the partial lack of correspondence, across patient types, between Wada memory asymmetry and level of risk. (Adapted from [46])

NIH-PA Author Manuscript

NIH-PA Author Manuscript

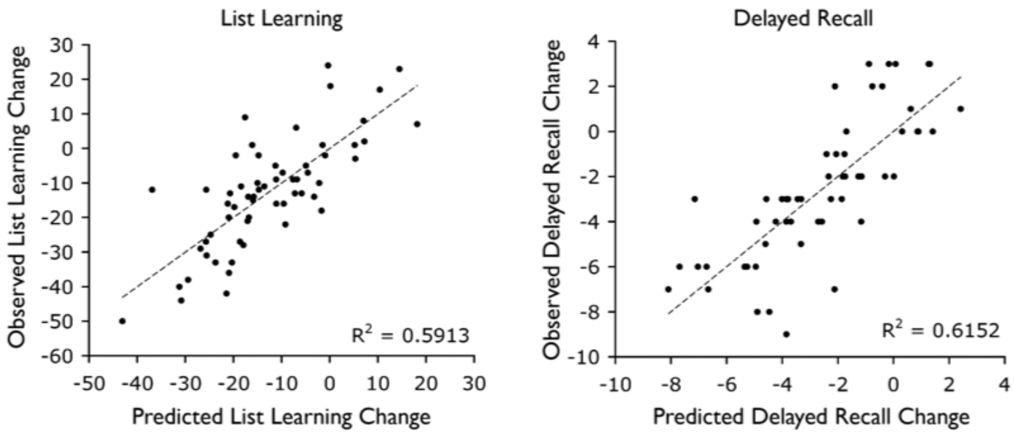

Figure 4.

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(Preoperative Score) - 0.280(Age at Onset) - 12.19(fMRI LI). Predicted delayed recall change scores were computed from the formula: 3.76 - 0.688(Preoperative Score) - 0.093(Age at Onset) - 2.14(fMRI LI). (Adapted from [46])

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 LI predicts outcome on scene recognition task in both surgery groups.
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 a hippocampus ROI predicts verbal memory outcome.
Richardson et al.	2006	12 L	Same as Richardson et al. (2004)	Same as Richardson et al. (2004)	Unilateral activation in ether left or right hippocampus ROI predicts verbal 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)	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 (Verbaler Lern- & Merkfaehigkeitstest)	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 ROI predicts verbal 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 is not correlated with verbal memory outcome.

Table 2

Preoperative predictors of verbal memory outcome in 60 left ATL surgery patients. List Learning and Delayed Recall refer to the Consistent Long-Term Recall and Delayed Recall subtests of the Selective Reminding Test. Simple correlation values and P values for each correlation are shown.

Predictor Variable	List Learning	P	Delayed Recall	P
Preoperative Score	-.662	<.0001	-.654	<.0001
FMRI Language LI	-.432	<.001	-.316	<.05
Wada Language Asymmetry	-.398	<.01	-.363	<.01
Age at Epilepsy Onset	-.341	<.01	-.390	<.01
Wada Memory Asymmetry	-.331	<.05	-.135	n.s.