Published in final edited form as:

Epilepsy Behav. 2008 May ; 12(4): 600–611. doi:10.1016/j.yebeh.2007.10.016.

The Use of Neuroimaging to Study Behavior in Patients with Epilepsy

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Abstract

Structural and functional neuroimaging continue to play an increasing role in the presurgical evaluation of patients with epilepsy. In addition to their value for localizing the epileptogenic zone and eloquent cortex, neuroimaging is contributing to our understanding of mood comorbidity in epilepsy. Although the vast majority of research has focused on patients with temporal lobe epilepsy (TLE), neuroimaging studies of patients with frontal lobe epilepsy (FLE) and primary generalized epilepsy are increasing in number. In this review, structural and functional imaging modalities that have received considerable research attention in recent years are reviewed, along with an assessment of their strengths and limitations for understanding behavior in epilepsy. In addition, advances in multimodal imaging are discussed along with their potential application to the presurgical evaluation of patients with seizure disorders.

Keywords

structural neuroimaging; functional neuroimaging; temporal lobe epilepsy; frontal lobe epilepsy; volumetric MRI; magnetoencephalography; functional magnetic resonance imaging; positron emission tomography; multimodal imaging

1. Introduction

Over the past several decades, almost every imaging technique that has been used to study seizure localization in patients with epilepsy has also been applied to the study of their behavior. Language and memory have emerged as the most frequently investigated behavioral domains due to their importance in presurgical planning. However, there is also an emerging literature demonstrating the utility of neuroimaging for understanding mood in epilepsy. Advances in structural and functional imaging, as well as the integration and co-registration of multimodal imaging, have helped to establish that chronic, intractable seizures can result in widespread cerebral changes that have important implications for behavior. Delineating the precise relationships between neuroimaging and discrete behaviors is challenging in that all imaging methods have their limitations. Nevertheless, advances in neuroimaging have provided

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considerable insight into specific biomarkers of behavior in patients with epilepsy and revolutionized our approach to treatment in patients with seizures disorders.

The goal of the current review is to highlight recent applications of neuroimaging to the study of behavior in patients with epilepsy. First, structural and metabolic correlates of cognitive and mood dysfunction in epilepsy are reviewed, with a focus on volumetric MRI, voxel-based morphometry (VBM), diffusion-tensor imaging (DTI), and magnetic resonance spectroscopy (^1H MRS). Second, recent applications of functional imaging, including positron-emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) are discussed. Third, research using advanced imaging that combines structural and functional measures (i.e., multimodal imaging) is reviewed, and their potential for elucidating the neural substrates of behavior in epilepsy is discussed.

2. Imaging of Structure and Metabolites in Epilepsy

2.1 Volumetric MRI

Volumetric MRI has long been used for quantifying structural pathology in patients with neurological disease and has been especially useful for predicting preoperative neuropsychological functioning and post-operative decline in patients with epilepsy. Initial studies focused exclusively on hippocampal volumes and their relationship to memory dysfunction in temporal lobe epilepsy (TLE) ((1–3), for a review, see (4)). These studies demonstrated a consistent relationship between reductions in left hippocampal volume, or hippocampal asymmetries, and impairments in verbal learning and memory, in TLE patients who were left-hemisphere dominant for language (1,2,5–9). More importantly, these studies established that patients *without* left hippocampal volume loss were at greatest risk for postoperative memory decline (7). The association between right hippocampal volumes and nonverbal learning and memory is tenuous, but has been reported in a few studies (7,10,11). In addition, there are data to support the role of other medial temporal lobe structures in verbal and visual memory, including the amygdala (8,12), mammillary bodies (8), and perirhinal cortex (9,13). In fact, there is some evidence that right amygdala volume is a stronger predictor of visual memory than right hippocampal volume (8,12). Undoubtedly, volumetric MRI has been important in validating the role of the hippocampus and other medial temporal lobe structures in learning and memory, and in determining which patients are at greatest risk for memory decline following temporal lobectomy.

Studies using volumetric MRI to investigate medial temporal lobe contributions to language functioning are limited in number. A recent study found that left hippocampal volume and perirhinal volume asymmetry independently predicted verbal fluency and confrontational naming in patients with TLE (13). In another study, Foundas et al. (14) demonstrated that TLE patients with left hemisphere dominance on the IAP had a larger planum temporale on the left. This relationship was reversed in a patient with right hemisphere language dominance. However, not all studies in TLE have supported the relationship between planum temporale asymmetry and language functioning (15).

More recent literature has focused on the relationship between extratemporal quantitative MRI and neuropsychological impairments in TLE. Hermann et al. (16) examined whole-brain and lobar volumes in patients with TLE and found significant reductions in frontal, temporal, and parietal lobe volumes in TLE patients compared to controls. Volume reductions in total brain tissue were associated with generalized cognitive impairment, and the association was particularly strong between cognitive impairment and total white matter volume. Conversely, Oyegbile et al. (17) found that cerebrospinal fluid (CSF) volume was a stronger predictor of overall cognitive impairment than either gray or white matter volume in TLE. In fact, increased CSF was associated with poorer scores on tests of intellectual functioning, memory, executive

functioning, and motor dexterity. Baxendale et al. (18) reported poorer global memory scores in patients with extratemporal pathology relative to patients without extratemporal pathology. Finally, Oyegbile et al. (19) found an association between increased whole-brain gyrification in patients with TLE and poorer performances on a variety of cognitive measures. These studies all used whole brain or lobar quantitative MRI measures. The relationships among specific cortical structures and cognitive performances have not been well-investigated in TLE and would appear to be a fertile ground for future research.

In addition to the relationship between volumetric MRI and cognitive impairment, there is accumulating evidence linking medial temporal lobe pathology to mood and behavior in epilepsy (20). In TLE, the most commonly reported findings are associations between hippocampal or amygdalar volumes and depression. One study found that a reduction in left hippocampal volume was associated with depression in TLE, but only for patients with a right-sided seizure focus (20). In several studies, bilateral increases in amygdala volumes have been linked to depression and dysthymia in TLE (21–23). Increased amygdala volumes have also been associated with psychosis in epilepsy (24) and there is some evidence that amygdalar atrophy is associated with interictal affective aggression in TLE (25). The question remains as to why opposite morphological changes to the hippocampus and amygdala would have similar effects on mood in TLE, especially with respect to why *increased* amygdala volumes would result in greater depression. Richardson et al. (21) propose several explanations for these findings, including the possibility that increases in amygdala volume are transient and may be secondary to increased regional blood flow and vascular volume. This is supported by research demonstrating that the amygdala is hyperactive in mood disorders, and that amygdalar enlargement is characteristic of acute depression, with subsequent shrinkage in recurrent and chronic forms of depression (26,27). However, much more research is needed to elucidate the complex nature of depression in epilepsy. Volumetric changes to medial temporal lobe structures appear to be one of many risk factors for mood disorder in TLE (for a recent review, see (26)).

2.2 Voxel-based morphometry (VBM)

VBM is an automated, quantitative imaging method that involves voxel-wise comparisons of the distribution of grey and white matter between groups of subjects (28). VBM studies have demonstrated reductions in temporal and extratemporal tissue concentrations in TLE (29), and there is some data linking regional reductions to cognitive impairment. For example, Bonilha et al. (30) performed VBM on 36 TLE patients with hippocampal atrophy and found that reductions in gray matter concentration of the hippocampus, entorhinal cortex, and perirhinal cortex were associated with general and verbal memory impairment. In addition, gray matter reductions in limbic and frontal structures, including the orbitofrontal and cingulate cortex, predicted poorer memory performances in TLE. These data support existing evidence that impaired memory can reflect damage to both temporal and frontal lobe systems in patients with TLE. However, the clinical utility of VBM is questionable in that it is intended for group comparisons and may lack sensitivity at the individual subject level (28).

2.3 Diffusion tensor imaging

Reductions in total or lobar white matter volume have been reported in patients with TLE, using VBM (31) and volumetric MRI (16,31). These studies provided initial insight into the association between global white matter pathology and cognitive impairment in epilepsy (16). Advances in diffusion-weighted imaging now provide an opportunity to quantify structural deterioration within specific white matter tracts in TLE and to delineate their clinical correlates. DTI tractography is a relatively new MRI technique for visualizing and quantifying the integrity of white matter tracts in the brain by measuring degrees of water diffusion and its directionality. That is, the diffusivity of water is stronger along white matter fibers and is

decreased orthogonal to those fibers. By applying diffusion-weighted gradients in multiple directions, the degree of anisotropy of overall motion in a voxel can be measured (32) and expressed as an index of the directionality of diffusion (fractional anisotropy; FA) or the relative volume of water movement (mean diffusivity; MD).

Within recent years, researchers have evaluated a small number of white matter tracts in TLE and found structural deterioration or asymmetries in the uncinate fasciculus (33), external capsule (34), corpus callosum (34), fornix (35), cingulum (35), and arcuate fasciculus (36). However, only a few studies have investigated the link between DTI measures and cognition in epilepsy. Diehl et al. (37) found that increased FA of the left and right uncinate fasciculus (UF) was associated with better immediate auditory memory; whereas, decreased diffusivity of the left UF was associated with better delayed auditory memory in patients with left TLE. Diffusion and anisotropic characteristics did not predict memory scores in patients with right TLE. In another study, Powell et al. (36) demonstrated an association between mean FA of the left arcuate fasciculus and fMRI language lateralization in patients with TLE. Finally, in a study evaluating FA and MD within frontotemporal white matter of patients with TLE and interictal psychosis, bilateral frontal FA reductions were associated with poorer verbal fluency and spatial span performances; whereas, left temporal FA reductions were associated with poorer verbal fluency only. Unlike previous studies, tractography measures did not predict neuropsychological status in TLE patients *without* interictal psychosis. Together, these studies provide evidence that the degree of diffusion within frontotemporal white matter is associated with neuropsychological functioning in patients with TLE. Studies comparing DTI with other structural measures (i.e., volumetric and VBM) are needed to establish whether or not DTI is a more sensitive and specific predictor of discrete cognitive performances than more traditional imaging techniques.

2.4 ¹H MRS

¹H MRS is an imaging technique that allows for measurements of specific brain metabolites. The most commonly evaluated metabolite is N-acetylaspartate (NAA), which is located primarily within healthy neurons and precursor cells (38). A reduction in NAA signal, or in its ratio to other metabolites such as creatine (Cr), is thought to reflect neuronal loss or dysfunction. In TLE, ¹H MRS has been used to evaluate the relationships between NAA/Cr levels and both memory and depression. Sawrie et al. (39) evaluated NAA/Cr ratios in 22 patients with TLE and reported that left hippocampal NAA/Cr reductions were associated with poorer verbal memory, and that the NAA/Cr ratio was a more sensitive measure of verbal memory than hippocampal volume. Other studies have supported the association between hippocampal NAA/Cr and both episodic and semantic memory in TLE (40–42), and there is some evidence that preoperative NAA/Cr ratios predict postoperative declines in verbal learning (43).

Thus far, only one study has systematically studied the relationship between metabolic disturbances and depression in epilepsy using ¹H MRS. Gilliam et al. (44) measured hippocampal NAA/Cr ratios in 31 patients with TLE and found that decreased NAA/Cr ratios were associated with higher levels of self-reported depression. No other clinical variables (e.g., disease duration, seizure type, quality of life) correlated with depression in their patient group. These data support both volumetric data and other metabolic studies (see section on PET) linking left hippocampal pathology to depression in TLE (26).

2.5 Limitations of Structural and Metabolite Imaging in Epilepsy

Structural imaging techniques have been paramount to our understanding of medial temporal lobe contributions to memory, language, and mood in patients with epilepsy. In addition, newer imaging techniques, including DTI and VBM, have revealed important associations between extratemporal pathology and impairment in a variety of cognitive domains. Finally, studies

measuring specific brain metabolites (i.e., NAA/Cr) have provided data supporting a key role of the left hippocampus in verbal memory and depression in TLE. Despite these contributions, quantitative information derived from brain structures and metabolites provides minimal insight into functional organization and reorganization in patients with epilepsy, which is no doubt critical to presurgical evaluations.

3. Functional Imaging in Epilepsy

The quest for identifying reliable, non-invasive methods for lateralizing and localizing eloquent cortex in patients with epilepsy has been a key initiative for years. Although no one technique has evolved to a gold-standard, there are several functional imaging methods, including fMRI, MEG, and PET, that have emerged as viable alternatives or additions to the more invasive intracarotid amobarbital procedure (IAP). However, the strengths of one technique are the limitations of another. In this section, functioning imaging techniques that have received considerable attention in recent years are discussed, along with comment regarding their limitations. Other types of functional imaging, including functional transcranial Doppler sonography, single-photon emission computed tomography, and near infrared spectroscopic mapping, have received less attention, and therefore, are not covered in this review. For applications of these techniques to the study of language in epilepsy, see a recent review by Abou-Khalil (45).

3.1 PET

PET provides a measurement of cerebral glucose metabolism using F-deoxyglucose (^{18}F FDG) or regional blood flow using ^{15}O -labeled water and has a spatial resolution of approximately 4mm (46). To date, a number of studies have demonstrated relationships between regional brain metabolism and both cognitive functioning (47–53) and mood (54) in patients with epilepsy. In TLE, studies of cognitive functioning have demonstrated associations between left perirhinal and inferior temporal hypometabolism and poor verbal associative memory (55), lateral temporal metabolic asymmetry and impaired verbal IQ and memory (50), left lateral temporal and thalamic metabolic asymmetry and impaired verbal memory and fluency, and left temporal pole hypometabolism and recognition of famous faces (56). As a presurgical tool, PET has demonstrated high concordance with the IAP (57,58) and intraoperative language mapping (59). In addition, there is evidence from FDG-PET indicating that prefrontal metabolic asymmetries in TLE are associated with poorer performances on tests of executive functioning and general cognitive ability (52). Thus, PET studies have demonstrated that widespread metabolic disturbances are present in patients with TLE, and that many of these disturbances have a neurocognitive correlate.

FDG-PET studies have also provided considerable insight into the relationship between regional brain dysfunction and cognitive impairment in patients with extratemporal epilepsy. In a series of functional PET studies, Swartz and co-workers (47–49) found that impairment in visual working memory was related to less activity in frontal lobe regions in patients with FLE and juvenile myoclonic epilepsy (JME) relative to controls. Instead, FLE and JME patients showed greater recruitment of temporal lobe regions during task performance, suggesting that posterior brain regions were attempting to compensate for prefrontal dysfunction, albeit poorly. Work from our own lab using FDG-PET has shown correlations between resting frontal, parietal, and limbic hypometabolism and executive dysfunction in patients with FLE and JME (53). In patients with FLE, the strongest relationships emerged between hypometabolism in the left frontal lobe and verbal fluency, whereas in both patient groups there were strong associations among left and right frontal hypometabolism and a measure of cognitive flexibility. Similar to previous studies, this study demonstrated that reductions in frontal lobe metabolism were associated with increases in medial temporal lobe metabolism in patients.

Studies have also demonstrated the utility of PET for understanding mood disorders in epilepsy. In particular, Gilliam et al. (54) reported greater resting temporal lobe hypometabolism in patients who reported higher levels of depression, and Victoroff et al. (60) found an association between the severity of left temporal lobe hypometabolism and the frequency of major depressive episodes in patients with epilepsy. There is also recent evidence demonstrating an association between reduced 5-HT(1A) receptor binding in the hippocampus and higher levels of self-reported depression in patients with TLE (61,62). In another study, a trend was noted for increased left amygdalar, but not hippocampal, metabolism to correlate with increased depression in TLE (21). Finally, there are data linking bilateral inferior frontal hypometabolism to depression in left TLE (63). Together, these studies support volumetric research by (1) implicating medial temporal and frontal lobe regions in mood disorders, and (2) suggesting a stronger correlation between depression and left-sided pathology in patients with TLE.

Limitations of PET—Despite reasonable spatial resolution, PET lacks sufficient temporal resolution in that the cerebral uptake of ^{18}F FDG-PET evolves over a 40-minute or longer time frame. In addition, PET is more invasive than fMRI and MEG, requiring injection of a radioactive tracer. Finally, PET is relatively expensive and not as widely available as fMRI.

3.2 FMRI

fMRI measures regional changes in cerebral blood flow, thus providing an indirect measure of neuronal activity (64). Since the advent of fMRI, a wealth of data has accumulated describing the network of regions involved in language and memory. fMRI studies of language lateralization in patients with TLE are exponentially increasing in number. Selected studies from the past 10 years are summarized in the top half of Table 1. These studies have been critical to our understanding of language organization and reorganization in patients with TLE—an area in which the contributions of structural MRI have been limited. To date, most of this literature has focused on cerebral activations associated with semantic decisions, silent word generation, covert repetition, and covert naming in controls and patients with TLE (for a comprehensive review, see (45)). These studies have demonstrated prominent activations in left prefrontal areas (45,65–67), with less consistent activations in temporoparietal regions (65). Such data have led some experts to conclude that fMRI may be better suited for localizing expressive language areas within the frontal lobe than receptive language areas within temporal lobe regions ((68,69), but see (70,71)). Overall, results suggest approximately 90% concordance between fMRI and IAP lateralization in patients with TLE, with less impressive results in patients with extratemporal epilepsy (72). In addition, there are data demonstrating that fMRI language activations complement electrocortical stimulation findings (73) and predict post-operative naming decline (74). Although no single fMRI task has emerged as superior for language lateralization, there is some evidence that a panel of tasks, including verbal fluency, reading comprehension, and auditory comprehension may provide the most reliable results (70).

Studies of memory localization in patients with TLE are also abundant and increasing in number. Key studies from recent years are presented in the bottom half of Table 1. Golby et al. (75) reported that encoding of verbal material (words) was associated with greater right temporal lobe activity in patients with left TLE; whereas, encoding of nonverbal material (faces, scenes, and designs) was associated with greater left temporal lobe activity in right TLE. These data suggest partial or total compensation by contralateral temporal lobe regions. Similar results were obtained using event-related fMRI in left TLE (76). In another study, extensive activations were observed in left prefrontal regions during encoding and retrieval of verbal information in patients with left TLE, but not controls (77). Still other studies demonstrate a widespread decrease in functional activity in frontal and temporal regions during recall in TLE relative to controls (78,79). Although fMRI studies are mixed as to how TLE affects memory-

related activations—some suggesting inter- or intrahemispheric reorganization and others providing no evidence for reorganization—these studies consistently demonstrate decreased activity in temporal lobe regions ipsilateral to the seizure focus.

Limitations of fMRI—Although fMRI is a technique with excellent spatial resolution (2–5mm), it has poor temporal resolution because the hemodynamic response takes several seconds to evolve, precluding a true spatiotemporal analysis of cognitive processing (80). Another limitation of fMRI is that it may lack sensitivity for detecting temporal lobe language areas that are of primary concern in patients undergoing temporal lobe resections. This may, in part, be due to the fact that fMRI is subject to geometric distortions and signal loss in the anterior temporal lobe (81). As previously stated, concordance with the IAP is high for TLE, but may drop to 75% or lower in patients with extratemporal epilepsy. Finally, there is evidence that the hemodynamic response in fMRI is suppressed in a sizable number of patients with lesions that result in abnormal vascularization (82,83), making fMRI unreliable in many patients with large gliomas or AVMs. Nevertheless, fMRI provides a cost-efficient, non-invasive method of language and memory localization, and its wide availability makes it a strong contender for eventually replacing the IAP.

3.3 MEG

MEG, when co-registered with MRI, has several advantages for studying cognitive processing compared to fMRI, PET, and EEG. First, MEG measures electrophysiological currents arising in the pyramidal neurons (84). Thus, it reflects neural activity directly (mainly postsynaptic currents) rather than indirectly (i.e., blood flow or metabolism). Second, MEG has excellent temporal resolution extending to the sub-millisecond range. Third, MEG is not distorted by tissues outside the brain that affect EEG, which may allow for greater spatial resolution and accuracy (85). Finally, MEG may be a powerful tool for identifying receptive language fields that are impacted by dominant temporal lobe resections (68,82).

During MEG recordings, event-related fields (ERFs) are measured that represent changes in field potentials time-locked to a sensory, motor, or cognitive event. These ERFs are similar to the well-known event-related potentials (ERP) obtained from EEG studies of cognitive processing (86). With respect to language and memory, two primary components are of interest—an increase in the amplitude of a negativity between 300 and 500ms, the *N400*, that is thought to reflect lexical-semantic processing (87) and an increase in the amplitude of a late positivity between 500 and 800ms (late positive component; LPC) that is thought to reflect episodic retrieval. Previous studies with EEG have shown both components to be reduced or altered in patients with TLE before and after temporal lobe resections (88,89). Although most MEG studies in patients with epilepsy do not measure the *N400* and LPC directly, the methods of source analysis employed (e.g., fitting all dipoles that emerge between 200 and 800ms after stimulus onset) presumably capture the majority of activity associated with these late, cognitive ERFs.

As with fMRI, there is an emerging literature demonstrating the utility of MEG for language localization in neurosurgical patients (Table 2; see (90) for a comprehensive review). In TLE, studies using receptive language paradigms have focused on late activations (>200ms) that likely reflect sustained *N400* effects. These studies have demonstrated a high concordance (approximately 90%) between MEG language lateralization and the IAP (69,91–94). Other investigators have used silent verb generation and picture naming tasks with comparable results (95,96). Most studies have used equivalent current dipoles (ECD) to determine language lateralization by modeling the distribution of activity every several milliseconds separately in each hemisphere. These studies have localized ECDs in the left and right temporal lobe, centered on the superior and middle temporal gyri and within the superior temporal sulcus

(97). However, when cognitive processes are distributed in nature (which is likely characteristic of language), ECDs may underestimate the regions involved. To overcome this limitation, distributed source solutions have been developed and studied in patients with epilepsy (95) and healthy controls (98–100). In particular, Bowyer et al. (95) studied language lateralization in patients with epilepsy using a current density technique (MR-FOCUSS) that estimates the *strength* of cortical activation between hemispheres. They reported 96% concordance between MEG language lateralization within Broca's area and the IAP using a verb generation task. Although distributed source solutions may offer a viable alternative to the traditional ECD model, data using these methods are currently limited and have not been well-validated against postoperative outcome.

Only one study has examined memory processing in patients with TLE using MEG (101), despite numerous MEG studies of encoding or retrieval of words (98,102–108), faces (109, 110), patterns (111), and letters (112–114) in other patient populations (111–115) and healthy controls. Hanlon et al. (101) used an associative object-memory test in two TLE patients with hippocampal sclerosis and reported a shift of MEG activations to the contralateral, undamaged hippocampus. This reorganization of memory-related processes supports an accumulating body of literature demonstrating interhemispheric reorganization in patients with left TLE (116–120). However, the study results were based on only two patients and the hippocampal activations were reported between 160–290ms—a time period that is too early to optimally capture cognitive processes (121). To date, no study has used MEG to directly examine memory for verbal and nonverbal material in a well-sized group of patients with epilepsy. This would appear to be another fertile avenue for research as whole-head MEG systems become more widely available and methods of source modeling advance.

Limitations of MEG—MEG lacks the spatial resolution of fMRI and PET and is only available at a handful of institutions, limiting its utility in many clinical settings. In addition, MEG may not be optimal for identifying expressive language cortex (but see (95)) and it is relatively insensitive to radial and deep sources. The latter limitation is noteworthy in that MEG may not directly detect hippocampal activity. Rather, hippocampal contributions to N400 and LPC are supported by intracranial EEG studies that have localized generators of these components to the hippocampus and other medial temporal lobe structures (86,122–125). Finally, MEG is very sensitive to metal artifacts. Therefore, metal implants in the head and chest may generate excessive noise, limiting the reliability of MEG results in a subset of patients (e.g., those with a vagus nerve stimulator). Although techniques have been developed to reduce interference from such devices (126), additional work in this area is warranted.

4. Multimodal Approaches to Imaging in Epilepsy

Thus far, studies using single-modality imaging have been presented and their limitations for imaging behavioral correlates of epilepsy have been discussed. The remainder of this review will address novel research that integrates or compares imaging modalities with complementary strengths and weaknesses. For example, techniques with high spatial resolution (i.e., fMRI) are combined with imaging techniques that have high temporal resolution (i.e., MEG). Capitalizing on the strengths of each method can advance our understanding of the neural substrates of behavior in epilepsy, as well as increase our confidence through cross-validation of the results.

4.1 FMRI/DTI

The combination of fMRI and DTI provides a unique method of evaluating how the structural integrity of fiber pathways in the brain may influence functional activations both proximal to and distant from the seizure focus. In particular, there are dense fiber pathways connecting the medial temporal lobe to regions within the inferior frontal lobe that presumably control

executive functions and expressive language skills—skills which are frequently impaired in patients with intractable TLE (127). In a recent study, Powell et al. (36) performed fMRI and tractography on a series of 14 patients with TLE and hippocampal sclerosis to test the hypotheses that (1) language connections in left TLE patients would mirror the functional activation patterns revealed by fMRI, and (2) that patients with more lateralized language function would have more lateralized structural connections. Powell et al. found that controls and patients with right TLE demonstrated left lateralized language (i.e., fMRI activations to verb generation) and structural asymmetries (i.e., greater volume and mean FA of the left superior longitudinal fasciculus; SLF) relative to patients with left TLE. Conversely, patients with left TLE showed more symmetric language activations, as well as greater volume and FA of the right compared to the left SLF. Correlations between fMRI language activations and tractography revealed that patients with greater structural asymmetry also demonstrated greater functional asymmetry. These data demonstrate structural and functional reorganization of language in patients with left TLE and highlight the role of fibers connecting Broca's and Wernicke's area (i.e., the left SLF) in language function. Additional studies that link these functional and structural asymmetries to neuropsychological performances will help to determine the clinical utility of combining fMRI/DTI for purposes of presurgical planning.

4.2 FMRI/MEG

One of the most promising multimodal approaches to the study of language and memory involves the combination of fMRI/MEG. Not only do fMRI and MEG have opposite strengths with regards to their spatial and temporal resolution, they may also be differentially sensitive to detecting language-related activity in frontal and temporal areas. In a recent study, Kamada et al. (68) compared fMRI and MEG results in 117 presurgical patients, 39 of whom had chronic epilepsy. FMRI tasks of verb generation and abstract/concrete word categorization produced consistent activation in the left inferior and middle frontal gyrus, lateral precentral gyrus, angular gyrus, and supplementary motor area. Conversely, an MEG categorization task produced dipole clusters localized mainly in the superior and inferior temporal lobe regions of the dominant hemisphere. In the 87 patients who also completed the IAP, the combination of fMRI and MEG lateralization was reportedly 100% concordant with the IAP, which exceeded concordance rates using either technique alone. These authors concluded that fMRI was in fact superior for identifying expressive language cortex, whereas MEG was superior for localizing temporal lobe language cortex. Similar results showing differential regional sensitivity of these methods have been obtained in studies with healthy controls (69). In a separate study, Grummich et al (82) performed fMRI and MEG language tasks on 172 presurgical tumor patients and found congruence between these methods in 77% of patients. In 19% of patients, Broca's or Wernicke's activity was observed in one modality but not the other. However, discrepancies were only found in 4% of the cases. It is of note that fMRI responses were suppressed in 53% of the patients with large gliomas. In these cases, MEG provided the only reliable information. Although studies are limited, combining results from fMRI and MEG appears to have considerable value in the presurgical evaluation of patients with temporal and extratemporal epilepsy.

4.3 Limitations of Functional Imaging

Regardless of whether single or multimodal functional imaging approaches are used to study behavior in epilepsy, there are a number of limitations that are relatively independent of modality. First, the activation patterns obtained in any study are highly dependent on the cognitive task being performed. Therefore, discrepancies across modalities and studies are generally confounded by differences in task design and analysis. This is particularly important when comparing results from studies using tasks that primarily activate frontal (i.e., word generation) versus temporal (i.e., semantic decision) language networks. Second, most studies determine laterality of language/memory by calculating "laterality indices" and using

thresholds that are arbitrarily defined and vary considerably across studies. In many cases, a patient with bilateral language representation may be artificially categorized as “left dominant” or “right dominant” when the metric used biases against mixed language dominance categorization. This is particularly problematic in patients with epilepsy, where a sizable number of patients have language represented bilaterally (128). Third, most functional imaging techniques are activation rather than deactivation paradigms. Therefore, they provide information as to which areas are recruited during a task, rather than which areas are essential for task performance. This may be the strongest criticism of functional imaging and the strength of deactivation paradigms (i.e., IAP). It is for this reason that the most important factor in assessing the utility of a method will be how well that method predicts post-operative outcome. Multimodal approaches to imaging offer clear advantages over single-modality imaging, especially in providing a method of cross-validating results. However, multimodal studies still have limitations, and more definitive studies of behavior will require advances in our understanding of the physiological processes underlying the various signals being measured by each modality (105).

5. Conclusion

As the armamentarium of imaging techniques available to researchers and clinicians expands, there will be more choices to make regarding what technology, or combination of technologies, provide the most valid, cost-efficient evaluation of cognition and mood in epilepsy. Quantitative measures of hippocampal volume provide valuable information for predicting the effects of surgery on verbal learning and memory, whereas hippocampal and amygdalar volumes may be equally important to understanding mood. Functional imaging, including fMRI and/or MEG, is needed to evaluate the degree to which reorganization of language and memory processes occur in patients with epilepsy. However, due to the inherent limitation of each modality, it is probable that a combination of imaging modalities will unveil the most information regarding the true neural correlates of behavior.

Acknowledgments

Supported by Grant Number K23NS056091 from the National Institute of Neurological Disorders and Stroke (NINDS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIH.

References

1. Kilpatrick C, Murrie V, Cook M, Andrewes D, Desmond P, Hopper J. Degree of left hippocampal atrophy correlates with severity of neuropsychological deficits. *Seizure* 1997;6(3):213–8. [PubMed: 9203250]
2. Griffith HR, Pyzalski RW, O’Leary D, Magnotta V, Bell B, Dow C, et al. A controlled quantitative MRI volumetric investigation of hippocampal contributions to immediate and delayed memory performance. *J Clin Exp Neuropsychol* 2003;25(8):1117–27. [PubMed: 14566585]
3. Griffith HR, Pyzalski RW, Seidenberg M, Hermann BP. Memory relationships between MRI volumes and resting PET metabolism of medial temporal lobe structures. *Epilepsy Behav* 2004;5(5):669–76. [PubMed: 15380118]
4. Trenerry MR, Westerveld M, Meador KJ. MRI hippocampal volume and neuropsychology in epilepsy surgery. *Magn Reson Imaging* 1995;13(8):1125–32. [PubMed: 8750326]
5. Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. *Ann Neurol* 1992;31(6):629–37. [PubMed: 1514774]
6. Loring DW, Murro AM, Meador KJ, Lee GP, Grattan CA, Nichols ME, et al. Wada memory testing and hippocampal volume measurements in the evaluation for temporal lobectomy. *Neurology* 1993;43(9):1789–93. [PubMed: 8414033]

7. Trener MR, Jack CR Jr, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. *Neurology* 1993;43(9):1800–5. [PubMed: 8414035]
8. Martin RC, Hugg JW, Roth DL, Bilir E, Gilliam FG, Faught E, et al. MRI extrahippocampal volumes and visual memory: correlations independent of MRI hippocampal volumes in temporal lobe epilepsy patients. *J Int Neuropsychol Soc* 1999;5(6):540–8. [PubMed: 10561935]
9. O'Brien CE, Bowden SC, Bardenhagen FJ, Cook MJ. Neuropsychological correlates of hippocampal and rhinal cortex volumes in patients with mesial temporal sclerosis. *Hippocampus* 2003;13(8):892–904. [PubMed: 14750652]
10. Baxendale SA, van Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF, et al. The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998;39(2):158–66. [PubMed: 9577995]
11. Jones-Gotman M. Right hippocampal excision impairs learning and recall of a list of abstract designs. *Neuropsychologia* 1986;24(5):659–70. [PubMed: 3785653]
12. Pegna AJ, Caldara-Schnetzler AS, Perrig SH, Lazeyras F, Khateb A, Mayer E, et al. Is the right amygdala involved in visuospatial memory? Evidence from MRI volumetric measures. *Eur Neurol* 2002;47(3):148–55. [PubMed: 11914552]
13. Alessio A, Bonilha L, Rorden C, Kobayashi E, Min LL, Damasceno BP, et al. Memory and language impairments and their relationships to hippocampal and perirhinal cortex damage in patients with medial temporal lobe epilepsy. *Epilepsy Behav* 2006;8(3):593–600. [PubMed: 16517214]
14. Foundas AL, Leonard CM, Gilmore R, Fennell E, Heilman KM. Planum temporale asymmetry and language dominance. *Neuropsychologia* 1994;32(10):1225–31. [PubMed: 7845562]
15. Dorsaint-Pierre R, Penhune VB, Watkins KE, Neelin P, Lerch JP, Bouffard M, et al. Asymmetries of the planum temporale and Heschl's gyrus: relationship to language lateralization. *Brain* 2006;129(Pt 5):1164–76. [PubMed: 16537567]
16. Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth RD, Wendt G, et al. Extratemporal quantitative MR volumetrics and neuropsychological status in temporal lobe epilepsy. *J Int Neuropsychol Soc* 2003;9(3):353–62. [PubMed: 12666760]
17. Oyegbile TO, Bhattacharya A, Seidenberg M, Hermann BP. Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. *Epilepsia* 2006;47(1):143–52. [PubMed: 16417542]
18. Baxendale SA, Sisodiya SM, Thompson PJ, Free SL, Kitchen ND, Stevens JM, et al. Disproportion in the distribution of gray and white matter: neuropsychological correlates. *Neurology* 1999;52(2):248–52. [PubMed: 9932939]
19. Oyegbile T, Hansen R, Magnotta V, O'Leary D, Bell B, Seidenberg M, et al. Quantitative measurement of cortical surface features in localization-related temporal lobe epilepsy. *Neuropsychology* 2004;18(4):729–37. [PubMed: 15506841]
20. Baxendale SA, Thompson PJ, Duncan JS. Epilepsy & depression: the effects of comorbidity on hippocampal volume--a pilot study. *Seizure* 2005;14(6):435–8. [PubMed: 16095926]
21. Richardson EJ, Griffith HR, Martin RC, Paige AL, Stewart CC, Jones J, et al. Structural and functional neuroimaging correlates of depression in temporal lobe epilepsy. *Epilepsy Behav* 2007;10(2):242–9. [PubMed: 17215168]
22. Tebartz van Elst L, Woermann F, Lemieux L, Trimble MR. Increased amygdala volumes in female and depressed humans. A quantitative magnetic resonance imaging study. *Neurosci Lett* 2000;281(2–3):103–6. [PubMed: 10704753]
23. Tebartz van Elst L, Woermann FG, Lemieux L, Trimble MR. Amygdala enlargement in dysthymia--a volumetric study of patients with temporal lobe epilepsy. *Biol Psychiatry* 1999;46(12):1614–23. [PubMed: 10624542]
24. Tebartz Van Elst L, Baeumer D, Lemieux L, Woermann FG, Koepp M, Krishnamoorthy S, et al. Amygdala pathology in psychosis of epilepsy: A magnetic resonance imaging study in patients with temporal lobe epilepsy. *Brain* 2002;125(Pt 1):140–9. [PubMed: 11834599]
25. van Elst LT, Woermann FG, Lemieux L, Thompson PJ, Trimble MR. Affective aggression in patients with temporal lobe epilepsy: a quantitative MRI study of the amygdala. *Brain* 2000;123(Pt 2):234–43. [PubMed: 10648432]

26. Kondziella D, Alvestad S, Vaaler A, Sonnewald U. Which clinical and experimental data link temporal lobe epilepsy with depression? *J Neurochem*. 2007
27. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999;19(12):5034–43. [PubMed: 10366636]
28. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000;11(6 Pt 1):805–21. [PubMed: 10860804]
29. Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. *Neuroimage* 2004;23(2):717–23. [PubMed: 15488421]
30. Bonilha L, Alessio A, Rorden C, Baylis G, Damasceno BP, Min LL, et al. Extrahippocampal gray matter atrophy and memory impairment in patients with medial temporal lobe epilepsy. *Hum Brain Mapp*. 2007
31. Yu A, Li K, Li L, Shan B, Wang Y, Xue S. Whole-brain voxel-based morphometry of white matter in medial temporal lobe epilepsy. *Eur J Radiol*. 2007
32. Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, et al. Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage* 2007;36(3):630–44. [PubMed: 17481925]
33. Rodrigo S, Oppenheim C, Chassoux F, Golestani N, Cointepas Y, Poupon C, et al. Uncinate fasciculus fiber tracking in mesial temporal lobe epilepsy. Initial findings *Eur Radiol* 2007;17(7):1663–1668.
34. Gross DW, Concha L, Beaulieu C. Extratemporal white matter abnormalities in mesial temporal lobe epilepsy demonstrated with diffusion tensor imaging. *Epilepsia* 2006;47(8):1360–3. [PubMed: 16922882]
35. Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Ann Neurol* 2005;57(2):188–96. [PubMed: 15562425]
36. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. Abnormalities of language networks in temporal lobe epilepsy. *Neuroimage* 2007;36(1):209–21. [PubMed: 17400477]
37. Diehl B, Lapresto E, Liu P, Bingaman W, Busch R. Diffusion tensor imaging characteristics of the uncinate fasciculus in temporal lobe epilepsy and correlates with memory scores. *Epilepsia* 2006;47(s4):68. [PubMed: 17239110]
38. Moffett JR, Namboodiri MA, Cangro CB, Neale JH. Immunohistochemical localization of N-acetylaspartate in rat brain. *Neuroreport* 1991;2(3):131–4. [PubMed: 1768855]
39. Sawrie SM, Martin RC, Knowlton R, Faught E, Gilliam F, Kuzniecky R. Relationships among hippocampal volumetry, proton magnetic resonance spectroscopy, and verbal memory in temporal lobe epilepsy. *Epilepsia* 2001;42(11):1403–7. [PubMed: 11879342]
40. Martin RC, Sawrie S, Hugg J, Gilliam F, Faught E, Kuzniecky R. Cognitive correlates of 1H MRSI-detected hippocampal abnormalities in temporal lobe epilepsy. *Neurology* 1999;53(9):2052–8. [PubMed: 10599780]
41. Sawrie SM, Martin RC, Faught RE, Maton B, Hugg JW, Kuzniecky RI. Nonlinear Trends in Hippocampal Metabolic Function and Verbal Memory: Evidence of Cognitive Reserve in Temporal Lobe Epilepsy? *Epilepsy Behav* 2000;1(2):106–111. [PubMed: 12609139]
42. Sawrie SM, Martin RC, Gilliam FG, Faught RE, Maton B, Hugg JW, et al. Visual confrontation naming and hippocampal function: A neural network study using quantitative (1)H magnetic resonance spectroscopy. *Brain* 2000;123 (Pt 4):770–80. [PubMed: 10734008]
43. Hanoglu L, Ozkara C, Keskinkilic C, Altin U, Uzan M, Tuzgen S, et al. Correlation between 1H MRS and memory before and after surgery in mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia* 2004;45(6):632–40. [PubMed: 15144428]
44. Gilliam FG, Maton BM, Martin RC, Sawrie SM, Faught RE, Hugg JW, et al. Hippocampal 1H-MRSI correlates with severity of depression symptoms in temporal lobe epilepsy. *Neurology* 2007;68(5):364–8. [PubMed: 17261683]
45. Abou-Khalil B. An update on determination of language dominance in screening for epilepsy surgery: the Wada test and newer noninvasive alternatives. *Epilepsia* 2007;48(3):442–55. [PubMed: 17319925]

46. Tharin S, Golby A. Functional brain mapping and its applications to neurosurgery. *Neurosurgery* 2007;60(4 Suppl 2):185–201. [PubMed: 17415154]discussion 201–2
47. Swartz BE, Halgren E, Simpkins F, Fuster J, Mandelkern M, Krisdakumtorn T, et al. Primary or working memory in frontal lobe epilepsy: An 18FDG-PET study of dysfunctional zones. *Neurology* 1996;46(3):737–47. [PubMed: 8618675]
48. Swartz BE, Halgren E, Simpkins F, Mandelkern M. Studies of working memory using 18FDG-positron emission tomography in normal controls and subjects with epilepsy. *Life Sci* 1996;58(22):2057–64. [PubMed: 8637437]
49. Swartz BE, Simpkins F, Halgren E, Mandelkern M, Brown C, Krisdakumtorn T, et al. Visual working memory in primary generalized epilepsy: an 18FDG-PET study. *Neurology* 1996;47(5):1203–12. [PubMed: 8909431]
50. Rausch R, Henry TR, Ary CM, Engel J Jr, Mazziotta J. Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Arch Neurol* 1994;51(2):139–44. [PubMed: 8304838]
51. Jokeit H, Ebner A, Arnold S, Schuller M, Antke C, Huang Y, et al. Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. *J Neurol* 1999;246(10):926–33. [PubMed: 10552240]
52. Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 1997;120 (Pt 12):2283–94. [PubMed: 9448582]
53. McDonald CR, Swartz BE, Halgren E, Patell A, Daines R, Mandelkern M. The relationship of regional frontal hypometabolism to executive function: a resting fluorodeoxyglucose PET study of patients with epilepsy and healthy controls. *Epilepsy Behav* 2006;9(1):58–67. [PubMed: 16713363]
54. Gilliam FG, Santos J, Vahle V, Carter J, Brown K, Hecimovic H. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia* 2004;45 (Suppl 2):28–33. [PubMed: 15186342]
55. Weintrob DL, Saling MM, Berkovic SF, Berlangieri SU, Reutens DC. Verbal memory in left temporal lobe epilepsy: evidence for task-related localization. *Ann Neurol* 2002;51(4):442–7. [PubMed: 11921050]
56. Griffith HR, Richardson E, Pyzalski RW, Bell B, Dow C, Hermann BP, et al. Memory for famous faces and the temporal pole: functional imaging findings in temporal lobe epilepsy. *Epilepsy Behav* 2006;9(1):173–80. [PubMed: 16766230]
57. Hunter KE, Blaxton TA, Bookheimer SY, Figlozzi C, Gaillard WD, Grandin C, et al. (15)O water positron emission tomography in language localization: a study comparing positron emission tomography visual and computerized region of interest analysis with the Wada test. *Ann Neurol* 1999;45(5):662–5. [PubMed: 10319891]
58. Tatlidil R, Xiong J, Luther S. Presurgical lateralization of seizure focus and language dominant hemisphere with O–15 water PET imaging. *Acta Neurol Scand* 2000;102(2):73–80. [PubMed: 10949522]
59. Bookheimer SY, Zeffiro TA, Blaxton T, Malow BA, Gaillard WD, Sato S, et al. A direct comparison of PET activation and electrocortical stimulation mapping for language localization. *Neurology* 1997;48(4):1056–65. [PubMed: 9109900]
60. Victoroff JI, Benson F, Grafton ST, Engel J Jr, Mazziotta JC. Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. *Arch Neurol* 1994;51(2):155–63. [PubMed: 8304841]
61. Hasler G, Bonwetsch R, Giovacchini G, Toczek MT, Bagic A, Luckenbaugh DA, et al. 5-HT(1A) Receptor Binding in Temporal Lobe Epilepsy Patients With and Without Major Depression. *Biol Psychiatry*. 2007
62. Theodore WH, Hasler G, Giovacchini G, Kelley K, Reeves-Tyer P, Herscovitch P, et al. Reduced hippocampal 5HT1A PET receptor binding and depression in temporal lobe epilepsy. *Epilepsia* 2007;48(8):1526–30. [PubMed: 17442003]
63. Bromfield EB, Altshuler L, Leiderman DB, Balish M, Ketter TA, Devinsky O, et al. Cerebral metabolism and depression in patients with complex partial seizures. *Arch Neurol* 1992;49(6):617–23. [PubMed: 1596197]

64. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A* 1986;83(4):1140–4. [PubMed: 3485282]
65. Lehericy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, et al. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 2000;54(8):1625–33. [PubMed: 10762504]
66. Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, et al. Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 1995;118 (Pt 6):1411–9. [PubMed: 8595473]
67. Yetkin FZ, Swanson S, Fischer M, Akansel G, Morris G, Mueller W, et al. Functional MR of frontal lobe activation: comparison with Wada language results. *AJNR Am J Neuroradiol* 1998;19(6):1095–8. [PubMed: 9672017]
68. Kamada K, Sawamura Y, Takeuchi F, Kuriki S, Kawai K, Morita A, et al. Expressive and receptive language areas determined by a non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography. *Neurosurgery* 2007;60(2):296–305. [PubMed: 17290180] discussion 305–6.
69. Billingsley-Marshall RL, Clear T, Mencl WE, Simos PG, Swank PR, Men D, et al. A comparison of functional MRI and magnetoencephalography for receptive language mapping. *J Neurosci Methods* 2007;161(2):306–13. [PubMed: 17157917]
70. Gaillard WD, Balsamo L, Xu B, McKinney C, Papero PH, Weinstein S, et al. fMRI language task panel improves determination of language dominance. *Neurology* 2004;63(8):1403–8. [PubMed: 15505156]
71. Weber B, Wellmer J, Schur S, Dinkelacker V, Ruhlmann J, Mormann F, et al. Presurgical language fMRI in patients with drug-resistant epilepsy: effects of task performance. *Epilepsia* 2006;47(5):880–6. [PubMed: 16686653]
72. Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, et al. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology* 2003;61(5):699–701. [PubMed: 12963768]
73. Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW. Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 2002;51(3):350–60. [PubMed: 11891830]
74. Sabsevitz DS, Swanson SJ, Hammeke TA, Spanaki MV, Possing ET, Morris GL 3rd, et al. Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology* 2003;60(11):1788–92. [PubMed: 12796532]
75. Golby AJ, Poldrack RA, Illes J, Chen D, Desmond JE, Gabrieli JD. Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. *Epilepsia* 2002;43(8):855–63. [PubMed: 12181004]
76. Richardson MP, Strange BA, Duncan JS, Dolan RJ. Preserved verbal memory function in left medial temporal pathology involves reorganisation of function to right medial temporal lobe. *Neuroimage* 2003;20 (Suppl 1):S112–9. [PubMed: 14597304]
77. Dupont S, Van de Moortele PF, Samson S, Hasboun D, Poline JB, Adam C, et al. Episodic memory in left temporal lobe epilepsy: a functional MRI study. *Brain* 2000;123 (Pt 8):1722–32. [PubMed: 10908201]
78. Dupont S, Samson Y, Van de Moortele PF, Samson S, Poline JB, Hasboun D, et al. Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2002;73(5):478–85. [PubMed: 12397138]
79. Dupont S, Samson Y, Van de Moortele PF, Samson S, Poline JB, Adam C, et al. Delayed verbal memory retrieval: a functional MRI study in epileptic patients with structural lesions of the left medial temporal lobe. *Neuroimage* 2001;14(5):995–1003. [PubMed: 11697931]
80. Yoo SS, Talos IF, Golby AJ, Black PM, Panych LP. Evaluating requirements for spatial resolution of fMRI for neurosurgical planning. *Hum Brain Mapp* 2004;21(1):34–43. [PubMed: 14689508]
81. Powell HW, Koepp MJ, Richardson MP, Symms MR, Thompson PJ, Duncan JS. The application of functional MRI of memory in temporal lobe epilepsy: a clinical review. *Epilepsia* 2004;45(7):855–63. [PubMed: 15230713]

82. Grummich P, Nimsky C, Pauli E, Buchfelder M, Ganslandt O. Combining fMRI and MEG increases the reliability of presurgical language localization: a clinical study on the difference between and congruence of both modalities. *Neuroimage* 2006;32(4):1793–803. [PubMed: 16889984]
83. Lehericy S, Biondi A, Sourour N, Vlaicu M, du Montcel ST, Cohen L, et al. Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations *Radiology* 2002;223(3):672–82.
84. Barkley GL, Baumgartner C. MEG and EEG in epilepsy. *J Clin Neurophysiol* 2003;20(3):163–78. [PubMed: 12881663]
85. Leahy RM, Mosher JC, Spencer ME, Huang MX, Lewine JD. A study of dipole localization accuracy for MEG and EEG using a human skull phantom. *Electroencephalogr Clin Neurophysiol* 1998;107(2):159–73. [PubMed: 9751287]
86. Halgren E. How can intracranial recordings assist MEG source localization? *Neurology and Clinical Neurophysiology* 2004;86:1–18.
87. Munte, TF.; Urbach, TP.; Duzel, E.; Kutas, M. Event-related brain potentials in the study of human cognition and neuropsychology. In: Boller, F.; Grafman, J.; Rizzolatti, G., editors. *Handbook of Neuropsychology*. Vol. 2. Elsevier Science; 2000. p. 1-97.
88. Olichney JM, Riggins BR, Hillert DG, Nowacki R, Tecoma E, Kutas M, et al. Reduced sensitivity of the N400 and late positive component to semantic congruity and word repetition in left temporal lobe epilepsy. *Clin Electroencephalogr* 2002;33(3):111–8. [PubMed: 12192660]
89. Lalouschek W, Gerschlagel W, Lehrner J, Baumgartner C, Lindinger G, Deecke L, et al. Event-related potentials in patients with temporal lobe epilepsy reveal topography specific lateralization in relation to the side of the epileptic focus. *Electroencephalogr Clin Neurophysiol* 1998;108(6):567–76. [PubMed: 9872428]
90. Salmelin R. Clinical neurophysiology of language: the MEG approach. *Clin Neurophysiol* 2007;118(2):237–54. [PubMed: 17008126]
91. Papanicolaou AC, Simos PG, Breier JI, Zouridakis G, Willmore LJ, Wheless JW, et al. Magnetoencephalographic mapping of the language-specific cortex. *J Neurosurg* 1999;90(1):85–93. [PubMed: 10413160]
92. Breier JI, Simos PG, Zouridakis G, Papanicolaou AC. Lateralization of activity associated with language function using magnetoencephalography: a reliability study. *J Clin Neurophysiol* 2000;17(5):503–10. [PubMed: 11085554]
93. Maestu F, Ortiz T, Fernandez A, Amo C, Martin P, Fernandez S, et al. Spanish language mapping using MEG: a validation study. *Neuroimage* 2002;17(3):1579–86. [PubMed: 12414296]
94. Papanicolaou AC, Simos PG, Castillo EM, Breier JI, Sarkari S, Patariaia E, et al. Magnetocephalography: a noninvasive alternative to the Wada procedure. *J Neurosurg* 2004;100(5):867–76. [PubMed: 15137606]
95. Bowyer SM, Moran JE, Weiland BJ, Mason KM, Greenwald ML, Smith BJ, et al. Language laterality determined by MEG mapping with MR-FOCUSS. *Epilepsy Behav* 2005;6(2):235–41. [PubMed: 15710310]
96. Hirata M, Kato A, Taniguchi M, Saitoh Y, Ninomiya H, Ihara A, et al. Determination of language dominance with synthetic aperture magnetometry: comparison with the Wada test. *Neuroimage* 2004;23(1):46–53. [PubMed: 15325351]
97. Lee D, Sawrie SM, Simos PG, Killen J, Knowlton RC. Reliability of language mapping with magnetic source imaging in epilepsy surgery candidates. *Epilepsy Behav* 2006;8(4):742–9. [PubMed: 16603415]
98. Dhond RP, Buckner RL, Dale AM, Marinkovic K, Halgren E. Spatiotemporal maps of brain activity underlying word generation and their modification during repetition priming. *J Neurosci* 2001;21(10):3564–71. [PubMed: 11331385]
99. Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, et al. Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron* 2000;26(1):55–67. [PubMed: 10798392]
100. Halgren E, Dhond RP, Christensen N, Van Petten C, Marinkovic K, Lewine JD, et al. N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage* 2002;17(3):1101–16. [PubMed: 12414253]

101. Hanlon FM, Weisend MP, Huang M, Lee RR, Moses SN, Paulson KM, et al. A non-invasive method for observing hippocampal function. *Neuroreport* 2003;14(15):1957–60. [PubMed: 14561928]
102. Staresina BP, Bauer H, Deecke L, Walla P. Magnetoencephalographic correlates of different levels in subjective recognition memory. *Neuroimage*. 2005
103. Marinkovic K. Spatiotemporal dynamics of word processing in the human cortex. *Neuroscientist* 2004;10(2):142–52. [PubMed: 15070488]
104. Marinkovic K, Dhond RP, Dale AM, Glessner M, Carr V, Halgren E. Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron* 2003;38(3):487–97. [PubMed: 12741994]
105. Dale AM, Halgren E. Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr Opin Neurobiol* 2001;11(2):202–8. [PubMed: 11301240]
106. Aine CJ, Adair JC, Knoefel JE, Hudson D, Qualls C, Kovacevic S, et al. Temporal dynamics of age-related differences in auditory incidental verbal learning. *Brain Res Cogn Brain Res* 2005;24(1):1–18. [PubMed: 15922153]
107. Maestu F, Paul N, Munoz-Cespedes JM, Campo P, Rios M, Alvarez-Linera J, et al. Could activity in anterior frontal regions predict performance on declarative memory tests? *Neuroreport* 2005;16(4):337–41. [PubMed: 15729134]
108. Duzel E, Habib R, Schott B, Schoenfeld A, Lobaugh N, McIntosh AR, et al. A multivariate, spatiotemporal analysis of electromagnetic time-frequency data of recognition memory. *Neuroimage* 2003;18(2):185–97. [PubMed: 12595175]
109. Halgren E, Raij T, Marinkovic K, Jousmaki V, Hari R. Cognitive response profile of the human fusiform face area as determined by MEG. *Cereb Cortex* 2000;10(1):69–81. [PubMed: 10639397]
110. Gonsalves BD, Kahn I, Curran T, Norman KA, Wagner AD. Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. *Neuron* 2005;47(5):751–61. [PubMed: 16129403]
111. Ciesielski KT, Hamalainen MS, Lesnik PG, Geller DA, Ahlfors SP. Increased MEG activation in OCD reflects a compensatory mechanism specific to the phase of a visual working memory task. *Neuroimage* 2005;24(4):1180–91. [PubMed: 15670696]
112. Maestu F, Arrazola J, Fernandez A, Simos PG, Amo C, Gil-Gregorio P, et al. Do cognitive patterns of brain magnetic activity correlate with hippocampal atrophy in Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2003;74(2):208–12. [PubMed: 12531952]
113. Maestu F, Fernandez A, Simos PG, Gil-Gregorio P, Amo C, Rodriguez R, et al. Spatio-temporal patterns of brain magnetic activity during a memory task in Alzheimer's disease. *Neuroreport* 2001;12(18):3917–22. [PubMed: 11742211]
114. Maestu F, Fernandez A, Simos PG, Lopez-Ibor MI, Campo P, Criado J, et al. Profiles of brain magnetic activity during a memory task in patients with Alzheimer's disease and in non-demented elderly subjects, with or without depression. *J Neurol Neurosurg Psychiatry* 2004;75(8):1160–2. [PubMed: 15258220]
115. Pekkone E, Hirvonen J, Ahveninen J, Kahkonen S, Kaakkola S, Huttunen J, et al. Memory-based comparison process not attenuated by haloperidol: a combined MEG and EEG study. *Neuroreport* 2002;13(1):177–81. [PubMed: 11924884]
116. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann N Y Acad Sci* 1977;299:355–69. [PubMed: 1011116]
117. Pataria E, Simos PG, Castillo EM, Billingsley-Marshall RL, McGregor AL, Breier JJ, et al. Reorganization of language-specific cortex in patients with lesions or mesial temporal epilepsy. *Neurology* 2004;63(10):1825–32. [PubMed: 15557497]
118. Maestu F, Saldana C, Amo C, Gonzalez-Hidalgo M, Fernandez A, Fernandez S, et al. Can small lesions induce language reorganization as large lesions do? *Brain Lang* 2004;89(3):433–8. [PubMed: 15120535]
119. Rausch R, Boone K, Ary CM. Right-hemisphere language dominance in temporal lobe epilepsy: clinical and neuropsychological correlates. *J Clin Exp Neuropsychol* 1991;13(2):217–31. [PubMed: 1864912]

120. Breier JI, Castillo EM, Simos PG, Billingsley-Marshall RL, Patariaia E, Sarkari S, et al. Atypical language representation in patients with chronic seizure disorder and achievement deficits with magnetoencephalography. *Epilepsia* 2005;46(4):540–8. [PubMed: 15816948]
121. Friedman D, Johnson R Jr. Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microsc Res Tech* 2000;51(1):6–28. [PubMed: 11002349]
122. Halgren E, Baudena P, Heit G, Clarke JM, Marinkovic K, Clarke M. Spatio-temporal stages in face and word processing. I. Depth-recorded potentials in the human occipital, temporal and parietal lobes [corrected]. *J Physiol Paris* 1994;88(1):1–50. [PubMed: 8019524]
123. Elger CE, Grunwald T, Lehnertz K, Kutas M, Helmstaedter C, Brockhaus A, et al. Human temporal lobe potentials in verbal learning and memory processes. *Neuropsychologia* 1997;35(5):657–67. [PubMed: 9153028]
124. Fernandez G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dimpelmann M, et al. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science* 1999;285(5433):1582–5. [PubMed: 10477525]
125. Heit G, Smith ME, Halgren E. Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature* 1988;333(6175):773–5. [PubMed: 3386719]
126. Taulu S, Simola J. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys Med Biol* 2006;51(7):1759–68. [PubMed: 16552102]
127. Hermann B, Seidenberg M. Executive system dysfunction in temporal lobe epilepsy: effects of nociferous cortex versus hippocampal pathology. *J Clin Exp Neuropsychol* 1995;17(6):809–19. [PubMed: 8847387]
128. Sabbah P, Chassoux F, Leveque C, Landre E, Baudoin-Chial S, Devaux B, et al. Functional MR imaging in assessment of language dominance in epileptic patients. *Neuroimage* 2003;18(2):460–7. [PubMed: 12595199]
129. Benke T, Koylu B, Visani P, Karner E, Brenneis C, Bartha L, et al. Language lateralization in temporal lobe epilepsy: a comparison between fMRI and the Wada Test. *Epilepsia* 2006;47(8):1308–19. [PubMed: 16922875]
130. Janszky J, Jokeit H, Kontopoulou K, Mertens M, Ebner A, Pohlmann-Eden B, et al. Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia* 2005;46(2):244–50. [PubMed: 15679505]
131. Jokeit H, Okujava M, Woermann FG. Memory fMRI lateralizes temporal lobe epilepsy. *Neurology* 2001;57(10):1786–93. [PubMed: 11723264]
132. Rabin ML, Narayan VM, Kimberg DY, Casasanto DJ, Glosser G, Tracy JI, et al. Functional MRI predicts post-surgical memory following temporal lobectomy. *Brain* 2004;127(Pt 10):2286–98. [PubMed: 15329352]
133. Richardson MP, Strange BA, Thompson PJ, Baxendale SA, Duncan JS, Dolan RJ. Pre-operative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain* 2004;127(Pt 11):2419–26. [PubMed: 15459025]
134. Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, et al. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsia* 2007;48(8):1512–25. [PubMed: 17430404]
135. Janszky J, Ollech I, Jokeit H, Kontopoulou K, Mertens M, Pohlmann-Eden B, et al. Epileptic activity influences the lateralization of mesiotemporal fMRI activity. *Neurology* 2004;63(10):1813–7. [PubMed: 15557495]
136. Avila C, Barros-Loscertales A, Forn C, Mallo R, Parcet MA, Belloch V, et al. Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR Am J Neuroradiol* 2006;27(3):498–503. [PubMed: 16551984]
137. Breier JI, Simos PG, Wheless JW, Constantinou JE, Baumgartner JE, Venkataraman V, et al. Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: a comparison. *J Child Neurol* 2001;16(2):124–30. [PubMed: 11292218]
138. Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, et al. Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *J Neurosurg* 1999;91(5):787–96. [PubMed: 10541236]

139. Patariaia E, Billingsley-Marshall RL, Castillo EM, Breier JI, Simos PG, Sarkari S, et al. Organization of receptive language-specific cortex before and after left temporal lobectomy. *Neurology* 2005;64(3):481–7. [PubMed: 15699379]

Table 1
fMRI Studies of Language and Memory in Patients with Epilepsy

Patients	Cognitive Task	Results	Ref.
<i>LANGUAGE</i>			
TLE	Semantic fluency, story listening, & sentence rep	Asymmetry of frontal, but not temporal, language areas was concordant with IAP results	(65)
TLE	Verbal fluency, reading comp, & auditory comp.	Consistent activation of left frontal and temporoparietal areas; Results concordant with IAP in 21 of 25 TLEs	(70)
TLE & ExTLE	Semantic decision task	fMRI results showed activation in inferior frontal and temporoparietal regions. Performance level influenced magnitude of activation, but not lateralization index	(71)
TLE & ExTLE	Covert word generation	91% overall concordance with IAP; fMRI was discordant in 3% of L TLE and 25% of left ExTLE	(72)
TLEs	Verb generation, picture naming, verbal fluency, & sentence comp	Combination of tasks was superior to any one task for localizing frontal and temporal language cortex Concordance with cortical stimulation was strong, but predictive validity of fMRI was limited due to over-estimation of language cortex relative to stimulation	(73)
L TLE	Semantic decision task	fMRI results showed 100% sensitivity and 73% specificity in predicting post-operative naming decline	(74)
TLE	Semantic decision task	Concordance with IAP was 89% in R TLE & 72.5% in L TLE; Frontal activation showed > concordance with IAP	(129)
TLE & ExTLE	Covert word generation	Concordance with IAP in 95% of patients; Right-hemisphere language was associated with left TLE	(128)
<i>MEMORY</i>			
TLE	Encoding of patterns, faces, scenes, and words	Verbal encoding activated right MTL in left TLE; nonverbal encoding activated left MTL in right TLE	(75)
L TLE	Encoding of words	Increased activation of the right hippocampus and parahippocampal gyrus in left TLE. Recall of emotional words recruited right amygdala.	(76)
L TLE	Retrieval of words learned during encoding	Bilateral parahippocampal activation (R>L) in controls and TLE. TLEs showed additional recruitment of extensive left prefrontal regions	(77)
R TLE	Visuospatial retrieval during an imaginative walk	Reduced ipsilateral MTL activations correlated with favorable memory outcome after right ATL	(130)
TLE	Mental navigation and recall of landmarks	MTL activation correctly lateralized the side of seizure onset in 90% of TLE patients	(131)
TLE	Encoding of visual scenes	Increased ipsilateral MTL activation predicted greater postoperative memory decline	(132)
L TLE	Event-related verbal encoding	Greater activity in left versus right hippocampus predicted greater verbal memory decline	(133)
TLE	Encoding of words, pictures, and faces	Greater activation in contralateral HC was associated with poorer memory performance	(134)
TLE & ExTLE	Visuospatial retrieval during an imaginative walk	75% of TLEs showed greater activation in contralateral MTL; ExTLEs more often had bilateral MTL activation	(135)
TL lesions	Encoding of complex scenes& Retrieval of visiospatial	>50% of TLs showed contralateral paraHC activations in both tasks; whereas controls showed bilateral paraHC; Memory task lateralization was different in 30% of TLs	(136)

Key: TLE = temporal lobe epilepsy; ExTLE = extratemporal lobe epilepsy; IAP = intracarotid amobarbital procedure; L = left; R = right; comp = comprehension; paraHC = parahippocampal

Table 2
MEG Studies of Language and Memory in Patients with Epilepsy

Patients	Cognitive Task	Results	Ref
<i>LANGUAGE</i>			
TLE	Auditory word recognition	100% of TLE showed activity in the STG; Concordance with IAP was found for 74 of 85; discordant in 11 TLEs	(94)
TLE	Verb generation & picture naming	Verb generation produced reliable activity in Broca's area & showed >90% concordance with IAP (measured by current source density technique-MR-FOCUSS)	(95)
TLE & ExTLE	Silent reading	95% concordance with IAP; beta & low gamma-band desynchronization in IFG & MFG predicted dominance (measured by Synthetic Aperture Magnetometry)	(96)
TLE & ExTLE	Auditory word recognition	Activity localized in posterior STG & MTG and SMG; Interrater reliability for language dominance was .88-.91	(97)
TLE	Auditory word recognition (Spanish equivalent)	Concordance with IAP in 7 of 8 patients; greatest language-related activity in the left TP area in all TLEs	(93)
TLE(8-18 yrs)	Visual and auditory word recognition	Concordance between IAP & MEG language laterality indices = .87; Concordance with IAP in 17 of 19 TLEs	(137)
TLE & L neoplasm	Visual word recognition	L TLE showed interhemispheric shift of language; Left neoplasm patients showed intrahemispheric shifts	(92)
TLE & tumor	Visual and auditory word recognition	Cortical stimulation was consistent with MEG receptive language clusters in all 13 patients	(138)
L TLE	Auditory word recognition	TLEs with preoperative bilateral MEG showed > right hemisphere activation post-ATL and poorer pre- and post-ATL cognitive functioning than patients with left hemisphere pre-operative MEG.	(139)
<i>MEMORY</i>			
2 TLEs	Transverse patterning	Controls showed right HC activity. Patients showed activity contralateral to the seizure focus.	(101)

Key: IFG = inferior frontal gyrus; MFG = middle frontal gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; SMG = supramarginal gyrus; TP = temporoparietal; HC = hippocampal.