Neural Plasticity Following Anterior Temporal Lobectomy

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Abstract

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This study followed patients with temporal lobe epilepsy from pre to post-surgical status in order to investigate neuroplasticity and recovery of memory function. Functional changes were characterized using BOLD fMRI acquisition during a scene memory encoding task. Neuropsychological testing provided a means of investigating memory function over time. Twenty patients, who were included in a prior investigation, were entered into this study before surgery, those who completed surgery (N=14) and were eligible were studied at one time-point after surgery and a cohort of those patients (N=11) were studied at an additional time-point after surgery. Fifteen controls were studied, with ten controls returning for a second scanning session. Patterns of functional activation were examined over time throughout the whole brain, as an asymmetry score between the posterior temporal lobe on the ipsilesional and contralesional side, and within the hippocampus and parahippocampus on the contralesional side. Age of onset, side of seizure and neuropsychological outcome were examined as factors contributing to neural plasticity. Subjects with a late age of onset showed declines on more neuropsychological measures than those with an early age of onset. Control HPF asymmetries remained relatively stable across time, while the subjects with TLE showed increases in asymmetry post-surgically. Whole brain activation pattern changes were evident in the posterior temporal lobes in both right and left-side seizure groups from the pre to first post-surgical

scan. The right-side seizure group showed a reversal of change in activation at the second post-surgical time-point, as well as an effect of age of onset which included medial frontal activation for the early onset group. The right-side seizure subjects consistently showed more contralateral (left-side) activation, compared to subject with left-side seizure. The HPF asymmetries became larger after surgery for both groups combined. Right and left-side seizure groups showed negative correlations between change in visual memory and post-surgical contralateral activation and positive correlations between change in verbal memory measures and post-surgical contralateral activation. Overall, subjects with TLE showed both functional and dysfunctional changes in activation from the pre to post-surgical time-points.

Introduction

Approximately 30 to 40 percent of patients with mesial temporal lobe epilepsy (mTLE) continue to have disabling seizures despite treatment with antiepileptic medicines. Surgical resection of the affected tissue dramatically improves seizure control; 60 to 70 percent of patients become free of seizures that impair awareness and about 40 percent of those patients are also free of auras (Engel et al., 2003; Wiebe, Blume, Girvin, & Eliasziw, 2001). Unfortunately, a frequent complication of resection of the mesial temporal lobe (mTL) is anterograde memory disorder or loss of ability to encode new information (Gleissner, Helmstaedter, Schramm, & Elger, 2004; Scoville & Milner, 1957; Trenerry, Jack, Cascino, Sharbrough, & So, 1996).

Presurgical evaluation includes a variety of techniques that are used to confirm seizure lateralization and attempt to predict language and memory function following the procedure (Lineweaver et al., 2006; Stroup et al., 2003). Determination of post-surgical risk for language and memory deficits allows clinicians to examine the risk-benefit ratio of undergoing temporal lobe resection (TLR). The Intracarotid Amobarbital Testing (IAT) is currently used to lateralize language and memory function by anesthetizing half of the brain and testing the other half for intact cognition (G. E. Powell, Polkey, & Canavan, 1987; Simkins-Bullock, 2000; Wada & Rasmussen, 1960). This procedure has been used for decades despite its many shortcomings, which include risk of brain injury, high cost, poor standardization, and unreliable procedures that compromise the validity of test results (Simkins-Bullock, 2000). Psychometric testing for general intelligence and

neuropsychological functioning is used to assess presurgical levels of cognitive functions and to counsel patients as to the expected cognitive outcomes following surgery.

Structural magnetic resonance imaging (MRI) and, more recently, functional MRI (fMRI) have been added to the presurgical evaluation in an attempt to improve lateralization of the seizure focus, lateralization of language and memory, and prediction of post-surgical memory outcome (Rabin et al., 2004; Richardson, Strange, Duncan, & Dolan, 2006; Stroup et al., 2003). Structural MRI measures include the quantification of hippocampal volumes to estimate hippocampal asymmetry and atrophy. Functional MRI evaluations involve measuring task-related blood oxygen level-dependent (BOLD) signal change during tasks that elicit language and memory processes.

The cognitive changes in patients with mTLE occur before the surgery, as a result of the pathological process of the epilepsy itself, and after the surgery in response to severed neuronal connections. Abnormal localization and lateralization of memory and language functions can be seen in the TLE brain (Brazdil et al., 2005; Richardson, Strange, Duncan, & Dolan, 2003). Reorganization of function is affected by hemispheric dominance, age of seizure onset, and the reduction in available healthy brain tissue (Griffin & Tranel, 2007). Differences in cortical organization between healthy subjects and patients with mTLE are evident both before and after surgery. Reorganization of function can have various behavioral results, ranging from improvement to decline in cognitive functioning (Hertz-Pannier et al., 2002; Jokeit, Ebner, Holthausen, Markowitsch, & Tuxhorn, 1996; Liegeois et al., 2004).

Looking at the plastic nature of the brain after invasive temporal lobectomy surgeries and in cases of patients with seizure disorders that require disconnection and

possibly removal of an entire cerebral hemisphere can potentially reveal the way in which the brain adapts to changes in structure. The rewiring of networks after an insult to the brain can be seen in the preservation or re-learning of functions such as memory and language. The role of the mTL in memory has been studied in patients with epilepsy and normal controls and is a prime target for studying the plasticity of a network. Since the mTL has been implicated in the formation and encoding of new memories (Squire, 1992), tasks requiring those abilities can be used to assess the integrity of the brain region pre-surgically and explore changes in response to surgical intervention.

Neuronal Plasticity and Models of Epilepsy

Plasticity at the level of the neuron can cause many changes in the route of information transfer. Long-term potentiation (LTP), axonal sprouting, synaptogenesis, neurogenesis, and synaptic remodeling are a few of the ways neurons can make new connections, increase their effectiveness, and spread their influence. These phenomena may be the result of injury, learning, or environmental or distant changes in brain structure and function. Neuronal cell injury or death may cause a response such as dendritic branching in order to avoid leaving former connections unattended. The brain's potential for making these changes may be unevenly distributed, with certain areas being more likely to exhibit such malleability. The limbic region has been found to show an increased propensity for experience-driven changes (Mesulam, 2000).

By creating models of injury to this region, such as is seen in temporal lobe epilepsy, researchers have found that the effects of the seizures themselves can create a type of "epileptic long-term potentiation" (Ben-Ari, 2001). This process can produce

axonal growth and synapse formation, which changes the threshold for further seizure activity. Through this possible mechanism, the diseased brain tissue may behave differently than the surrounding healthy tissue and change the dynamics of neuronal connections locally and at more distant locations. These changes were found to occur over a long period of time during which there was epileptic activity. The reworking of the networks may be constantly changing in a patient with active epilepsy and the functional anatomy would therefore be in flux prior to any surgical intervention. The changes in the circuitry, found by Ben-Ari (2001) were long-term alterations in synaptic patterns.

In the short-term, LTP response in the hippocampi have not been found. Patients who have a seizure focus in the hippocampus have been compared to patients with seizure foci elsewhere in the temporal lobe in order to determine if LTP occurs in the same way in each group (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000). Beck et al. (2000) found that, in the case of a hippocampal seizure focus, there was severe impairment in the ability of the synapses to modify themselves either through LTP or depotentiation. LTP induction in hippocampal tissue from patients with a hippocampal seizure focus is far less than induction from patients with extra-hippocampal focus, possibly because seizure activity has saturated the potentiation (Cooke & Bliss, 2006). The lack of response reveals a hippocampus that is responding in a dysfunctional way to stimuli. The link between the short-term effects of a stagnant hippocampus and the long-term result of "epileptic LTP", described by Ben-Ari (2001), is unclear, but may both contribute to the memory deficits found in patients with TLE. Beck et al. (2000) made a link between the decreased synaptic plasticity and declarative memory deficits that have been found in similar patient populations (Helmstaedter, Kurthen, Linke, & Elger, 1997).

The rewired networks resulting from “epileptic LTP” may be less efficient at supporting memory circuits than the networks of a normal healthy brain.

At the level of cortical organization, changes in the localization and lateralization of memory and language can be seen in brains with TLE. These changes are affected by hemispheric dominance, age of seizure onset, and the reduction in available healthy brain tissue. The plasticity at the level of the cortex is revealed through the differential organization of normal healthy subjects and patients with TLE. Recent advances in translational neuroscience have allowed for the combination of imaging with experimental physiological techniques, which reveal cortical network changes following LTP induction in rats. A recent study showed BOLD MRI changes before and after LTP-induced physiologic changes using high frequency stimulation in rats (Canals, Beyerlein, Merkle, & Logothetis, 2009). Direct stimulation was followed by a change in BOLD signal in the hippocampus proper as well as in the perirhinal cortex, prefrontal cortex, nucleus accumbens, and anterior olfactory nucleus, with higher relative potentiation in the contralateral hippocampus and entorhinal formation. The BOLD signal and physiological measures varied together and maintained a stable baseline. These findings reveal that in a healthy rat brain, local stimulation modulates synaptic weights and affects distant and bilateral hippocampal connections to subcortical and cortical structures.

A limitation in this study was disambiguating the neural plastic changes that occur as a result of years of seizure activity and changes that are a direct result of removal of the anterior temporal lobe. Post-surgical changes cannot be considered solely a result of surgery, but must be considered in the context pre-existing abnormal circuitry as described in animal models and pre-surgical studies of patients with TLE.

Memory Function and the Medial Temporal Lobe

The essential role of the mTL in memory became clear following a bilateral temporal lobe resection for the treatment of epilepsy in patient H.M. (Scoville & Milner, 1957). Following surgery, this patient had great difficulty retaining any new information. Patient H.M. maintained the ability to correctly perceive stimuli and hold information in working memory as long as he continued to perceive or rehearse the information. If he was distracted from the items, the information was lost and could not be retrieved. Milner and others concluded that perception and immediate, uninterrupted recall were not mediated by the mTL (Frisk & Milner, 1990; Pigott & Milner, 1993). However, the retention of new information, anterograde memory, required healthy, intact mTL structures, including the hippocampus. Other patients who have had less severe bilateral mTL damage, primarily restricted to the hippocampal formation, have been reported to have similar, but less severe, deficits including impairment of recognition memory (Reed & Squire, 1997; Rempel-Clower, Zola, Squire, & Amaral, 1996). Studies of animal models of the mTL structures have concluded that bilateral amygdala damage alone does not impair memory, while isolated bilateral hippocampal or parahippocampal damage leads to impairment, with more damage correlating with more dysfunction (Zola-Morgan, Squire, Amaral, & Suzuki, 1989). These findings support the central role of the mTL in memory encoding and reveals the devastating effects of mTL lesions on memory function.

Temporal Lobe Epilepsy and Temporal Lobectomy

Mesial temporal lobe epilepsy (mTLE) is most commonly associated with hippocampal sclerosis, although other lesions of the mTL and unknown etiologies can also be associated with mTLE (Engel, 1996). Non-sclerotic lesions can include tumors, scars, vascular malformations, congenital cysts, and dysplasias. Hipppocampal sclerosis is present in 60-75% of TLE cases and is characterized by neuronal cell loss in hippocampal layers CA1, CA3, CA4, the subiculum, and the dentate gyrus. These changes are detectable with MRI and appear as hippocampal atrophy and signal change on T2 images (Fuerst et al., 2001). The cause of hippocampal sclerosis is unknown, although there are numerous reports of an association between sclerosis and febrile seizures (Cendes et al., 1993; Davies et al., 1996).

The brain tissue from which the seizure originates is referred to as the "seizure focus". Patients with mTLE may have sclerosis of the left or right mTL or bilateral pathology. Some patients may also have the mTLE syndrome but not have detectable sclerosis on imaging. The sites that produce seizure represent the areas targeted for surgery and removal of these areas results in seizure reduction (Wiebe et al., 2001).

Patients with temporal lobe epilepsy experience both simple partial seizures, which preserve awareness, and complex partial seizures during which there is altered consciousness and extreme changes in behavior. Simple partial seizures may include psychic, gustatory, olfactory, and autonomic symptoms, while complex partial seizures typically include staring and automatisms, defined as stereotyped, repetitive, involuntary movement (e.g. lip smacking) followed by post-ictal amnesia (Victor, Ropper, & Adams,

2001; Wiebe et al., 2001). Two-thirds of patients also experience generalized tonic-clonic seizures.

Patients experience social, cognitive and physical difficulties as a result of the seizure disorder and eagerly seek treatment to reduce or eliminate seizure activity. A surgical treatment option is often not offered until patients have tried many pharmacotherapy treatment regimens, despite the fact that patients may benefit from resection of the mTL early in the course of the disease due to ongoing damage within the mTL and between the mTL and other brain regions. Patients who fail to respond to two trials of different antiepileptic medications are unlikely to achieve seizure freedom through pharmacotherapy (Spencer, 2002). Given the diminishing return of additional medication trials and the known psychosocial, psychological and cognitive impact of continued uncontrolled epilepsy, patients are offered the option of surgical treatment, which usually involves resection of a portion of the anterior temporal lobe (Engel et al., 2003). Surgical treatment has been shown to improve seizure control, quality of life, rates of employment and school attendance, over medication treatment alone, in a randomized control trial (Wiebe et al., 2001).

Given the positive outcomes of surgery and the impact of seizure control on all aspects of functioning, surgery is a reasonable choice for those patients who have poor seizure control. The cost-benefit analysis of surgery clearly sides in favor of surgery in many cases, although there are a significant minority of patients in whom presurgical testing does not clearly predict positive outcome for seizure control and cognitive functioning (Spencer, 2002). In addition, while seizure control is the primary outcome measure and is more easily predicted than post-surgical cognitive functioning, the

cognitive sequelae of surgery remains a major area of patient dissatisfaction (Baxendale & Thompson, 2005). Clinical decision making in these cases is more difficult and requires extensive presurgical testing. Current standard of care includes a combination of EEG monitoring, brain imaging (MRI, PET, and/or SPECT), neuropsychological testing, and the intracarotid amobarbital test (IAT) in the surgical decision-making process. These tests are reliable for predicting surgical outcome (Kilpatrick, Cook, Kaye, Murphy, & Matkovic, 1997), but not as successful in predicting the extent of possible post-operative cognitive decline (Baxendale, Thompson, Harkness, & Duncan, 2006; Davies, Bell, Bush, & Wyler, 1998). Neuropsychological testing offers the best prediction of post-operative cognitive functioning, but does not inform the model of how such change is manifested in the underlying neural networks. Examining changes in the functional imaging data from the pre to post-surgical state should improve our understanding of how measurable behavioral change takes place.

Neuropsychological Deficits in Temporal Lobe Epilepsy

Neuropsychological testing is performed prior to temporal lobectomy to measure cognitive functioning and characterize the functioning of the mTL. The behavioral performance on these tests has been used to estimate the deficits already acquired as a result of the seizure disorder, determine seizure laterality based on the asymmetry of deficits, and predict post-surgical memory functioning (Akanuma et al., 2003; Davies et al., 1998). Performance on neuropsychological batteries not only reflects the cognitive ability of the patient at the moment of testing, but also the effect of the duration and course of the seizure disorder. Earlier onset of seizure and longer duration of the seizure

disorder are associated with a decrease in neuropsychological functioning in general intelligence and language for patients with left TLE and memory for patients with left or right TLE (Fuerst et al., 2001). Additionally, a higher level of education is associated with preserved cognitive abilities over the lifetime in patients with TLE (Jokeit & Ebner, 1999).

Mesial TLE is associated with deficits in general intelligence, language, visuospatial function, and memory (Hermann, Seidenberg, Schoenfeld, & Davies, 1997). Material-specific relationships have been reported between the left mTL and verbal memory and the right mTL and visual memory (O'Brien, Bowden, Bardenhagen, & Cook, 2003). Before surgery, patients with left side seizure onset have lower verbal memory scores (Gleissner, Helmstaedter, Schramm, & Elger, 2002). Despite these reports, material-specificity of neuropsychological measures in this population does not always allow for accurate determination of side of seizure.

Pre-surgical neuropsychological testing results are associated with seizure laterality. The highest estimates report correct identification of seizure lateralization by neuropsychological testing in 80-90% of cases (Akanuma et al., 2003). More conservative estimates were published by Loring et al. (2000) using the Memory Assessment Scales (MAS; Williams, 1991). They reported that verbal and visual memory performance was significantly different for left and right TLE patients, but that correct right/left side seizure classification for individual patients was only accurate in two-thirds of cases. Discrepancies between EEG lateralization and neuropsychological findings may reflect that although seizures may start in one mTL, the effects of chronic TLE can be seen in cognitive dysfunction in both mTLs. More accurate lateralization has been found

when neuropsychological assessment is performed in the postictal period, possibly revealing a closer association between the underlying pathology and cognitive function (Pegna, Qayoom, Gericke, Landis, & Seeck, 1998).

Other factors impacting cognition in mTLE are concurrent psychiatric disorders and treatment with antiepileptic medications (Hoppe, Elger, & Helmstaedter, 2007). The impact of depression on neuropsychological performance above and beyond the baseline dysfunction in the mTLE population is unclear and may be dependent on the contribution of frontal lobe dysfunction (Helmstaedter, 2004). Medications can have an effect of neuropsychological function, particularly in the cases of polytherapy and monotherapy with zonisamide, clobazam, topiramate, phenobarbital, and clonazepam (Helmstaedter, 2004). Randomized placebo-controlled studies in normal subjects show significant effects of antiepileptic medication on neuropsychological functioning in several domains, including verbal memory, verbal fluency, and psychomotor speed (Meador et al., 1995; Salinsky et al., 2002; Salinsky et al., 2005).

Neuropsychological Deficits Following Temporal Lobectomy

Memory functioning following selective temporal lobe resection (TLR) has been studied extensively since the first report of patient H.M. described severe anterograde amnesia after bilateral removal of the mTL (Scoville & Milner, 1957). The majority of cognitive outcome studies report neuropsychological deficits for most patients after surgery, although there are some reports of cognitive improvement in some patient subgroups, which are frequently independent of post-surgical seizure control (Baxendale & Thompson, 2005; Jokeit & Ebner, 1999; O'Brien et al., 2003; Rausch et al., 2003;

Seidenberg et al., 1998; Wachi et al., 2001). Baxendale and Thompson (2005) described verbal memory decline in twice as many left TLR patients as right TLR patients and verbal memory improvement in twice as many right TLR patients as left TLR patients. Chiaravalloti and Glosser (2001) found that left TLR patients declined and right TLR patients improved on measures of verbal memory while right TLR patients declined and left TLR patients improved on measures of visuospatial memory. Material-specific changes have been shown to be a common outcome of unilateral TLR; verbal memory deficits following left TLR and visual memory deficits following right TLR (Hermann, Seidenberg, Haltiner, & Wyler, 1995). As shown by the mixed picture of improvement and decline in right and left TLR patients, a strict material-specific interpretation of right and left TL function cannot be concluded. Rather, there is a shared burden of verbal and visual memory function between the right and left TL.

Many studies use pre-surgical cognitive functioning, demographics and other pre-surgical evaluation data, such as imaging and IAT, to predict post-surgical cognitive decline. Older age at the time of surgery and left sided TLR have been associated with greater post-surgical verbal memory decline (Alpherts, Vermeulen, van Rijen, da Silva, & van Veelen, 2006; Davies et al., 1998). Pre-surgical neuropsychological functioning predicts postoperative memory performance. Some studies report that this relationship is only present in patients with left TLR while others report similar findings for right and left side TLR patients (Helmstaedter & Elger, 1998). Hermann et al. (1995) reported that better preoperative memory performance was associated with a decrease in memory performance for both right and left TLE patients. Higher pre-surgical neuropsychological scores and older age of onset were predictors of verbal recall and learning decline post-

surgically in both left and right TLE patients (Baxendale, Thompson, Harkness, & Duncan, 2007). Baxendale and colleagues (2006) also reported that higher preoperative verbal learning in right and left TLE patients predicted verbal learning decline, but that older age at time of surgery and lower pre-surgical verbal IQ added to the prediction of verbal decline only in right TLE patients. Both studies by Baxendale et al. (2006, 2007) employed reliable change indices to quantify change on the verbal memory components. They determined that patients with greater than a ten point raw score decline on the total score for a 5-trial list learning task were significantly worse than their pre-surgical cognitive state. Changes specific to the dominant TLE group were reported by Engel et al. (2003), demonstrating that good pre-operative memory functioning, older age at time of surgery and IAT asymmetry were associated with post-surgical verbal learning decline, a ten percent decline on some measures of the Wechsler Memory Scale.

Right anterior temporal lobectomy is associated with deficits in recognition and recall of visual patterns and designs, details in a visual scene, and the arrangement of objects in space (Pigott & Milner, 1993). Right mTLE patients are also slower than left TLE patients in identifying changes in visual detail (Baxendale, Thompson, & Van Paesschen, 1998). Additional lateralizing deficits include impairment on navigation and scene recognition memory in right TLE patients and impairment of memory for event details in left TLE patients (Spiers et al., 2001). The time course of post-surgical cognitive functioning does not always reveal the same pattern of change. The literature includes several long-term follow-up studies that indicate persistent verbal memory decline after left TLR, but only temporary verbal memory deficits or some improvement after right TLR (Gleissner et al., 2004; Trenerry et al., 1996). Follow-up at one year and

greater than nine years showed persistent decreases in verbal memory for left TLR patients (Rausch et al., 2003). A six-year follow-up study showed that left TLR patients experienced ongoing memory acquisition and consolidation decline for up to two years post-surgery, while right TLR patients showed initial gains in memory functioning that were not maintained over extended follow-up (Alpherts et al., 2006). The left TLR group recalled eight fewer words over five list learning trials on the "15 Word Test" (an adaptation of the Auditory Verbal Learning Test) at their two year follow-up, while the right TLR group recalled five more words six months after surgery, but only one more than their pre-surgical performance at the 2-year follow-up. The dynamic nature of post-surgical cognitive change is described through performance on neuropsychological tests, but is rarely linked to neuronal correlates through examination of post-surgical imaging studies. Combining these sources of information can add to our understanding of post-surgical recovery and cognitive decline.

Pre-surgical Reorganization of Function

Neuropsychological data and pre-surgical imaging data convey patterns of adaptation to pathological processes in the temporal lobe. In addition, there is a growing literature showing cross-modal use of brain areas for perception and cognitive functions such as Braille reading in the blind and recovery of function after stroke, which support the idea of both developmental and ongoing reorganization throughout the brain (Hamilton, Keenan, Catala, & Pascual-Leone, 2000; Sadato, Okada, Honda, & Yonekura, 2002; Saito, Otsuki, & Ueno, 2007). These studies show plastic changes required to meet a new set of functional demands. Studies in recovery of language function after a stroke

that includes cortex involved in language processing have produced mixed results. Some studies conclude that recovery of function is associated with a rightward language shift while others show detrimental effects of right-sided reorganization and behavioral improvement with intrahemispheric increase in function (Crinion & Leff, 2007; Crosson et al., 2007; Liegeois et al., 2004; Meinzer et al., 2008; Thulborn, Carpenter, & Just, 1999). Reorganization of function includes the following three views: functional, dysfunctional, and nonfunctional (Maccotta, Buckner, Gilliam, & Ojemann, 2007). A functional view assumes an adaptive response, a nonfunctional view indicates that additional activation does not interfere with or improve task-related behavior and a dysfunctional view posits that additional activation is detrimental to cognitive tasks.

Studies on recovery of function and fMRI show that language rehabilitation programs can improve language function even years after onset of aphasia resulting from a cerebrovascular event. The imaging analyses show perilesional change after training and illustrates that recovery of function is not restricted to the very young or a critical period of early language acquisition (Meinzer et al., 2008). An important difference between the studies in aphasia and the question of reorganization in TLE is that while reorganization of language function may still be dependent on the developmental level of the patients (time of the injury), mesial temporal structures that are evolutionarily older and that share memory function, may not be as constrained given a smaller degree of material specific lateralization (Helmstaedter & Elger, 1998). Given that severe language deficits are seen following only unilateral damage and severe memory deficits require bilateral damage, plastic change following TLR may be possible later in life. Additionally, while plastic changes may be possible and produce the next best network,

behavioral compensation in the case of a neurologic injury may also serve to improve cognitive function by making use of cognitive resources such as executive controls, including attention and organization.

Pre-surgical changes in neuropsychological functions and functional imaging analyses can provide insight into the brain's reorganization response to years of seizures. Reorganization is influenced by the brain maturity at the time of the injury and location, extent and bilaterality of the injury (Stefan & Pauli, 2002).

One indicator of the extent of the injury is continuation of seizures after resection. Seidenberg et al. (1997) showed that patients who have a seizure-free outcome, early age of recurrent seizures and had hippocampal sclerosis identified pre-surgically, had better memory outcome than those who either did not have sclerosis or were not seizure free. They argued that the localized pathology allowed for reorganization of memory systems, whereas resected non-sclerotic tissue led to memory decline. This still leaves open the question of whether the shift was intra- or interhemispheric. The patients with good memory and seizure-free outcome after surgery may have reorganized some of their memory function to perilesional areas or to the contralateral hemisphere prior to surgery, although the exact location is unknown without confirming imaging data. The diseased tissue may have been interfering with efficient memory function and removal allowed for improvement. Additionally, patients who had a decline in memory function and did not have sclerosis may have lost function because the resected tissue had maintained a role in memory function.

Age of onset has long been studied for its contribution to the neuropsychological profile of TLE and prediction of outcome following TLR. While early age of onset and

more years with seizures has been consistently associated with greater cognitive decline over time and increased mTL pathology, it's effect on post-surgical outcome is not as well-defined (Fuerst et al., 2001). It may be the case that subjects who acquire injury early in life have not completely lateralized language functions and have more bilateral or contralateral representation resulting in less efficient functioning over the following decades. This reorganization of function may allow for improved preservation of cognition after surgery due to functions remaining intact in the contralateral hemisphere (Griffin & Tranel, 2007). These conclusions are controversial and other studies have shown mixed results. Late onset and traditional organization of language function as assessed by IAT has been associated with poor post-surgical outcome for verbal memory and general neuropsychological functioning in several studies, while others have reported an association with improvement in visual memory (Griffin & Tranel, 2007; G. E. Powell, Polkey, & McMillan, 1985; Saykin, Gur, Sussman, O'Connor, & Gur, 1989).

Further examination of developmental age was examined by Helmstaedter et al. (1998) who showed a relationship between both pre-surgical memory and age at the time of surgery and change in verbal learning. Patients who were under 15 years of age at the time of surgery were unchanged or improved in learning and data-acquisition tasks of verbal memory. Only 65% of patients between 15 and 30 years of age had unchanged learning abilities and 61% of patients over 30 years of age showed significant decline. This result may support the notion of behavioral compensation for loss of function, which declines with age. Post-operative decline in consolidation and retrieval of information was uniform across the age groups, possibly due to the mesial temporal lobe support for these aspects of memory function that are not as dependent on a critical period of

development. In addition to age, the integrity of other verbal functions were related to outcome, with better postoperative fluency, comprehension and reasoning correlating with better verbal learning.

Detre and colleagues (1998) examined task-related BOLD signal change in the mTL during memory scene-encoding in normal controls and mTLE patients, revealing more asymmetry in the patient mTL than in the normal controls. Controls showed bilateral activation, with only slight asymmetry within the hippocampal formation, suggesting that the task was encoded as both visuospatial and verbal information and should therefore recruit bilateral areas in a normal, healthy brain. This shows bilateral involvement of the mTL during encoding, suggesting redundancy in mTL support for memory functions. The asymmetry ratios determined by fMRI have been shown to be in agreement with IAT memory laterality and show converging evidence that there are neural network changes in TLE patients prior to surgery (Deblaere et al., 2005; Detre et al., 1998). A study by Jokeit, Okujava, and Woermann (2001) used an fMRI paradigm to examine memory for familiar visuospatial knowledge of mental navigation and landmarks. Their group also investigated asymmetry in the mTL in patients with temporal lobe epilepsy and reported correct lateralization of seizure onset in 90% of patients and confirmed the lack of asymmetry in normal control subjects, again showing that cognitive functions are supported by a different distribution of networks in patients with TLE than in controls. Correcting for possible task performance differences, Richarson et al. (2003) showed that subjects with left-sided epilepsy have more activation in the right hippocampus and parahippocampal gyrus compared to controls during fMRI of subsequent verbal memory even when subjects had similar behavioral performance.

Taken together the data on memory processing prior to surgery shows reorganization of function in TLE patients.

Reorganization is also evident in language processing in TLE patients. Language shifts have been reported in the literature through pre-surgical investigation of language laterality and lesion studies. It is the use of the IAT to lateralize language that helped inform the first theories on functional reorganization in epilepsy, including reports of bilateral and right-sided representation of language (Rasmussen & Milner, 1977). Studies have shown a range of language lateralization, 63-96% left lateralized, 0-32% bilateral, and 0-12% right lateralized in epilepsy patients, although there is little basis for comparison with the normal population given the invasiveness of the IAT (Reviewed in: Springer et al., 1999).

Non-invasive functional imaging has allowed for comparative studies of language lateralization in normal and epilepsy populations and revealed clues about the ability of cognitive functions to reorganize in the context of neurological dysfunction. This non-invasive technique is already used at many epilepsy centers to lateralize language function, in addition to or instead of IAT (Binder et al., 1996; Rutten, Ramsey, van Rijen, Alpherts, & van Veelen, 2002; Woermann et al., 2003). In the investigation of language, fMRI has been demonstrated to successfully lateralize function and correlate with IAT and have good predictive power and reliability (Binder et al., 1996; Gaillard et al., 2004; Rutten, Ramsey, van Rijen, Alpherts et al., 2002; Rutten, Ramsey, van Rijen, & van Veelen, 2002). Springer et al. (1999) showed that a higher percentage of epilepsy patients had bilateral and right lateralized activation patterns on language tasks than control subjects. The effect was even greater for patients who acquired their brain injury or began

to have intractable seizures before five years of age, although there was a linear relationship between age of injury and lateralization, indicating that reorganization may be able to take place outside of a "critical period". None of the one-hundred control subjects had a right-lateralized pattern. Since this study included some cases of neocortical epilepsy it may place more emphasis on a critical period than a cohort of only TLE patients. They conclude that prior estimates of right-lateralized language, based on IAT and lesion studies, overestimate the incidence of atypical language in the normal population. The TLE population may therefore be more atypical than previously believed. Studies have suggested that the localization of seizures to more lateral and neocortical areas (sensory auras) produces atypical speech lateralization, while temporo-limbic spread was associated with typical lateralization (Janszky, Jokeit et al., 2003). One of the key benefits of using fMRI to investigate lateralization is the ability to observe patterns of laterality, instead of relying on an insensitive dichotomous measure such as right or left lateralization.

Janszky et al. (2003) showed that more patients with left TLE have language shift from the left to the right hemisphere than is present in patients with right TLE and the normal population. This represents a functional reorganization of language into the right hemisphere, which would not be predicted by stroke studies in aphasia as an optimal route of reorganization, but may reveal a difference between reorganizing function in response to a chronic condition and reorganization in response to an acute brain injury. They did not show an effect of age at onset, age at injury or gender when they restricted their population to TLE patients with circumscribed hippocampal sclerosis. An age cut-off for reorganization of function in this population may not accurately represent change

before or after surgery although age at onset contribution continues to be debated (Janszky, Ebner et al., 2003; Springer et al., 1999). Springer et al. (1999) reports in an fMRI study of TLE patients and controls that reorganization is possible well into adulthood, but that more right-sided representation of language is associated with an earlier age of onset. Brazdil et al. (2005) reported an fMRI study demonstrating both inter and intrahemispheric functional reorganization in left TLE patients on a silent word generation task in which they were given a letter and asked to generate words that begin with the letter. Intrahemispheric differences between controls and patients included less activation in Broca's area (BA 44 and 45) and interhemispheric differences included less activation of the right middle frontal gyrus in left TLE patients. They also showed more bilateral distribution of language with a lower age of seizure onset.

Left TLE patients showed less left and greater right-sided activation and right TLE patients showed less right and greater left-sided activation on several cognitive tasks compared to controls (H. W. Powell et al., 2007). They also showed that more activation in the damaged left hippocampus correlated with better verbal memory scores, while greater activation in the damaged right hippocampus correlated with better nonverbal memory performance. This is in line with a dysfunction view of reorganization, where more activation contralateral to the lesion is associated with worse performance.

Post-surgical Reorganization of Function

Assessment of changes after surgery becomes complicated by the traumatic effect of the surgery itself and the absence of a clinical need for IAT procedures. fMRI and other imaging techniques are helping to create the emerging picture of how the post-

surgical brain reacts, adapts and reorganizes itself in response to the surgical lesion. Much of the study of changes after surgery for TLE focused on the impairment and recovery of language. Language is unique in its almost complete lateralization of function to the left hemisphere in the normal population (Springer et al., 1999). The ability of one part of the brain to take over the function of another is therefore most clearly demonstrated in the recovery of language function after hemispherectomy.

Language transfer from one hemisphere to the other due to syndromes such as Rasmussen's encephalitis has been shown through improvement in language functioning on neuropsychological tests and interhemispheric reorganization on fMRI (Loddenkemper, Wyllie, Lardizabal, Stanford, & Bingaman, 2003). Conventional practices have confined hemispherectomy surgeries to children under the age of six until recently, for fear of not recovering language function in the remaining hemisphere after the presumed critical age of language acquisition. Language transfer has been documented as late as age fifteen in patients who were treated for their seizures with hemispherectomy of the language-dominant hemisphere (Loddenkemper et al., 2003). A case of serial fMRI performed pre- and post-hemispherotomy in a nine-year old child revealed left-hemisphere dominance for language pre-surgically and right-hemisphere support of language post-operatively, suggesting inter-hemispheric reorganization (Hertz-Pannier et al., 2002). Right hemispheric activation was in the same regions as the pre-surgical left hemispheric activation, predominantly inferior and middle frontal gyri and supplementary motor area. This was the first time pre and post-surgical data could be compared in a child who had already completely developed left-lateralized language. The authors suggest a hypothesis of disinhibition of pre-existing networks, which take over

the language function when the preferred left-sided network is no longer intact, supporting a functional view of reorganization.

Case studies of patients with lesions have revealed individual changes in various areas of cognition where cohort studies may not be feasible given the low incidence and variability of the lesion sites and sizes. A case study of a patient with a seizure focus in the right parietal lobe used fMRI to show reorganization of spatial functions from right to left parietal regions. The patient showed more activity than normals in regions contralateral to the resected right parietal lobe during three spatial reasoning tasks (Zacks, Michelon, Vettel, & Ojemann, 2004). Performance was qualitatively similar, but he was slower and more prone to error. This subject acquired his injury at twenty-nine years of age, indicating that plastic changes can occur well into adulthood.

Post-surgical changes (calculated using reliable change indices) were also examined in three left-sided TLE patients who had a pre-surgical pattern of cognitive function resembling a shift of function to the right hemisphere (Gleissner, Helmstaedter, & Elger, 2002). These patients showed extreme nonverbal memory deficits and relatively preserved verbal memory prior to surgery. IAT testing revealed right-sided language dominance in two patients and left-sided language dominance in the third patient. After left-sided temporal lobe surgery, the patients all had a significant improvement in nonverbal memory. Additionally, the patient with left-sided language dominance did not become amnestic after the left-sided surgery, revealing that there was probably a pure memory shift, dissociated from the rest of her verbal abilities. Such a remarkable change in the nonverbal memories of the patients reveals a plasticity of the remaining temporal lobe to take on new functions. The patients were all past adolescents and well beyond the

age at which functional reorganization is typically thought to occur (Marcotte & Morere, 1990; Woods & Carey, 1979). This is contrary to earlier reports, which claimed that memory in the left hemisphere can remain intact after right-sided temporal lobe damage at any age, but that the right hemisphere can only support memory if left-sided temporal lobe damage occurs at an early age (Jokeit et al., 1996). The findings of Gleissner, Helmstaedter, and Elger (2002) indicate that although aging and brain maturation may play some role in the ability of the brain to rewire itself after surgery, a patient past adolescence may still be able to regain memory or language function through cortical plasticity.

Very few group studies have used imaging to examine the response of neural systems to temporal lobe resection. One such study examined post-surgical imaging and reading skills. Normal reading ability after surgery is associated with activation patterns in the left middle temporal gyrus that approximates normal patterns. This included activation in both normals and patients in regions in the right hippocampus and right inferior temporal sulcus that were only present in subjects who had normal reading (Noppeney, Price, Duncan, & Koepp, 2005). Patients with better reading also recruited the right inferior frontal gyrus during the reading task, an area not involved in reading in normal controls. The recruitment of normally functioning tissue plus the addition of the right inferior frontal gyrus is associated with improved language skills and together supports a functional view of reorganization.

The only group study to date to examine pre-surgical and post-surgical fMRI data looked at word and face classification tasks and incidental memory in a cohort of 24 patients before surgery and 17 of those patients following surgery. They found that left

TLE patients had bilateral frontal activation during the language task pre-surgically and showed a change to a more lateralized (left > right) activation pattern post-surgically, which resembled the control group activation pattern (Maccotta et al., 2007). The lack of decline on cognitive measures led to the conclusion that the additional activation did not interfere with the normal network and was therefore not in line with the dysfunctional view of reorganization.

Very few studies have investigated cortical plasticity of higher order cognitive functions in adults or memory reorganization in any population. The mounting evidence of neuroplasticity in increasingly older children and adolescents suggest that investigations of adult neuroplastic changes related to temporal lobe resection are the logical next step in investigating both memory recovery in TLE and the neuroplastic process after TL resection.

Study Aims and Hypotheses

Aim 1: Investigate whole brain changes in BOLD signal from the pre to post-surgical session.

Hypothesis 1: The contralesional hemisphere will show greater activation and the ipsilesional hemisphere will show less activation post-surgically in patients who decline on neuropsychological measures, specifically these changes will be observed in the temporal lobes and the prefrontal regions.

Hypothesis 2: Early age of onset will be associated with less change following surgery.

Aim 2: Examine changes within the contralesional hippocampus, parahippocampus and hippocampus, parahippocampus and fusiform (HPF) region from the pre to post-surgical session.

Hypothesis 1: An increase in activation in the contralateral hippocampus ,parahippocampus, and HPF will be associated with late age of onset and decline in neuropsychological measures that match the material-specificity, of the resected side, verbal memory for left-sided seizure and visual memory for right-sided seizure.

Aim 3: Compare asymmetry of BOLD activation within the perilesional regions of the temporal lobe from the pre- to post-surgical scan.

Hypothesis 1: An increase in asymmetry in perilesional regions, with contralateral activation greater than ipsilateral activation, will be associated with late age of onset.

Hypothesis 2: An increase in asymmetry, with ipsilesional activation greater than contralesional activation, will be associated with an improvement in neuropsychological measures that match the material-specificity of the resected side (e.g.: for left TLE patients, an increase in perilesional activation in the left TL compared to contralesional activation in the right TL will be associated with improvement in verbal memory).

Aim 4: Investigate the presence of ongoing post-surgical neuronal plasticity by comparing two post-surgical fMRI scans in a small cohort of the total enrolled participants in order to determine whether neuronal plasticity can be demonstrated to be an ongoing post-surgical process.

Hypothesis 1: BOLD activation changes will be observed between the first post-surgical scan and the second post-surgical scan if there is demonstrated change in memory. Specifically, changes observed in Aim 2 and 3 are expected to be observable between time-point 2 and 3.

METHODS

Participants

Twenty patients with refractory nonlesional or lesional TLE undergoing presurgical evaluation for temporal lobectomy were recruited from the Penn Epilepsy Center at the Hospital of the University of Pennsylvania and the Comprehensive Epilepsy Center at Thomas Jefferson University. A combination of clinical MRI findings, EEG, IAT, and neuropsychological testing was used to lateralize the side of seizure. Patients with brain tumors, traumatic brain injuries, and vascular lesions involving the temporal lobe, extratemporal epilepsy, prior temporal lobectomy, or contraindications to MRI were excluded. Patients with severe mental retardation who were likely to be unable to cooperate with the MRI examination were also excluded. All patients who undergo temporal lobectomy receive routine clinical follow-up at one month and between six and twelve months. Clinical outcome of seizure control between six and twelve months post-surgically was collected. Age of seizure onset was used to stratify subjects into an early and late age of onset group. The early onset (EO) group was defined by onset of continuous seizures at or before age nine and the late onset (LO) group was defined by onset of continuous seizures after age nine, in accordance with the use of this variable in the epilepsy literature (Griffin & Tranel, 2007). The post-surgical imaging component included the subset of patients who underwent surgery and agreed to return for post-surgical follow-up. Fourteen patients returned for a post-surgical scanning session and eleven of those patients returned for a second post-surgical scanning session.

Fifteen control subjects were recruited from the University of Pennsylvania community. Ten subjects returned for a second scanning session in order to determine the

reliability of the task related BOLD signal over time. Three subjects were excluded due to interscan differences that did not allow for a direct comparison of the reliability of the BOLD data. Subjects with a history of neurologic illness, psychiatric disorders or contraindications to MRI were excluded. Neuropsychological testing was not performed with control subjects since adequate normative data exists for comparison with the patient population.

Neuropsychological Testing

A complete neuropsychological battery was completed pre-surgically and provides baseline full-scale IQ from the Wechsler Adult Intelligence Scale III (WAIS-III; Psychological, 1997). Visuospatial memory functioning was examined using pre- to post-surgical change scores from the Visual Reproduction subtest of the Wechsler Memory Scale III (WMS-III) as well as the Faces subtest of the Warrington Recognition Test. Verbal memory functioning was examined using pre to post-surgical change scores from the Logical Memory subtest of the WMS-III and the California Verbal Learning Test-Version II (CVLT-II). The Beck Depression Inventory – II (BDI-II) was used to assess for the presence of depressive symptoms pre and post-surgery. Change scores were examined using paired samples t-tests.

Structural and Functional MRI Data Acquisition

All MRI scanning was carried out using protocols approved by the University of Pennsylvania and Drexel University Investigational Review Boards (IRB), and all subjects provided their informed consent to participate. The only absolute

contraindications to MRI studies are the presence of intracranial or intraocular ferrous metal, or a pacemaker.

Imaging was conducted on a 3T Siemens Trio MRI scanner (Siemens, Germany) using a product T/R head coil. High-resolution anatomical MRI scans with voxel sizes of 0.9766 x 0.9766 x 1mm were collected both for volumetric measurement and for localization of functional data.

Standard gradient-echo echoplanar (EPI) imaging was used for blood oxygenation level dependent (BOLD) contrast. The Siemens platform provides a gradient-echo EPI sequence with prospective motion correction capable of whole-brain coverage with 3 mm isotropic voxels at TR=3 sec and TE=30 msec. The use of high voxel resolution reduces dephasing due to static susceptibility gradients, improving the detection of dynamic susceptibility changes (BOLD contrast) in the mTL.

The fMRI Memory Task

Memory for complex scenes was assessed using a block-design experiment, with novel visual scenes alternating with a control scene (Figure 1). Scenes were selected from the Photodisc® archive to be difficult to encode using an exclusively verbal strategy. A single scene of random noise was shown during the control condition. Subjects were instructed to remember the novel scenes for a subsequent recognition test, and to passively view the control scene. Subjects performed a self-paced forced-choice recognition task after stimulus presentation, indicating whether or not they had previously viewed the target scene. Memory function was calculated using a discrimination score for the scene recognition task, which was defined by the Two-High Threshold Theory. The

memory score equals the number correct divided by the total possible correct minus the number of false positives divided by the total possible false positives (Snodgrass & Corwin, 1988).

Following surgery, fourteen subjects returned to complete the post-surgical scene memory task and scan, followed by the recognition test. The post-surgical testing included an alternative version of the complex scene-encoding stimulus in order to avoid practice effects. Change in discrimination score from pre to post-surgery was calculated as an index of memory outcome. A subset of the control subjects also completed a second scan. Additionally, eight of the patients returned for a second post-surgical scanning session. The first scan for the control group and the pre-surgical scan is referred to as time point 1 (TP1), the second scan for the control group and the post-surgical scan is referred to as time point 2 (TP2). The second post-surgical scanning session for the patients is referred to as time point 3 (TP3).

The scene memory task includes seven blocks of novel, complex visual scenes that were alternated with seven blocks of a control (scrambled) scene. Novel visual scenes were presented for 3600ms, with a 400ms interstimulus interval, for 9 scenes per 36-second block, for a total of 63 images. Stimulus presentation was performed during BOLD scanning and the recognition test was performed in the scanner. No image acquisition occurred during the recognition test.

The behavioral task paradigm was implemented in E-prime (Psychology Software Tools, Pittsburgh, PA) running on a PC laptop. Responses made in the scanner were recorded using a fiberoptic response system (FORP; Current Designs, Philadelphia PA). The FORP also provides a trigger pulse at the beginning of each scanner TR for

synchronization of the task with scanning. Images were projected onto a video screen that the subject sees using a mirror mounted on the head coil.

Structural and Functional Data Processing

The hippocampal (Figure 2), parahippocampal (Figure 3), and HPF (Figure 4) ROIs were manually segmented in SNAP on an epilepsy template or control template and implemented in Insight Toolkit (ITK) (Yushkevich et al., 2006). Prior studies of scene memory encoding in the TLE population have examined an HPF region of interest (Rabin et al., 2004). The hippocampal ROI was manually determined from structural MRI by two raters with training provided by a neuroradiologist and an epileptologist. Anatomical boundaries were determined using published guidelines (Jack, Theodore, Cook, & McCarthy, 1995; Watson et al., 1992). Neuroanatomical atlases were used to verify boundaries during segmentation (Duvernoy, 2005; Mai, 2003). Coronal, axial and sagittal planes were used to perform all segmentations and were used continuously as references to distinguish and confirm the anatomical boundaries and landmarks in three-dimensional space in consecutive slices.

The fMRI data was analyzed using Statistical Parametric Mapping (SPM5) software (Friston et al., 1995). Data were motion corrected based on the rigid-body transformation, coregistered to the structural image, and smoothed with an isotropic 6mm Gaussian kernal. For whole brain comparisons (Aim 1), data were normalized into a standard spatial reference frame. Post-surgical normalization was conducted in collaboration with the Penn Image Computing and Science Lab, whose members have been working with this data set and have developed normalization techniques to take into

account abnormal brain structure. A simple boxcar function was used to perform the cognitive subtraction analysis. Statistical parametric maps of activation associated with complex scene encoding was generated for each patient using a general linear model.

Whole Brain Analyses

Visual inspection of whole brain activation for the task minus the baseline for the patient and control groups was compared at time points one and two. The whole brain activation maps for task minus control were compared using a repeated-measures ANOVA with a between-subject factor. The within subject factor was defined as the change in BOLD signal before and after surgery and the between subject factor was age of onset. Right and left side seizure subjects were compared separately. In addition, maps representing paired t-tests of the change in BOLD signal from pre to post-surgery were produced for the right side seizure group and left side seizure group.

Region of Interest Analyses

The contralateral hippocampal, parahippocampal and HPF ROIs were used to restrict the functional maps to the area of interest. Activation was quantified by the percentage of suprathreshold voxels in the region for the pre-surgical and post-surgical scans. A change scores from the pre to post-surgical time-points was calculated for use in some analyses. A 2-way mixed model ANOVA compared the change in activation across side of seizure and age of onset. The relationship between the post-surgical activation and change in neuropsychological outcome was examined with correlation analysis.

Asymmetry Analyses

Prior studies of scene memory encoding in the TLE population examined a region of interest that included the hippocampus, parahippocampal gyrus, and fusiform gyrus (Rabin et al., 2004). A modified ROI was created by removing the portion of the ROI that fell within the area of resection on the post-surgical scan (Figure 5). A conservative estimate of the resection area was used bases on the subject with the most extensive resection. That modified ROI was used to extract the suprathreshold voxels on the ipsilesional and contralesional side to create an asymmetry ratio (AR) for the pre-surgical and post-surgical time points. The AR was calculated by subtracting the ipsilesional side (I) from the contralesional side (C) and dividing by the sum of the ipsilesional and contralesional sides [(C-I)/(C+I)]. A 2-way mixed model ANOVA compared the pre and post-surgical ARs across age of onset and side of seizure. The relationship between the post-surgical activation and change in neuropsychological outcome was examined with correlation analysis.

Power Considerations

The low subject enrollment in this study may result in unstable correlations between variables. There is little data on power analyses applied specifically to functional imaging. Some groups report calculations that require a pilot sample of the experimental paradigm in order to calculate the appropriate group size for sufficient power (Hayasaka, Peiffer, Hugenschmidt, & Laurienti, 2007). If a power analysis were conducted, the estimation of the effect size would dependent on two types of variability, the within scan variability from one scan point to the next, and the between-subject variability, which

addresses the ability of the task to produce a signal change (Desmond & Glover, 2002). According to Desmond and Glover (2002), a mean percent change signal change across subjects and inter-subject variability of 0.5% would require eleven to twelve subjects in order to obtain 80% power at $\alpha = 0.05$.

Results

Subject Characteristics

There were no significant differences between patients with right and left side seizures for age, years of education, and years with seizures (Table 2). The intracarotid amobarbital test (IAT) lateralized memory to the contralesional side for four of the subjects with right-sided seizures and five of the subjects with left-sided seizures. IAT data was unavailable or incomplete for five subjects. Seizure outcome was rated using the Engel classification, which designates the presence of seizures and improvement (Engel, Van Ness, & Rasmussen, 1993). Nine subjects were classified as Engel Class I indicating freedom from disabling seizures, three subjects were classified as Engel Class II indicating the presence of rare disabling seizures, and two subjects were classified as Engel Class IV indicating no worthwhile improvement. All subjects were on anti-epileptic medication prior to surgery. Following surgery, medication regimens were altered over time, typically reducing dosages and discontinuing some medications. Data on medication regimens and dosages at each post-surgical follow-up were not available for all subjects and were therefore not included in analyses. There were no significant differences between the right and left side seizure groups on the time delay to post-surgical neuropsychological follow-up [$t(12)= -0.208$, $p=0.839$], the first post-surgical fMRI study (TP2) [$t(12)= -0.227$, $p=0.824$] and the second post-surgical fMRI study (TP3) [$t(9)= -0.538$, $p=0.603$]. In addition, the months to follow-up was not significantly different [$t(26)=0.860$, $p=0.397$] for the months to neuropsychological testing ($M = 9.57$, $SD = 7.4$) and the months to the first post-surgical study ($M = 7.57$, $SD = 4.5$).

Neuropsychological testing was not completed twice post-surgically. The second post-surgical time-point was on average, 17 months post-surgery (M = 17.55, SD = 7.8).

Behavioral Data: Scene Memory Task and Neuropsychological Measures

Recognition memory performance on the scene memory task for trials presented during scanning was examined for patients, pre and post-surgery and controls (Table 3). A one-way ANOVA showed no difference between pre-surgical performance for right and left-sided seizure patients and controls [$F(2,28)=1.523$, $p=0.237$]. There was a significantly different performance for post-surgical right and left-sided seizure patients and controls [$F(2,28)=6.066$, $p=0.007$]. Tukey's post-hoc tests revealed lower performance for both right ($p=0.014$) and left-sided ($p=0.04$) seizure patients compared to controls.

Intelligence scores, based on the WAIS-III, were within the Low Average to Average range for the full-scale IQ (M = 97.00, SD = 16.6), verbal IQ (M = 96.57, SD = 16.2), and performance IQ (M = 96.36, SD = 16.9). Neuropsychological measures pre and post-surgery were compared using paired samples t-tests. Measures were examined separately for right and left-sided seizure patients and included tests of visuospatial memory, Visual Reproduction-WMS-III (VRI, VRII) and Faces-Warrington Recognition Test, and verbal memory, Logical Memory-WMS-III (LMI, LMII), California Verbal Learning Test – Version II (CVLT-II).

Standardized scores for performance on neuropsychological measures characterize the cognitive state of the sample before surgery. The WMS-III Visual Reproduction and Logical Memory measures are reported as scaled scores (M=10,

SD=3), the Warrington Recognition Test is presented as qualitative descriptions based on percentile ranges, the CVLT-II total learning score is presented as T-scores (M=50, SD=10), and the CVLT-II short and long delay scores are presented as z-scores. For subjects with right-side seizures, visual memory measures of design memory were in the Low Average to Average range [VRI: M=9.5, SD=3.1; VRII: M=9.3, SD=2.3] and facial recognition ranged from the Low to High Average range, with the majority of subjects scoring in the Average range. On measures of verbal memory, subjects with right-side seizures scored in the Low Average to Average range on story memory [LMI: M=9.3, SD=2.7; LMII: M=9.5, SD=2.1] and list learning [CVLT-II, Total: M=48.6, SD=9.7; Short Delay: M= -0.43, SD=1.2; Long Delay: M= -0.86, SD=1.3]. For subjects with left-side seizure, visual memory measures of design memory ranged from Borderline to Average [VRI: M=6.7, SD=4.2; VRII: M=8.1, SD=2.2] and facial recognition ranged from the Below Average to High Average range, with the majority of subjects scoring in the Average range. On measures of verbal memory, subjects with left-side seizures scored in the Borderline to Average range on story memory [LMI: M=6.9, SD=4.7; LMII: M=7.0, SD=3.5] and list learning [CVLT-II, Total: M=45.6, SD=17.7; Short Delay: M= -1.1, SD=2.1; Long Delay: M= -1.1, SD=2.1].

Subjects with right and left sided seizures had significant declines on measures of verbal memory, specifically several CVLT-II measures. They declined on initial learning [R, $t(6)=2.772$, $p=0.032$; L, $t(6)=5.303$, $p=0.002$], total learning [R, $t(6)=2.944$, $p=0.026$; L, $t(6)=2.598$, $p=0.041$], and short delay recall [R, $t(6)=2.500$, $p=0.047$; L, $t(6)=2.386$, $p=0.05$]. There were no significant changes in level of depression from the pre to post-surgical time-point.

Performance on neuropsychological measures was also compared for subjects with early and late ago of seizure onset. For subjects with an early age of onset, there was a significant decline in only one measure, initial learning on the CVLT-II [t(6)=4.044, p=0.007]. Subjects with a late age of onset showed declines on four scores on the CVLT-II, initial learning [t(5)=2.739, p=0.041], multiple-trial learning [t(5)=4.663=p=0.006], total learning [t(5)=3.630, p=0.015], and short delay recall [t(5)=3.227, p=0.023].

Patient and Control Neuroimaging Data

Patients and controls were compared on neuroimaging data, at the pre-surgical and the post-surgical sessions. A left-right asymmetry ratio was calculated for controls and both contralateral-ipsilateral and left-right asymmetry ratios were calculated for patients to compare region containing the hippocampus, parahippocampus, and fusiform gyrus (HPF). Contralateral-ipsilateral asymmetry was used for comparing patient and control groups, while left-right asymmetry was used to display differences between right and left-side seizure groups. HPF regions for controls included the entire region, while the HPF region for patients was modified to exclude the area of resection as described above. A two-way mixed model ANOVA did not show a session by group interaction [F(1,19)=1.899, p=0.184]. There was no main effect of group, collapsed across the two time-points [F(1,19)=0.752, p=0.397]. There was a main effect for session [F(1,19)=5.837, p=0.026], with a greater magnitude of asymmetry at the second time point. In order to determine if the control or patient group contributed more to the session effect, a repeated measures t-test was performed for each group. The controls did not have a significant change across sessions [t(6)= -1.66, p=0.148]. The patient group had a

more positive asymmetry at the post-surgical time-point [t(13)= -2.783, p=0.016], indicating more contralateral and less ipsilateral activation. Comparing the left-right asymmetries between the right and left-sided seizure patient groups, there was no significant difference at the pre-surgical time-point [t(12)= -0.424, p=0.679], but at the post-surgical time-point, right-sided seizure patients had more positive asymmetries [t(12)=3.01, p=0.011], indicating greater left-side activation and left-side seizure patients had more negative asymmetries, indicating greater right-side activation.

An additional post-hoc analysis of the unmodified HPF asymmetry at TP1 was conducted to examine the entirety of the region prior to surgery (Figure 8). A one-way ANOVA showed significant differences [F(2,10)=12.887, p<0.001]. Tukey's post-hoc tests revealed greater asymmetry with left greater than right activation in the right-side seizure group (p<0.001) than in the control group. The left-side seizure patient group also had greater asymmetry than the control group (p=0.005) with left greater than right activation.

Whole Brain Analyses (Aim 1 and 4)

Whole brain maps of right and left-side seizure patients at the pre and post-surgical time-points are included in Figures 9 through 16. Visual inspection showed some differences in the areas of activation. For subjects with right-side seizures, there was less overall activation at the first post-surgical time-point compared to the pre-surgical time-point, including in the posterior temporal lobes, followed by an increase in overall activation at the second post-surgical time-point, again including the posterior temporal lobes. For subjects with left-side seizures, there was less overall activation at the first

post-surgical time-point compared to the pre-surgical time-point, including in the posterior temporal lobes. The group map at the second post-surgical time-point yielded a map which contained small clusters of activated voxels throughout the brain which did not appear to represent a pattern of activation as was evident in the group maps at the pre-surgical and first post-surgical time-points. Therefore the maps from the second post-surgical time-point were not comparable to the other time-points. Whole brain repeated-measures analyses comparing pre and post-surgical time-points did not produce a map of activated voxels even with a low statistical threshold and without correcting for multiple comparisons. Therefore the comparison did not yield interpretable activation maps. Additionally, whole brain maps of only the subjects who participated in the second post-surgical scan were examined at the pre-surgical and first post-surgical time-points (Figures 12 and 16). Visual inspection revealed similar decline in activation for the right-side seizure group, but less decline was evident for the left-side seizure group.

The effect of early and late seizure onset on whole brain activation was examined separately at the pre-surgical and post-surgical time-points. Visual inspection showed some differences in the areas of activation. For subjects with right-side seizure, early onset was associated with a greater extent of activation, with more involvement of superior and anterior brain areas, including medial frontal areas, both at the pre-surgical and post-surgical time-points (Figures 17 and 18). For subjects with left-side seizure, early onset was associated with a slightly greater extent of activation at each time-point, but the difference was minimal (Figures 19 and 20).

Contralateral Hippocampus, Parahippocampus and HPF ROI Analyses (Aim 2 and 4)

The effects of age of onset and side of seizure on the change in contralateral hippocampal and parahippocampal activation were examined separately with two-way mixed model ANOVAs. Change from TP1 to TP2 and TP2 to TP3 were examined separately.

Statistical values for change from TP1 to TP2 are included in Tables 7 and 8. There were no within-subject effects for change in activation between TP1 and TP2, between-subject effects for differences in activation between age of onset or interaction effects for session and age of onset within the contralateral hippocampus. There were no within-subject effects for change in activation between TP1 and TP2, between-subject effects for differences in activation between age of onset or interaction effects for session and age of onset within the contralateral parahippocampus. There were no within subject effects for change in activation between TP1 and TP2 or interaction effects for session and side of seizure within the contralateral hippocampus, although there was a between-subjects main effect for differences in activation between subjects with left and right-side seizures within the parahippocampus [$F(1,9)=11.318$, $p=0.006$]. Subjects with right-side seizure disorder had more contralateral parahippocampal activation than subjects with left-side seizures pre-surgically [$t(12)=4.876$, $p<0.001$] and trended toward significantly more activation post-surgically [$t(12)=1.953$, $p=0.075$].

There were no within-subject effects for change in activation between TP1 and TP2, between-subject effects for differences in activation between age of onset or interaction effects for session and age of onset within the contralateral HPF. There were no within subject effects for change in activation between TP1 and TP2 or interaction

effects for session and side of seizure within the contralateral HPF region, although there was a between-subjects effect for difference in activation between subjects with left and right-side seizures within the HPF [$F(1,12)=20.637$, $p=0.001$]. Subjects with right-side seizure had more contralateral HPF activation than subjects with left-sided seizure pre-surgically [$t(12)=7.922$, $p<0.001$] and post-surgically [$t(12)=2.466$, $p=0.030$].

Statistical values for change from TP2 to TP3 are included in tables 9 and 10. There were no within-subject effects for change in activation between TP1 and TP2, between-subject effects for differences in activation between age of onset or interaction effects for session and age of onset within the contralateral hippocampus, parahippocampus, or HPF region. There were no within-subject effects for change in activation between TP1 and TP2, between-subject effects for differences in activation between subjects with left and right-side seizures or interaction effects for session and side of seizure within the contralateral hippocampus and parahippocampus. There were no within subject effects for change in activation between TP1 and TP2 or interaction effects for session and side of seizure within the contralateral HPF region, although there was a between-subjects main effect for differences in activation between subjects with left and right-side seizures within the HPF region [$F(1,9)=6.970$, $p=0.027$]. Subjects with right-side seizures had more contralateral HPF activation than subjects with left-side seizures at both post-surgical time-points [TP2: $t(12)=2.466$, $p=0.030$, TP3: $t(12)=7.922$, $p<0.001$].

Correlations among neuropsychological measures are included in Tables 11 and 12. The mean and standard deviations for neuropsychological performance at the pre and post-surgical time-points are included in Table 4. For subjects with right-side seizures,

change in recognition memory for faces was negatively correlated with post-surgical contralateral hippocampal activation (r= -0.769, p=0.043) (see Figure 21). Change in immediate story memory was correlated with post-surgical contralateral hippocampal (r=0.856, p=0.014), parahippocampal (r=0.924, p=0.003), and HPF activation (r=0.917, p=0.004). In addition, change in delayed story memory was correlated with post-surgical contralateral hippocampal activation (r=0.828, p=0.021).

For subjects with left-side seizures, change in immediate design memory was negatively correlated with post-surgical contralateral hippocampal activation (r= -0.881, p=0.009). Change in delayed story memory was correlated with post-surgical contralateral hippocampal (r=0.850, p=0.016) and parahippocampal activation (r=0.775, p=0.041) (see figure 22). Several measures of list learning were correlated with post-surgical contralateral hippocampal and parahippocampal activation, including trial 5 (H: r=0.938, p=0.002, PH: r=0.897, p=0.006), total learning (H: r=0.888, p=0.008, PH: r=0.833, p=0.020), short-delay recall (H: r=0.761, p=0.047, PH: r=0.780, p=0.039), and long-delay recall (H: r=0.783, p=0.037; PH: r=0.759, p=0.048).

Modified HPF Asymmetry Analyses (Aim 3 and 4)

The effects of age of onset and side of seizure on the change in modified HPF asymmetry ratios were examined separately with two-way mixed model ANOVAs. Change from TP1 to TP2 and TP2 to TP3 were examined separately.

Statistical values for change from TP1 to TP2 are included in tables 7 and 8. There was an overall within-subject effect for change in activation between TP1 and TP2 for the HPF asymmetry ratio [F(1,11)=7.151, p=0.022], but no between-subject effects of

age of onset or interaction between session and age of onset for the HPF AR. Comparison of the TP1 and TP2 HPF asymmetry ratios with a paired t-test showed greater asymmetry, contralateral greater than ipsilateral activation, at the post-surgical time-point than at the pre-surgical time-point [$t(13)= -2.783$, $p=0.016$]. In addition to the within-subject effect described above, there was a between subjects main effect of side of seizure for the HPF AR [$F(1,12)=8.648$, $p=0.012$]. Post-hoc t-tests of the mean differences at the pre and post-surgical time-points revealed that subjects with right-side seizure disorder had a negative asymmetry ratio and subjects with left-side seizures had a positive asymmetry ratio at the pre-surgical time-point [$t(12)= -3.754$, $p=0.003$]. There was no difference between groups at the post-surgical time-point [$t(12)= -1.143$, $p=0.275$].

Statistical values for change from TP2 to TP3 are included in tables 9 and 10. There were no within-subject, between-subject or interaction effects for age of onset or side of seizure and HPF AR between the two post-surgical time-points.

There were no correlations between change in neuropsychological measures and post-surgical asymmetry ratio at either post-surgical time-point.

Discussion

This study examined the effects of surgical intervention for mesial temporal lobe epilepsy on the neural systems underlying memory encoding. The longitudinal design allowed for within subject comparisons (N=14) of BOLD activation before and after removal of the anterior temporal lobe. In addition, 11 subjects returned for a second post-surgical scan to examine on-going effects during the post-surgical period. Group differences between subjects with right and left-side seizure and subjects with an early or late age of seizure onset were examined before and after surgery. In addition, the relationship between BOLD activation patterns and changes in neuropsychological performance was examined to address the question of functional, dysfunctional or nonfunctional changes (Maccotta et al., 2007).

The cognitive status of the sample included in this study was similar to prior reports of subjects with TLE (Hermann et al., 1997). The subjects with right-side seizures had Low Average to Average visual and verbal memory performance, an overall higher level of performance than subjects with left-side seizures. Those subjects with left-side seizures showed greater variability in performance and more overall impairment in verbal memory, ranging from Borderline to Average performance.

There were significant pre to post-surgical declines in verbal memory measured by list learning, including initial learning, learning over repeated trials, and short delay recall. The declines were significant for subjects with right and left-side seizures. Subjects with an early age of seizure onset declined on initial list learning, while those

with a late age of onset declined on initial list learning, learning over repeated trials, and short delay recall. The presence of greater declines in the late age of onset group is consistent with the finding of other studies indicating more cognitive decline following surgery for those patients whose seizures began later in life (Baxendale et al., 2007). Recognition memory for the scene memory task presented during the fMRI scan revealed differences between patient and control groups and between subjects with right and left-side seizure. Subjects with both right and left-side seizure performed worse than controls on the recognition memory test for the scene memory task following surgery, but not before surgery.

In order to establish the usefulness of repeated BOLD fMRI scans in detecting change across time, subjects with TLE were compared to controls who were scanned at multiple time-points. Right and left-side seizure subjects did not differ from controls on asymmetry ratios within the modified HPF region at the first time-point. At the second time-point, right and left-side seizure subjects differed from each other with more pronounced lateralization with the contralateral side greater than ipsilateral. The left-side seizure subjects were significantly more asymmetric than controls. As expected, control asymmetry remained relatively stable across the two time-points. This finding suggests that the patient group behaved differently than controls over time. Future studies with larger samples may determine the reliability of activation patterns in a healthy control group and in a non-surgical patient group. It is notable that the pre-surgical mean for the right-side seizure group was negative, reflecting more right-side than left side activation. This finding was unexpected given prior reports of lateralizing HPF asymmetry in a previous study from which this sample was drawn and is attributable to the modified

region that only included the posterior aspects of the HPF region (Mechanic-Hamilton et al., 2009; Rabin et al., 2004). Examination of the whole HPF region pre-surgically revealed the expected lateralization in the right-side seizure group to the left side, although the left-side seizure patients did not show a similar lateralization to the contralateral side. The left-side seizure patients had a greater range of activation asymmetry, which may have contributed to this result. The posterior and anterior aspects of the hippocampus have been found to process information differently, with the anterior aspects performing relational processing and the posterior aspects processing novelty (Binder, Bellgowan, Hammeke, Possing, & Frost, 2005). Such differences in processing may contribute to the lateralization difference found with the whole HPF region compared to the modified HPF region, which includes only the posterior aspects of the mesial temporal lobe.

Group analyses of right and left-side seizure subjects at each time point were employed to determine the presence of global changes in activation patterns. Visual inspection of whole brain activation showed decreases in overall activation from the pre-surgical to the first post-surgical time-point. As expected, these changes were evident in the posterior temporal lobes. This supports the conclusion that changes in patterns of activation occur following temporal lobectomy, but the result did not support the expected lateralized changes. Ongoing changes from the first to second post-surgical time-point were only evident in the right-side seizure group. Between the two post-surgical time-points, the change was reversed with more activation at the second post-surgical time-point, including in the posterior temporal lobes. Such fluctuations in changes have been reported for cognitive function following surgery. Alpherts et al.

(2006) showed continued decline in verbal memory in patients with left-side resection up to two years post-surgically. Patients with right-side seizures showed initial gains in memory encoding six months after surgery. These reversed at the two-year follow-up and returned to baseline memory performance. The present study supported the findings of dynamic cognitive change during the post-surgical period for subjects with right-side seizure reported by Alpherts et al (2006).

The effect of age of onset was also examined using whole brain activation and showed differences in areas of activation for right-side seizure patients. An early age of onset was associated with additional activation in superior and anterior regions including medial frontal lobes at both the pre and post-surgical time-points. The activation appeared bilateral, and did not change over time. Given that visual inspection analyses are exploratory, they are of limited value in reaching generalizeable conclusions, but may be of use in determining future areas of investigation, such as focused region of interest studies. The only previous study of fMRI activation following surgery reported changes in the frontal lobes from the pre to post-surgical time-points (Maccotta et al., 2007). The present study did not replicate this finding, but did indicate that age of onset may influence the recruitment of regions outside of the temporal lobes during memory encoding. Maccotta et al. (2007) did not analyze their data by age of onset and had a range from infancy to 40 years for seizure onset.

Shifts in cognitive functions to non-tranditional regions or homologous structures in the contralateral hemisphere have been reported in the literature on recovery of function in areas such as aphasia due to cerebrovascular disease and language transfer following hemispherectomy (Loddenkemper et al., 2003; Meinzer et al., 2008). This

study aimed to look at contralateral activation in the hippocampus, parahippocampus and HPF regions in order to determine if changes in BOLD activation were related to side of seizure, age of onset, and changes in neuropsychological measures.

Comparisons between subjects with right and left-side seizures revealed some group differences. Subjects with right-side seizure had more contralateral parahippocampal activation prior to surgery and trended toward significantly more after surgery. They also had more contralateral HPF activation both before and after surgery than the subjects with left-side seizure. In addition, the right-side seizure group continued to have more contralateral HPF activation at the second post-surgical time-point. The right-side seizure subjects consistently showed more contralateral (left-side) activation, compared to subjects with left-side seizures. The reason for this discrepancy may be related to the task and the differences in accommodation to the task due to the dysfunctional right medial temporal lobe. The performance on the task was similar for both groups, so a discrepancy could not account for the difference in activation. Among control subjects, bilateral activation during this task is thought to represent complex visual input, verbal labeling and verbalization of the scene content. A slight rightward shift is sometimes observed, possibly related to a reliance on more visual input. Subjects with right-side seizure may rely more heavily on the verbalization of the content, whereas the left-side seizure subjects maintain the typical reliance on visual input. Analyses of age of onset effects did not yield significant results.

Asymmetry in activation across the contralateral and ipsilateral temporal lobes provides for a within subject comparison of differential involvement of homologous brain regions during a task. Asymmetry analyses have been used to establish lateralized

language and memory function in a pre-surgical population (Golby et al., 2001; Rabin et al., 2004; Rutten, Ramsey, van Rijen, Alpherts et al., 2002; Springer et al., 1999). This study examined a modified HPF asymmetry within the posterior aspect of the HPF region on each side in order to examine changes in asymmetry following surgery. This was expected given the loss of input from the ipsilateral medial temporal lobe. Before surgery, the right-side seizure group had more negative asymmetry than the left-side seizure group, but there was no difference between groups at the time-points following surgery. There was no effect of age of onset on the asymmetry at each time-point or the change in asymmetry. This was unexpected, given findings of effects of age of onset on lateralization of language and the detrimental effects of late age of onset on post-surgical cognitive outcome (Baxendale et al., 2007; Saykin et al., 1989).

Neuropsychological change following surgery has included reports of material-specific change in right and left-side seizure patients, as well as, mixed verbal and visual memory changes in some populations of patients (Baxendale & Thompson, 2005; Rausch et al., 2003; Wachi et al., 2001). This study examined the relationship between neuropsychological change and the post-surgical activation on the contralateral side, including the hippocampus, parahippocampus, HPF, and the HPF asymmetry. Among subjects with right-side seizures, change in recognition memory for faces was negatively correlated with contralateral hippocampal activation following surgery. The more activation in the contralateral left hippocampus after surgery, the greater the decline on the visual memory test. Change in story memory was correlated with post-surgical contralateral hippocampal, parahippocampal and HPF activation. The more activation in the contralateral left hippocampus after surgery, the greater the improvement in verbal

memory. For subjects with left-side seizures, change in memory for designs was negatively correlated with post-surgical contralateral hippocampal activation. Change in delayed story memory and several measures of list learning were correlated with post-surgical contralateral hippocampal and parahippocampal activation. The more activation in the contralateral right hippocampus after surgery, the greater the decline on the visual memory test and the greater the improvement in verbal memory. There was no relationship between post-surgical HPF asymmetry and neuropsychological change.

The pattern of relationships between neuropsychological change and post-surgical activation including decline on visual memory and improvement on verbal memory with increased contralateral activation, was unexpectedly similar for each group. The association between the contralateral hemisphere and declines on visual memory tests may represent a dysfunctional change associated with the processing of visual information, while the association between the contralateral hemisphere and improvement in verbal memory may represent a functional change associated with adaptive alterations in neural circuitry. This relationship may be related to the findings of minimal changes in visual memory and prominent verbal memory changes following resection. This finding supports the idea that visual memory relies less than verbal memory on the resected circuits. Changes in the mesial temporal lobe circuitry as measured by functional activation, are therefore likely to be disadvantageous when visual memory systems are subserved and are likely to be compensatory when verbal memory systems are subserved. An additional consideration in examining the relationship between neuropsychological tests of visual memory and post-surgical activation is the extent to which performance on each task can be aided by verbalization of the stimuli.

The right-side seizure group showed a relationship between activation and the Warrington Face Recognition Memory Test, which is not easily verbalized, while the left-side seizure group showed a relationship between activation and the Visual Reproduction subtest of the WMS-III, which is frequently reported clinically as highly verbalizable. Such differences may lead to patients utilizing different strategies depending on their side of seizures on tasks used to assess visual memory.

The lack of BOLD activation findings from the pre to post-surgical time-points may reflect the small sample size and low power of the study. It may also reflect the findings of differences in LTP function in pathological tissue compared to healthy tissue or a link between decreased synaptic plasticity and hippocampal seizure focus (Ben-Ari, 2001; Cooke & Bliss, 2006). The network changes that occur as a result of long-term seizure activity may result in connections that are less efficient at responding to additional insult such as surgical resection. This results in less cortical reorganization than would be expected based on literature of cortical plasticity following cerebrovascular events (Meinzer et al., 2008).

The predominance of negative findings within the mesial temporal lobes may indicate that the investigation of changes in memory circuits should be expanded to regions that are less impacted by the direct effects of disease pathology, but that contribute significantly to memory formation through hippocampal connections. Investigating specific hippocampal-neocortical connections before and after hippocampal removal may help to uncover the effects of changes in hippocampal connections on the distribution of memory traces throughout the neocortex. Connections to the hippocampus from the anterior cingulate, amygdala and other regions traditionally associated with the

Circuit of Papez may undergo differential strengthening and weakening as a result of mesial temporal lobe resection. The reciprocal connections throughout the limbic system and cortex with the mesial temporal lobe indicate that there is ample opportunity for disconnection effects and subsequent re-wiring of circuits. Additionally, prefrontal regions which project to the hippocampus via the retrosplenial, perirhinal and entorhinal cortices, and are associated with working memory functions may become more heavily relied upon for consolidating and distribution functions as a result of weakened or more lateralized hippocampal connections (Nieuwenhuys, Voogd, & Van Huijzen, 2008).

Strengths and Limitations

The longitudinal within-subject design is a strength of this study. There are few studies available in the literature that examine change in BOLD activation over time and only one has examined seizure patients (Maccotta et al., 2007). In addition, subject retention was a strength. Although there was a small original cohort of twenty, fourteen of the fifteen subjects who underwent temporal lobe resection returned for follow-up and eleven of those subjects returned for an additional post-surgical study. Finally, the use of a template based on subjects with epilepsy for normalization of images allowed for movement of the individual subjects into a template space that accounted for the unique characteristics of brain structure in this population.

The major limitation of this study was the small sample size. Others were the variability in follow-up intervals, lack of multiple follow-up visits for neuropsychological testing and use of regions of interest based on the template image and not individual subjects. The small sample size likely contributed to less reliable group maps for whole

brain comparisons. It may also have resulted in low power for detecting small effects related to side of the seizure and age of onset. The variability in the time to follow-up was difficult to control due to practical impediments. A tightly controlled interval to follow-up and multiple follow-ups with neuropsychological testing would allow for tracking the dynamic change in cognitive status post-surgically (Alpherts et al., 2006). The modified HPF regions used in the asymmetry ratios were based on the removal of a conservative estimate of resection boundaries based on the subjects with the greatest resections. Although there was little variation in many of the resections, a conservative estimate applied to all subjects may had led to a small region of interest and an underestimate of the area undergoing post-surgical change.

Directions for Future Work

Follow-up work to this study would include addressing the limitations above and pursuing additional analyses and imaging techniques. To address variability in intervals between surgery and the post-surgical assessments, time can be entered into activation analyses as a covariate. Additional approaches to analyzing the imaging data would include using a frame approach to mapping the hippocampus and parahippocampus in order to gain information about changes in sub-regions of these structures. The approach in this study was to compare values that represented the entirety of the structure, and a spatial correspondence based analysis would allow for increased sensitivity (Yushkevich et al., 2007).

In addition, a change to the task and additional analyses of the current dataset would account for the involvement of the mesial temporal lobe in the “default mode”

(Greicius, Krasnow, Reiss, & Menon, 2003; Raichle & Snyder, 2007). An active baseline could be added to account for hippocampal activity associated with the "default mode." The active baseline would serve to suppress the default network and allow for detection of greater signal change between the active baseline blocks and the task blocks (Stark & Squire, 2001). Additional analyses of the deactivations included in the current dataset may provide information about differences in modulation of the "default mode" in subjects with TLE. Such findings in subjects with Alzheimer's disease have been reported to involve the mesial temporal lobe (Greicius, Srivastava, Reiss, & Menon, 2004).

The effect of gender on processing of visual information within the epilepsy population is another direction of future research. Utilizing visual memory tasks that have known gender dependent performance effects would allow for dissociation of underlying neural circuitry based on components of visual processing. Such comparisons may inform both the interpretation of imaging data within the epilepsy population and data on gender differences.

Conclusions

The results of this study show that longitudinal BOLD fMRI can be used to examine group differences over time. Control HPF asymmetries remained relatively stable across time, while the subjects with TLE showed increases in asymmetry following surgery. Whole brain activation patterns showed changes form the pre to post-surgical time-points, with continued changes over the post-surgical sessions. Age of onset was associated with greater neuropsychological deficits in the late age of onset group and

medial frontal activation in the early onset group among subjects with right-side seizure disorder. Post-surgical contralateral activation in the mesial temporal lobe was associated with changes in both verbal and visual memory. This may reflect both functional improvement and impairment.

Table 1
Functional Imaging Variables Included in Analyses

Region	Variable Name	Calculation
HA	Absolute Contralateral (C)	$\frac{\text{N of positive contralateral HA voxels}}{\text{N of voxels in contralateral HA}}$
PH	Absolute Contralateral (C)	$\frac{\text{N of positive contralateral PH voxels}}{\text{N of voxels in contralateral PH}}$
HPF	Absolute Contralateral (C)	$\frac{\text{N of positive contralateral HPF voxels}}{\text{N of voxels in contralateral HPF}}$
	Modified Asymmetry Ratio (AR_{mod})	1. Ipsilateral HPF region – Area of resection (I_{mod}) Contralateral HPF region – Mirror image of area of resection (C_{mod}) 2. $(C_{mod}-I_{mod})/(C_{mod}+I_{mod})$

Note. HA=hippocampus, PH=parahippocampus, HPF=hippocampus, parahippocampal gyrus, and fusiform gyrus; I=Ipsilateral, C=Contralateral; A left-right asymmetry ratio was also calculated in order to compare patients and controls (left-right)/(left+right).

Table 2
Patient Demographics

Side of Seizures	N	Gender		Age		Handedness			Years of Education		Years With Seizures		IAT Memory Lateralization		
		M	F	M	SD	R	L	B	M	SD	M	SD	R	L	U
Right	7	2	5	40.4	11.8	6	1	0	13.0	2.1	26.5	12.6	0	5	2
Left	7	2	5	38.1	16.1	4	2	1	11.9	1.9	23.1	13.9	4	0	3
All Subjects	14	4	10	39.3	13.6	10	3	1	12.4	2.0	24.7	12.9	4	5	5

Note. R=Right; L=Left; B=Bilateral; U=Unavailable Data; IAT=Intracarotid Amobarbital Test; Engel Class I=free of disabling seizures; Engel Class II=rare disabling seizures; Engel Class III=worthwhile improvement; Engel Class IV=no worthwhile improvement.

Table 3
Scene Memory Task Discrimination Score

Group	Right-sided Seizure		Left-sided Seizure		Controls		F (2,28)
	M	SD	M	SD	M	SD	
Pre-Surgical/ Time-Point 1	0.666	0.18	0.628	0.25	0.769	0.17	1.523
Post-Surgical	0.487	0.24	0.528	0.24	N/A	N/A	6.066 *

Note. The difference in performance was between each patient group and the control group in all comparisons.
* $p < .05$

Table 4

Pre and Post-Surgical Neuropsychological and Psychological Test Scores

Side Seizure	Measure	Time Point	M	SD	df	t
Right-Sided Seizure	Warrington Faces	Pre	44.71	3.1	6	0.372
		Post	44.29	2.6		
	WMS-III VR-I	Pre	83.33	10.7	5	1.941
		Post	74.00	5.9		
	WMS-III VR-II	Pre	51.71	15.5	6	1.113
		Post	44.00	17.5		
	WMS-III LM-I	Pre	32.71	9.3	6	-0.767
		Post	35.43	8.0		
	WMS-III LM-II	Pre	21.43	6.6	6	0.560
		Post	19.29	8.6		
	CVLT-II Trial 1	Pre	7.29	1.5	6	2.772 *
		Post	5.43	1.7		
	CVLT-II Trial 5	Pre	12.29	2.4	6	0.856
		Post	11.14	3.0		
	CVLT-II Total	Pre	50.43	8.5	6	2.944 *
		Post	44.29	11.4		
	CVLT-II Short Delay	Pre	11.14	2.8	6	2.500 *
		Post	9.74	3.5		
	CVLT-II Long Delay	Pre	10.43	3.0	6	0.946
		Post	9.00	5.3		
	CVLT-II Long Delay – Trial 5	Pre	-1.86	2.2	6	0.167
		Post	-2.14	4.5		
	BDI-II	Pre	11.50	17.4	5	1.278
		Post	6.67	8.8		
Left-Sided Seizure	Warrington Faces	Pre	45.67	4.5	5	-0.363
		Post	46.00	5.9		
	WMS-III VR-I	Pre	70.29	20.9	6	0.484
		Post	66.14	19.8		
	WMS-III VR-II	Pre	39.17	15.1	5	-0.402
		Post	43.00	28.9		
	WMS-III LM-I	Pre	28.86	16.7	6	0.943
		Post	25.00	15.4		
	WMS-III LM-II	Pre	14.86	9.9	6	0.776
		Post	12.29	11.1		
	CVLT-II Trial 1	Pre	6.57	2.1	6	5.303 *
		Post	4.43	1.8		
	CVLT-II Trial 5	Pre	10.43	4.2	6	1.947
		Post	8.29	4.5		
	CVLT-II Total	Pre	45.00	17.9	6	2.598 *
		Post	35.29	16.2		
	CVLT-II	Pre	8.57	5.2	6	2.386 *

	Short Delay	Post	4.57	4.7		
	CVLT-II Long Delay	Pre	8.43	5.5	6	1.412
		Post	5.14	5.2		
	CVLT-II Long Delay – Trial 5	Pre	-2.00	2.9	6	0.824
		Post	-3.14	2.1		
	BDI-II	Pre	5.50	4.80	3	0.585
		Post	4.25	3.30		

Note. WMS-III = Wechsler Memory Scale – 3rd Edition; VR-I=Visual Reproduction, Immediate Recall; VR-II=Visual Reproduction, Delayed Recall; LM-I=Logical Memory, Immediate Recall; LM-II=Logical Memory, Delayed Recall; CVLT-II=California Verbal Learning Test-2nd Edition; BDI-II=Beck Depression Inventory-2nd Edition.

* $p < .05$

Table 5

Modified Hippocampal, Parahippocampal, and Fusiform Gyrus Function in Patients and Controls at TP1 and TP2

Group	Right-side Seizure		Left-sided Seizure		Controls		F (2,20)
	M	SD	M	SD	M	SD	
Pre-Surgical/ TP1	-0.067	0.066	-0.053	0.052	-0.004	0.039	2.852
Post-Surgical/ TP2	0.039	0.084	-0.087	0.072	0.015	0.015	7.511 *[ab]

Note. TP1=Time-point one; TP2=Time-point two; C=contralateral; I=ipsilateral; TLE=Temporal Lobe Epilepsy

[a] Significant difference between right and left-sided seizure groups.

[b] Significant difference between left-side seizure group and control group.

* $p < .05$

Table 6

Contralateral ROIs and Modified HPFAR at TP1, TP2, and TP3 for Right and Left Side Seizure, Early and Late Age of Seizure Onset

Group	Region	TP1		TP2		TP3		df	t	df	t
		M	SD	M	SD	M	SD		TP1/ TP2		TP2/ TP3
All	Contra H	0.849	0.16	0.836	0.19	0.865	0.17	13	0.235	10	-0.607
	Contra PH	0.627	0.20	0.636	0.26	0.672	0.21	13	-0.165	10	-0.776
	Contra HPF	0.628	0.23	0.605	0.26	0.663	0.23	13	0.457	10	-0.908
	Mod. HPF AR	-0.007	0.08	0.063	0.08	0.040	0.10	13	-2.783 *	10	1.432
Right Side Seizure	Contra H	0.869	0.13	0.817	0.22	0.881	0.17	6	1.128	5	-2.104
	Contra PH	0.788	0.11	0.761	0.25	0.762	0.19	6	0.406	5	-0.410
	Contra HPF	0.832	0.11	0.752	0.25	0.798	0.21	6	1.202	5	-1.186
	Mod. HPF AR	-0.067	0.07	0.039	0.08	0.032	0.09	6	-2.404	5	0.451
Left Side Seizure	Contra H	0.828	0.19	0.856	0.16	0.846	0.18	6	-0.277	4	0.601
	Contra PH	0.466	0.14	0.512	0.23	0.564	0.18	6	-0.512	4	-0.626
	Contra HPF	0.425	0.08	0.459	0.19	0.501	0.12	6	-0.462	4	-0.397
	Mod. HPF AR	0.053	0.05	0.087	0.07	0.049	0.13	6	-1.783	4	1.447
Early Onset	Contra H	0.860	0.19	0.840	0.22	0.813	0.22	6	0.265	5	0.093
	Contra PH	0.612	0.18	0.641	0.26	0.606	0.15	6	-0.296	5	-0.049
	Contra HPF	0.591	0.23	0.610	0.27	0.602	0.22	6	-0.211	5	-0.087
	Mod. HPF AR	-0.019	0.09	0.080	0.07	0.050	0.13	6	-2.207	5	1.500
Late Onset	Contra H	0.844	0.15	0.869	0.15	0.944	0.04	5	-0.267	3	-0.579
	Contra PH	0.629	0.26	0.597	0.30	0.736	0.29	5	0.502	3	-1.247
	Contra HPF	0.652	0.26	0.577	0.30	0.728	0.28	5	1.326	3	-1.442
	Mod. HPF AR	0.023	0.07	0.068	0.07	0.036	0.07	5	-1.809	3	1.873

Note. ROI=Region of interest; HPF=hippocampus, parahippocampus, fusiform gyrus; AR=asymmetry ratio; TP1=Time-point one; TP2=Time-point two; TP3=Time-point three; Contra H=contralateral hippocampus; Contra PH=contralateral parahippocampus.

* $p < .05$

Table 7
Two-Way Mixed Model ANOVAs: TP1/TP2 Session by Early/Late Onset

		df	F
Contralateral Hippocampus	Within-Subjects	1,11	0.001
	Between-Subjects		0.007
	Interaction		0.143
Contralateral Parahippocampus	Within-Subjects	1,11	0.001
	Between-Subjects		0.011
	Interaction		0.254
Contralateral HPF	Within-Subjects	1,11	0.261
	Between-Subjects		0.011
	Interaction		0.728
Modified HPF AR	Within-Subjects	1,11	7.151*
	Between-Subjects		0.190
	Interaction		1.003

Note. TP1=Time-point one; TP2=Time-point two; HPF=hippocampus, parahippocampus, fusiform gyrus; AR=asymmetry ratio.
* $p < .05$

Table 8
Two-Way Mixed Model ANOVAs: TP1/TP2 Session by Side of Seizure

		df	F
Contralateral Hippocampus	Within-Subjects	1,12	0.053
	Between-Subjects		0.000
	Interaction		0.537
Contralateral Parahippocampus	Within-Subjects	1,12	0.026
	Between-Subjects		11.318 *
	Interaction		0.427
Contralateral HPF	Within-Subjects	1,12	0.214
	Between-Subjects		20.637 **
	Interaction		1.320
Modified HPF AR	Within-Subjects	1,12	8.490 *
	Between-Subjects		8.648 *
	Interaction		2.252

Note. TP1=Time-point one; TP2=Time-point two; HPF=hippocampus, parahippocampus, fusiform gyrus; AR=asymmetry ratio.
* $p < .05$
** $p = .001$

Table 9
Two-Way Mixed Model ANOVAs: TP2/TP3 Session by Early/Late Onset

		df	F
Contralateral Hippocampus	Within-Subjects	1,8	0.031
	Between-Subjects		1.179
	Interaction		0.100
Contralateral Parahippocampus	Within-Subjects	1,8	0.945
	Between-Subjects		0.241
	Interaction		0.827
Contralateral HPF	Within-Subjects	1,8	1.010
	Between-Subjects		0.203
	Interaction		0.784
Modified HPF AR	Within-Subjects	1,8	3.240
	Between-Subjects		0.196
	Interaction		0.259

Note. TP2=Time-point two; TP3=Time-point three; HPF=hippocampus, parahippocampus, fusiform gyrus; AR=asymmetry ratio.

Table 10
Two-Way Mixed Model ANOVAs: TP2/TP3 Session by Side of Seizure

		df	F
Contralateral Hippocampus	Within-Subjects	1,9	0.255
	Between-Subjects		0.091
	Interaction		2.596
Contralateral Parahippocampus	Within-Subjects	1,9	0.616
	Between-Subjects		4.002
	Interaction		0.221
Contralateral HPF	Within-Subjects	1,9	0.727
	Between-Subjects		6.970 *
	Interaction		0.003
Modified HPF AR	Within-Subjects	1,9	2.326
	Between-Subjects		0.512
	Interaction		1.069

Note. TP2=Time-point two; TP3=Time-point three; HPF=hippocampus, parahippocampus, fusiform gyrus; AR=asymmetry ratio.
* $p < .05$

Table 11

Correlations between TP2 Post-Surgical Imaging Data and Neuropsychological Change

Side of Seizure	Measure	Contra H	Contra PH	Contra HPF	Modified HPF AR
Right Side of Seizure	Warrington Faces	-0.769 *	-0.564	-0.555	0.327
	WMS-III				
	VR-I	0.672	0.750	0.757	-0.150
	VR-II	0.607	0.440	0.439	0.164
	LM-I	0.856 *	0.924 **	0.917 **	-0.391
	LM-II	0.828 *	0.456	0.641	0.455
	CVLT-II				
	Trial 1	0.730	0.473	0.472	-0.144
	Trial 5	0.671	0.174	0.393	0.495
	Total	0.610	0.516	0.635	-0.304
	Short Delay	0.488	0.093	0.242	0.407
	Long Delay	0.206	0.170	0.308	0.027
	Long Delay – Trial 5	-0.341	0.014	-0.035	-0.362
	Scene Memory Task	0.478	0.692	0.623	-0.071
Left Side of Seizure	Warrington Faces	0.323	0.172	0.307	-0.350
	WMS-III				
	VR-I	-0.881 **	0.033	0.115	0.565
	VR-II	-0.220	0.712	0.750	-0.201
	LM-I	0.425	0.633	0.520	-0.218
	LM-II	-0.013	0.850 *	0.775 *	-0.154
	CVLT-II				
	Trial 1	0.324	0.502	0.539	0.110
	Trial 5	0.000	0.938 **	0.897 **	-0.553
	Total	-0.055	0.888 **	0.833 *	-0.391
	Short Delay	-0.142	0.761 *	0.780 *	-0.182
	Long Delay	-0.286	0.783 *	0.759 *	-0.336
	Long Delay – Trial 5	-0.480	0.570	0.562	-0.125

Scene Memory Task	0.216	-0.019	-0.041	0.132

Note. H=Hippocampus; PH=Parahippocampus; HPF=Hippocampus, Parahippocampus, Fusiform Gyrus; WMS-III = Wechsler Memory Scale – 3rd Edition; VR-I=Visual Reproduction, Immediate Recall; VR-II=Visual Reproduction, Delayed Recall; LM-I=Logical Memory, Immediate Recall; LM-II=Logical Memory, Delayed Recall; CVLT-II=California Verbal Learning Test-2nd Edition.

* $p < .05$

** $p < .01$

Table 12
Correlations between TP3 Post-Surgical Imaging Data and Neuropsychological Change

Side of Seizure	Measure	Contra H	Contra PH	Contra HPF	Modified HPF AR
Right Side of Seizure	Warrington Faces	-0.810	-0.569	-0.728	0.587
	WMS-III				
	VR-I	0.659	0.850 *	0.837 *	-0.293
	VR-II	0.553	0.539	0.628	0.195
	LM-I	0.882 *	0.742	0.843 *	-0.504
	LM-II	0.630	0.334	0.578	0.089
	CVLT-II				
	Trial 1	0.698	0.263	0.504	-0.481
	Trial 5	0.481	-0.027	0.288	0.090
	Total	0.877 *	0.574	0.748	-0.590
	Short Delay	0.477	0.048	0.307	0.291
	Long Delay	0.595	0.641	0.704	-0.308
	Long Delay – Trial 5	-0.014	0.493	0.245	-0.308
	Scene Memory Task	0.530	0.563	0.559	0.251
Left Side of Seizure	Warrington Faces	0.545	-0.896	-0.994 **	-0.107
	WMS-III				
	VR-I	-0.255	-0.075	-0.094	0.760
	VR-II	0.047	-0.859	-0.774	0.693
	LM-I	0.379	0.587	0.243	-0.457
	LM-II	0.152	0.286	-0.002	0.033
	CVLT-II				
	Trial 1	-0.049	0.538	0.389	0.293
	Trial 5	-0.039	-0.330	-0.553	-0.093
	Total	-0.337	0.131	-0.058	-0.012
	Short Delay	-0.330	-0.012	-0.192	0.011
	Long Delay	-0.288	-0.146	-0.325	-0.049

Long Delay – Trial 5	-0.428	-0.028	-0.174	-0.021
Scene Memory Task	-0.128	0.671	0.443	-0.711

Note. H=Hippocampus; PH=Parahippocampus; HPF=Hippocampus, Parahippocampus, Fusiform Gyrus; WMS-III = Wechsler Memory Scale – 3rd Edition; VR-I=Visual Reproduction, Immediate Recall; VR-II=Visual Reproduction, Delayed Recall; LM-I=Logical Memory, Immediate Recall; LM-II=Logical Memory, Delayed Recall; CVLT-II=California Verbal Learning Test-2nd Edition.
* $p < .05$
** $p < .01$

Figure 1
Scene Memory Paradigm for fMRI

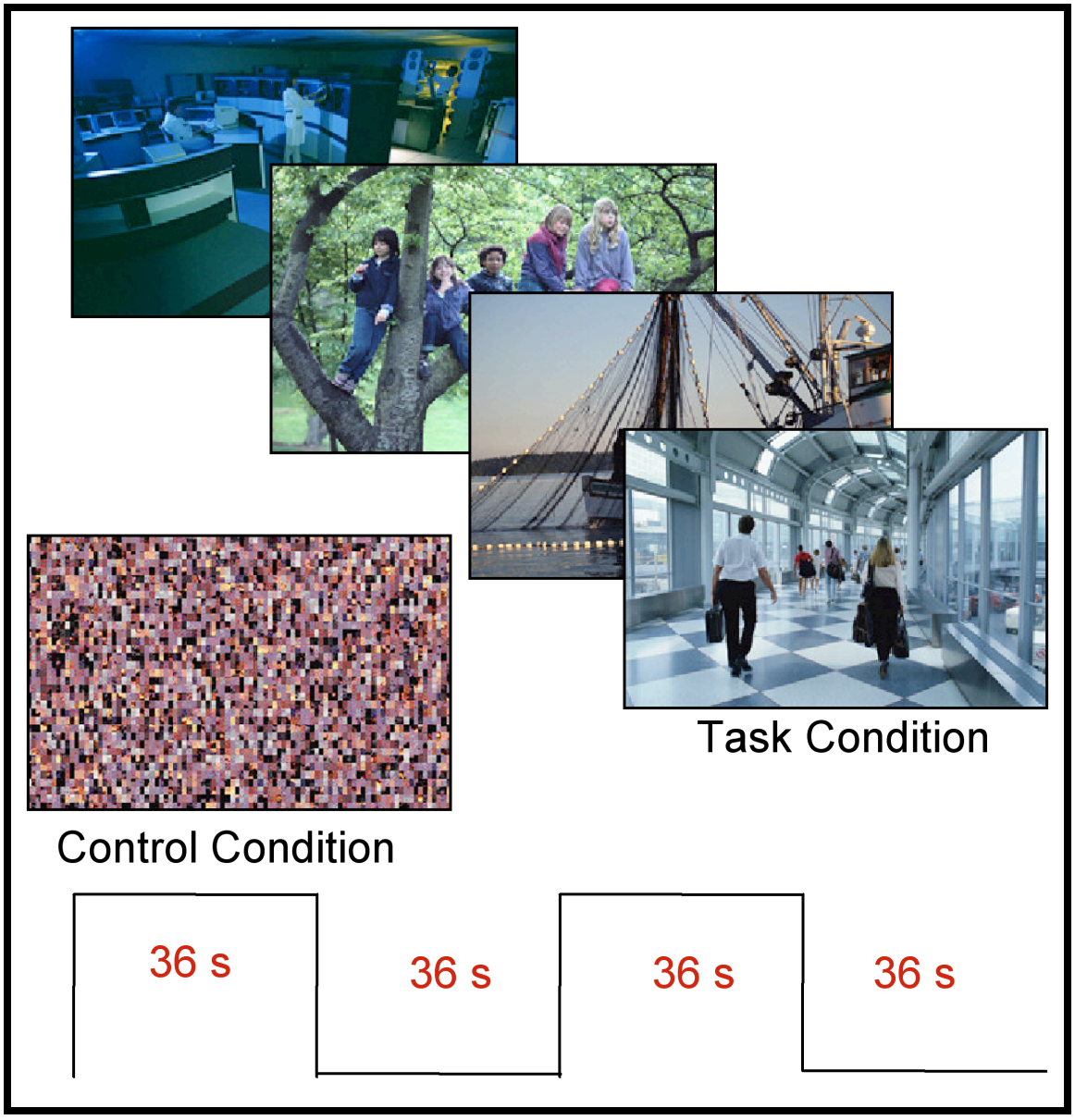


Figure 2
Hippocampal Region of Interest

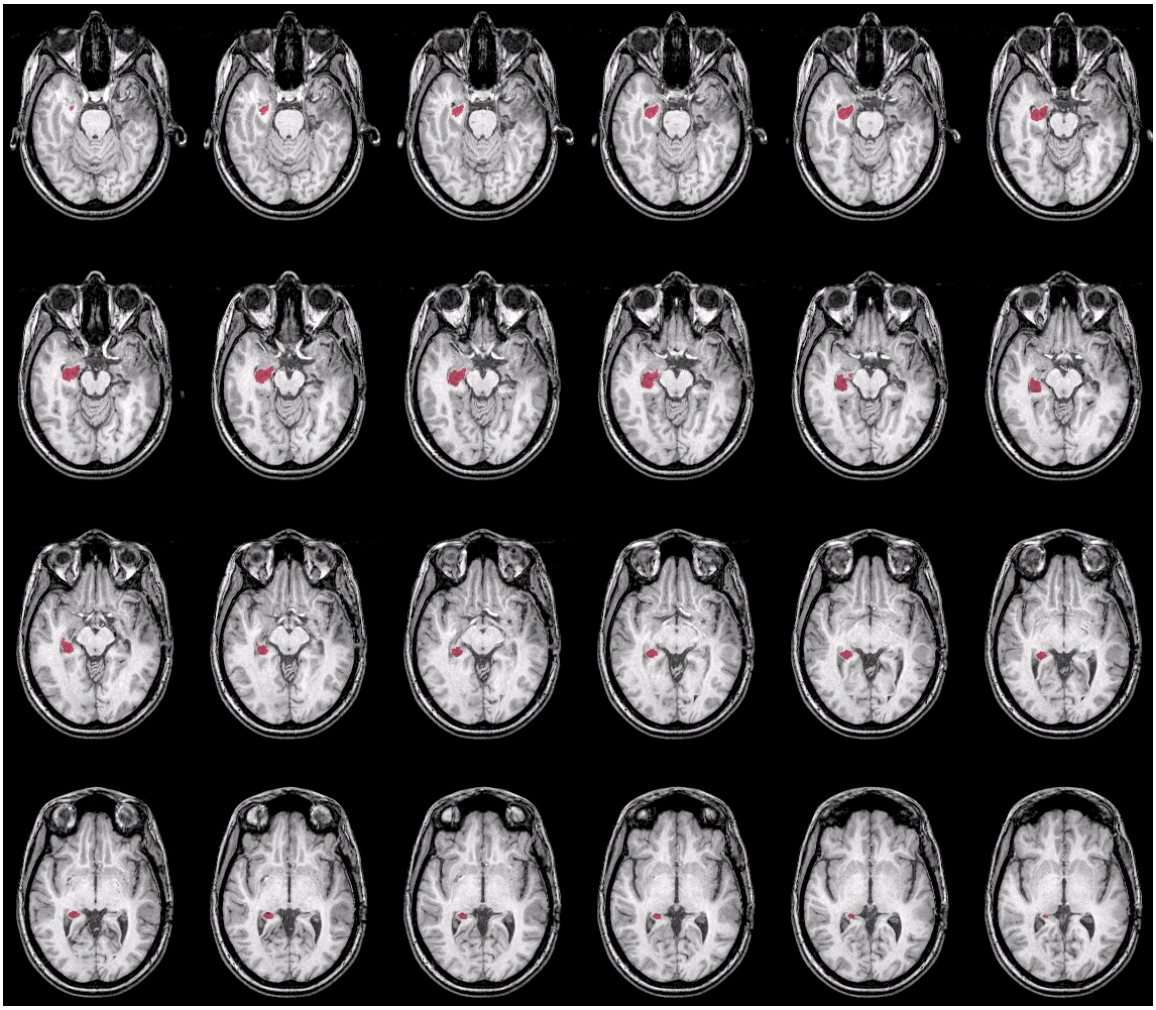


Figure 3
Parahippocampal Region of Interest

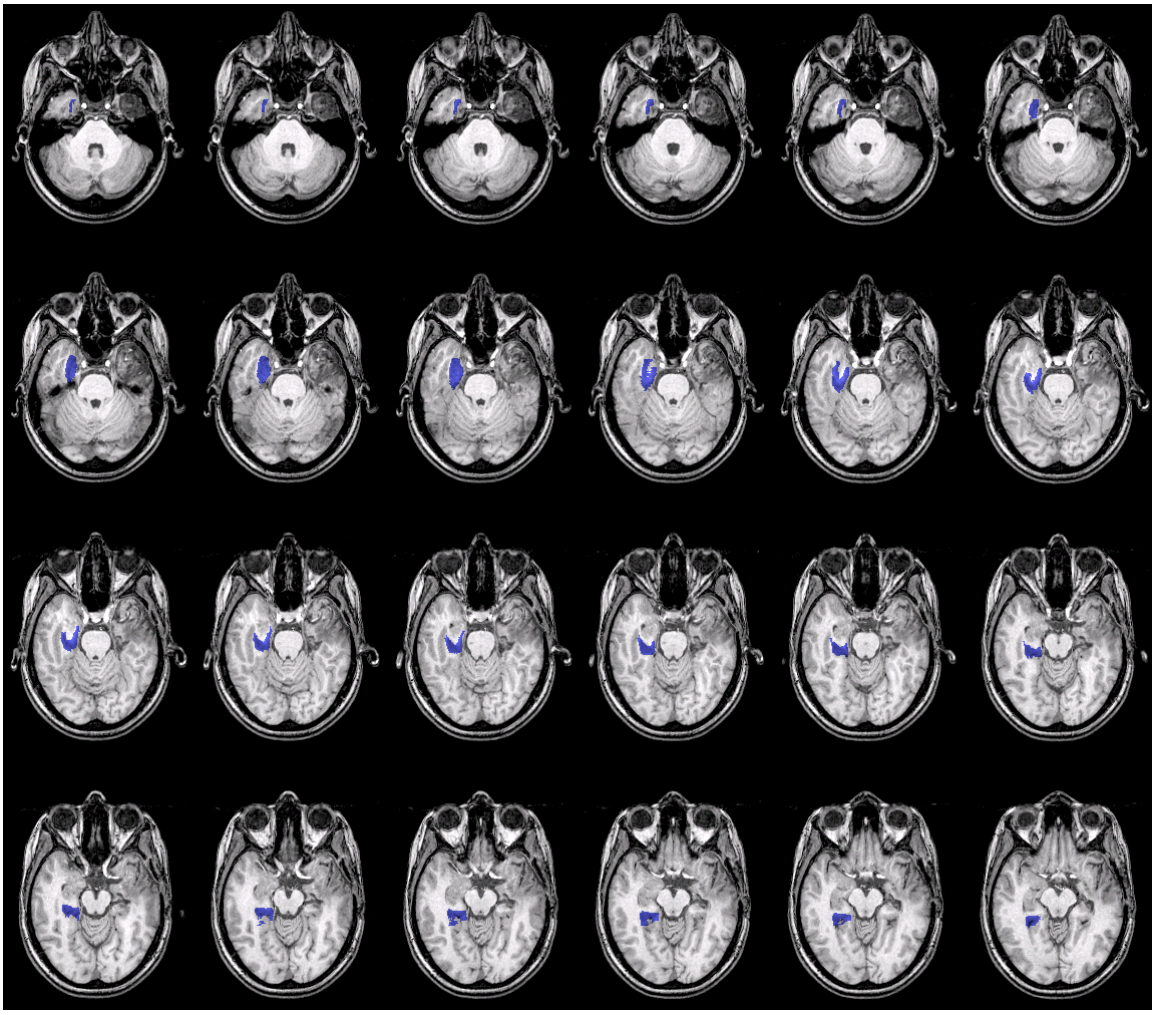


Figure 4
Hippocampal, Parahippocampal and Fusiform Gyrus (HPF) Region of Interest

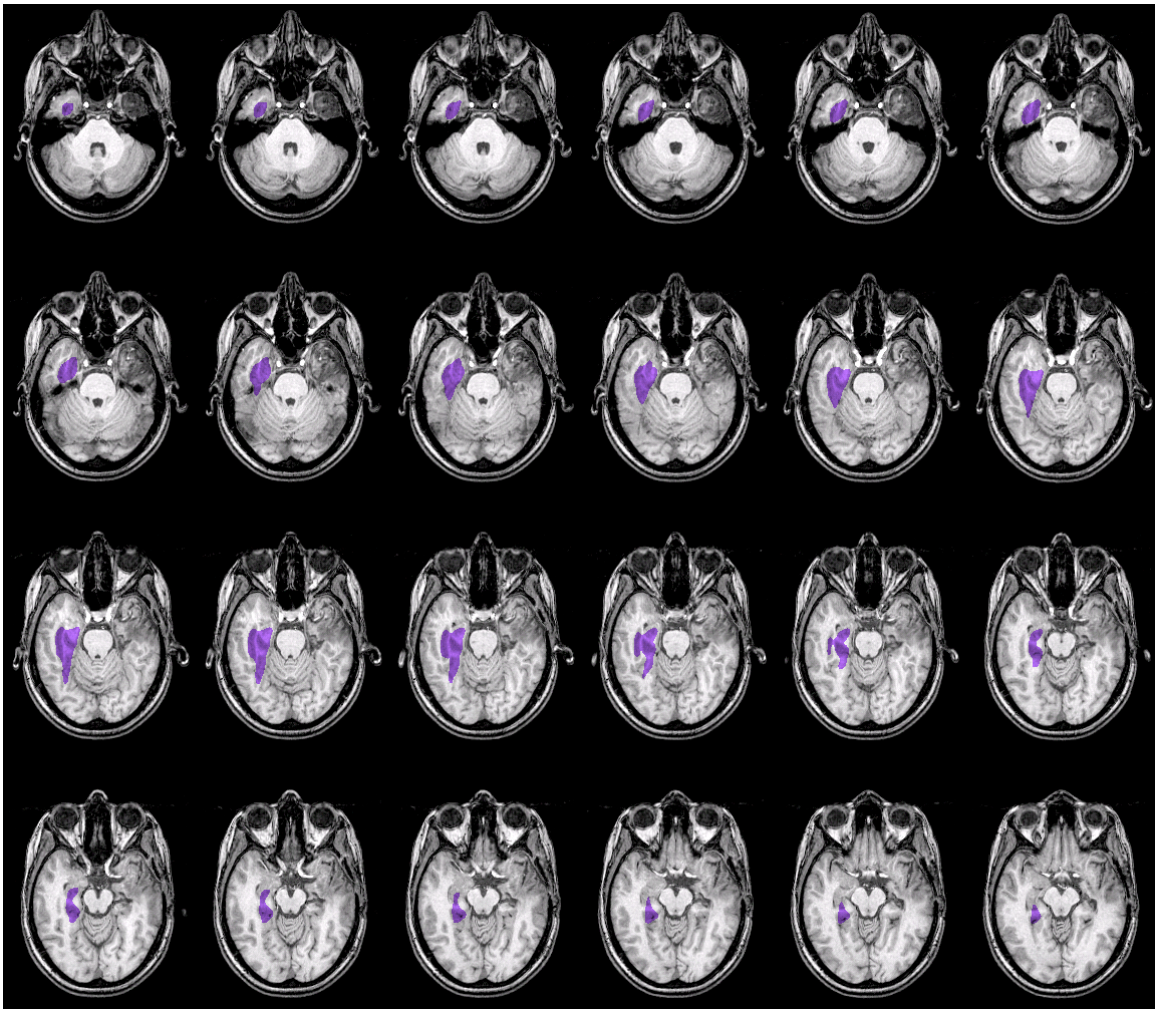


Figure 5
Modified HPF AR Region of Interest, Resection Removed

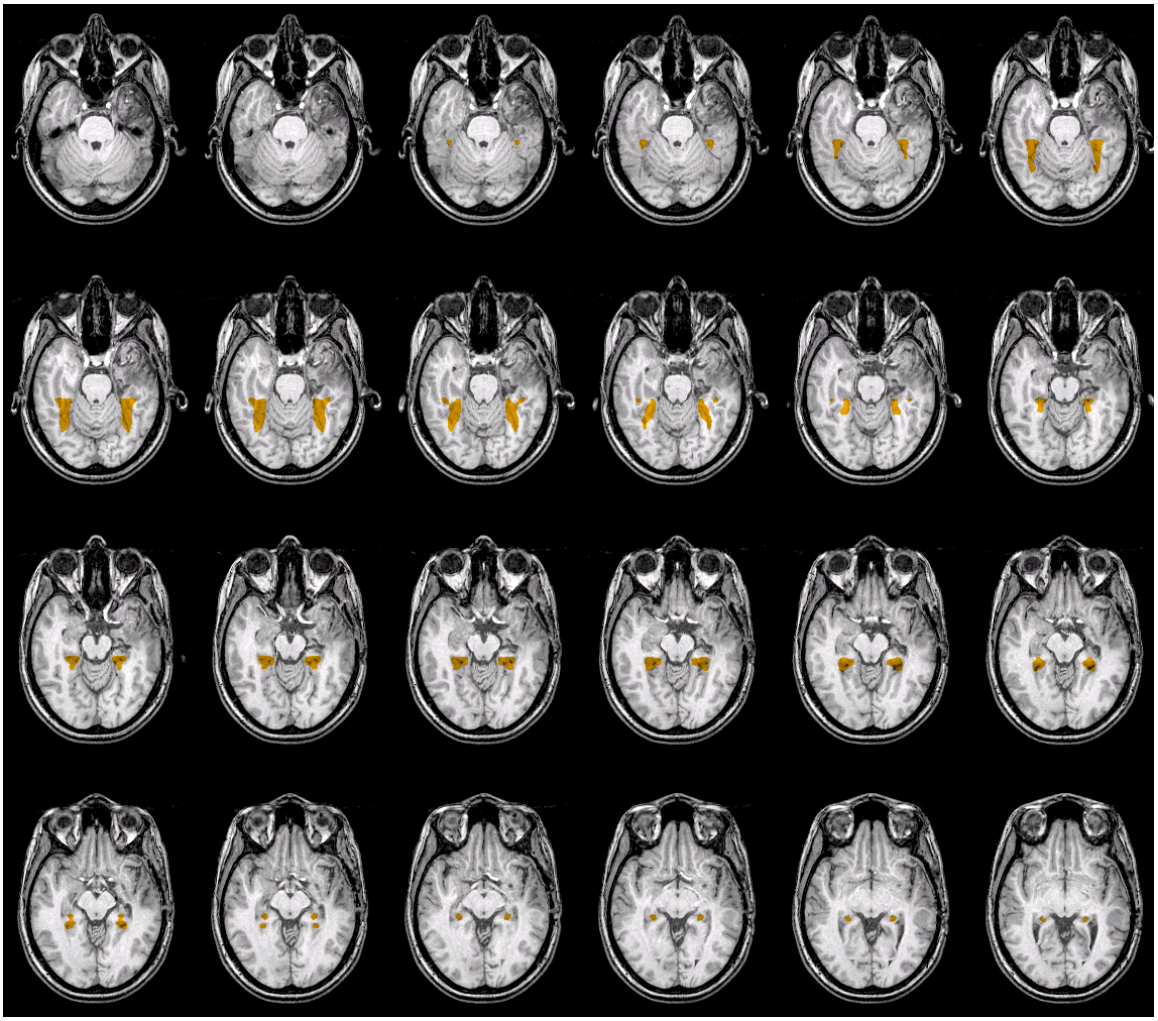


Figure 6

Group differences in HPF asymmetry ratios at time-point 1 and time-point 2 for Controls, Right and Left-side Seizure

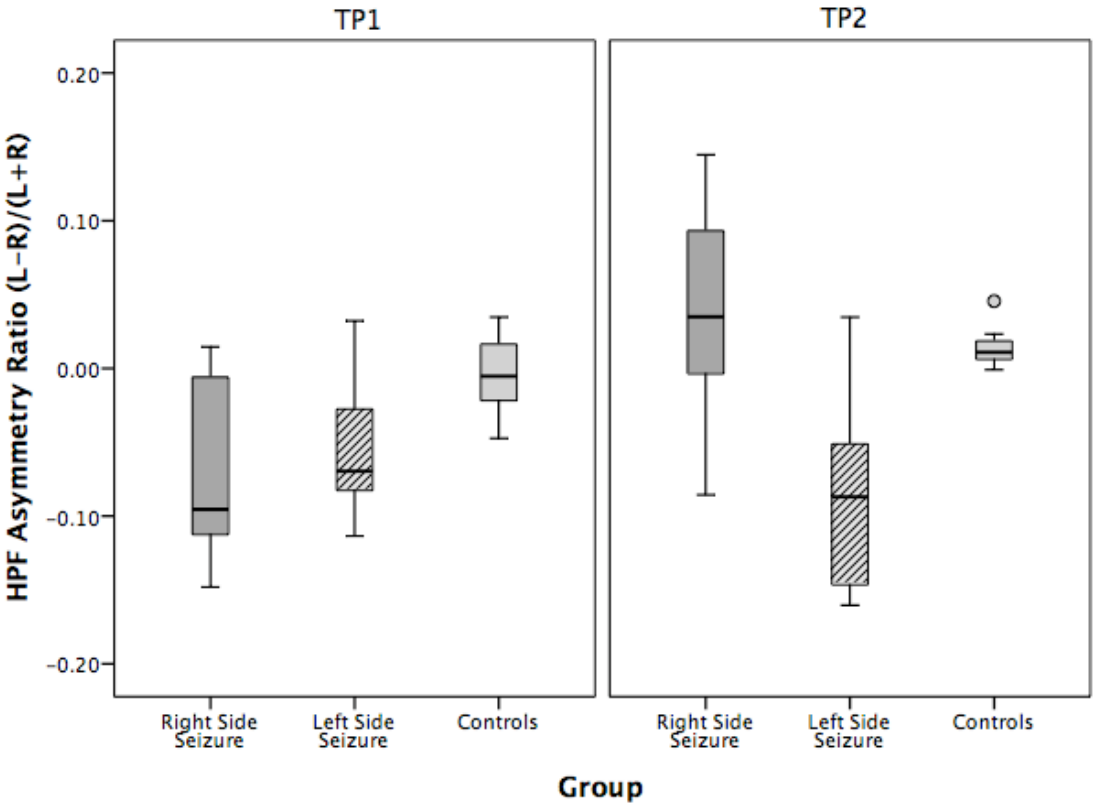


Figure 7

Group differences in HPF asymmetry ratios at time-point 1 and time-point 2 for Patients and Controls

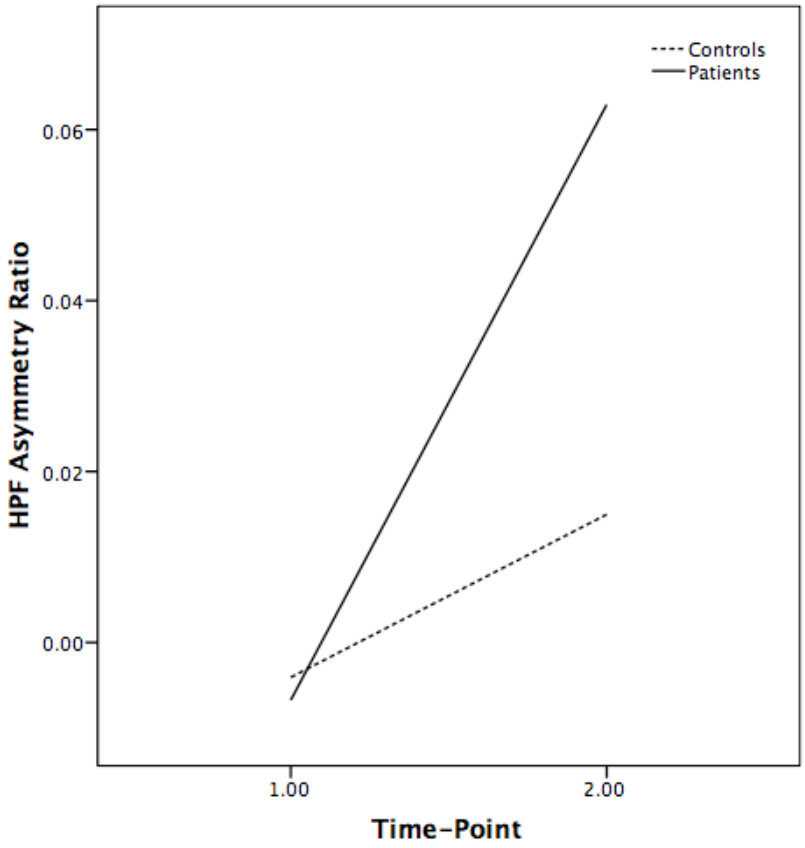


Figure 8

Group differences in asymmetry ratios for the whole HPF region and the modified HPF region for Controls, Right and Left-side Seizure

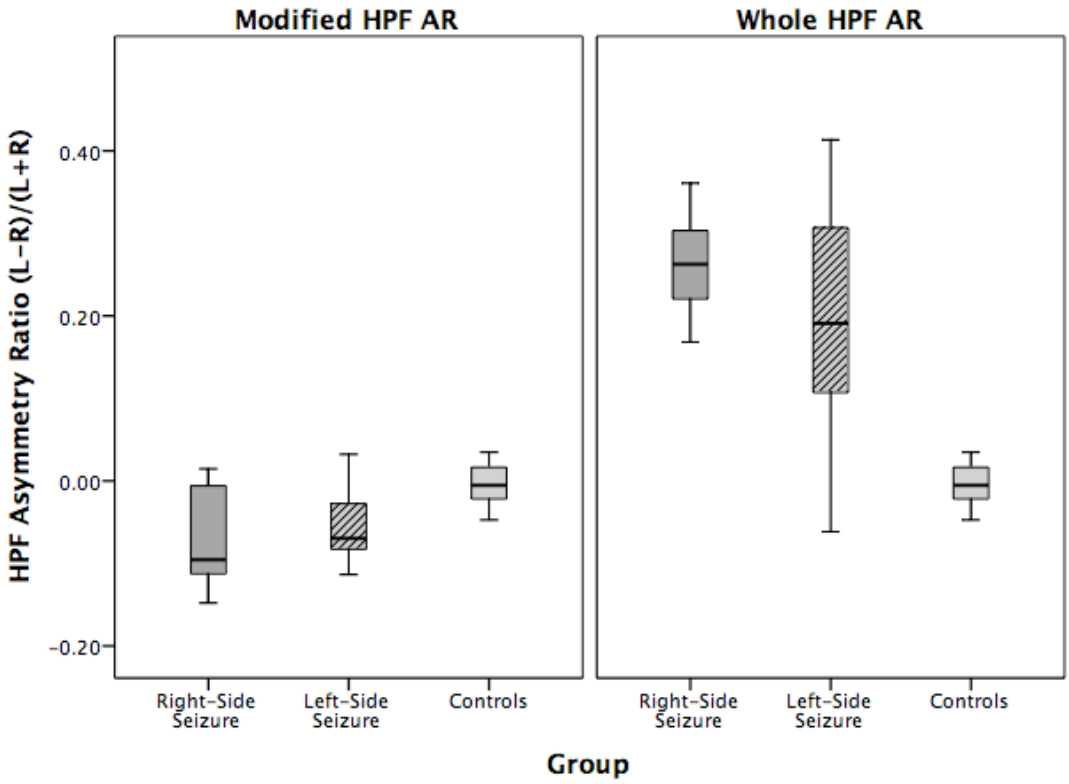


Figure 9

Pre-surgical scan: whole brain activation maps for subjects with left-side seizure

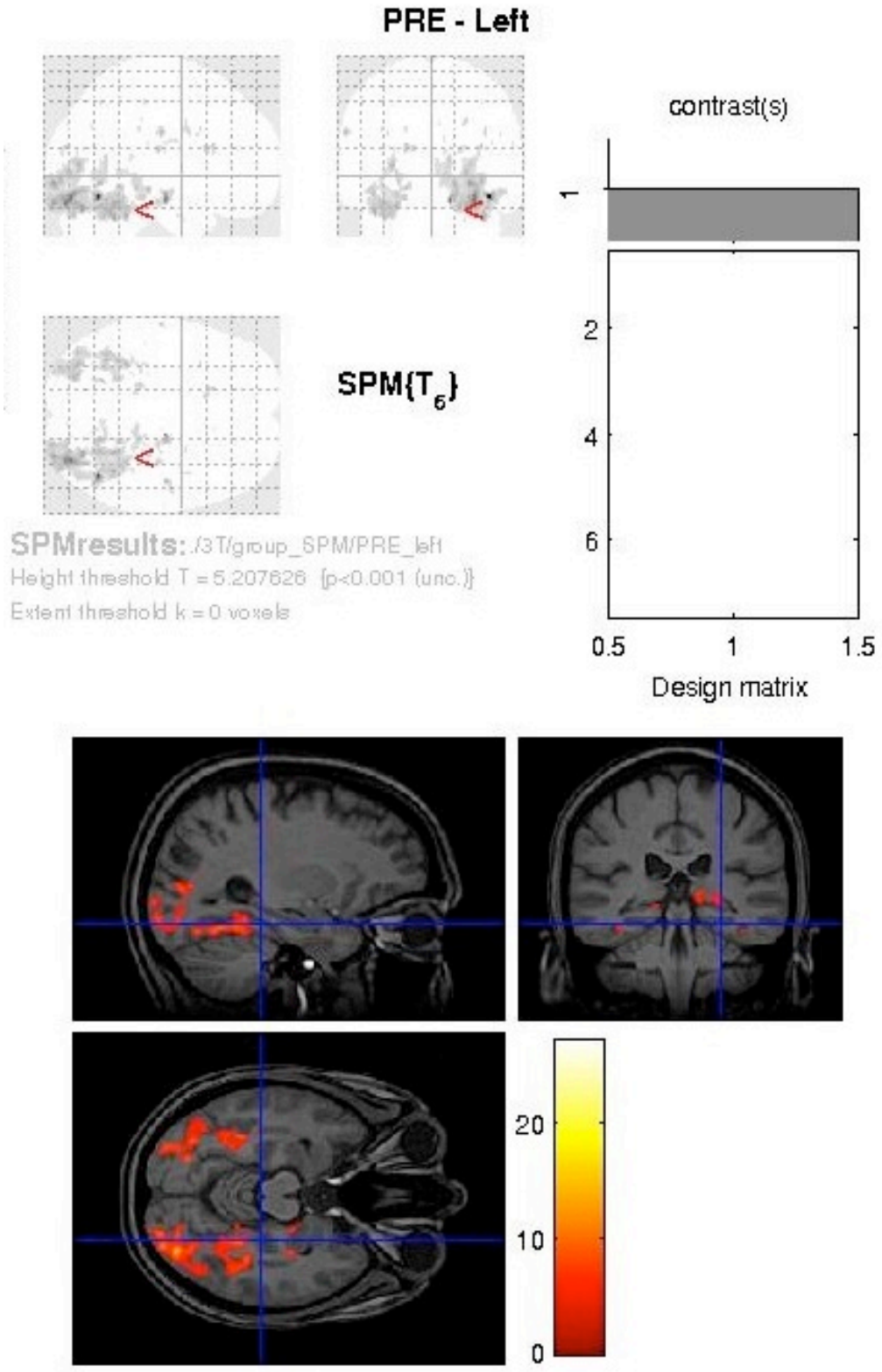


Figure 10

First post-surgical scan: whole brain activation maps for subjects with left-side seizure

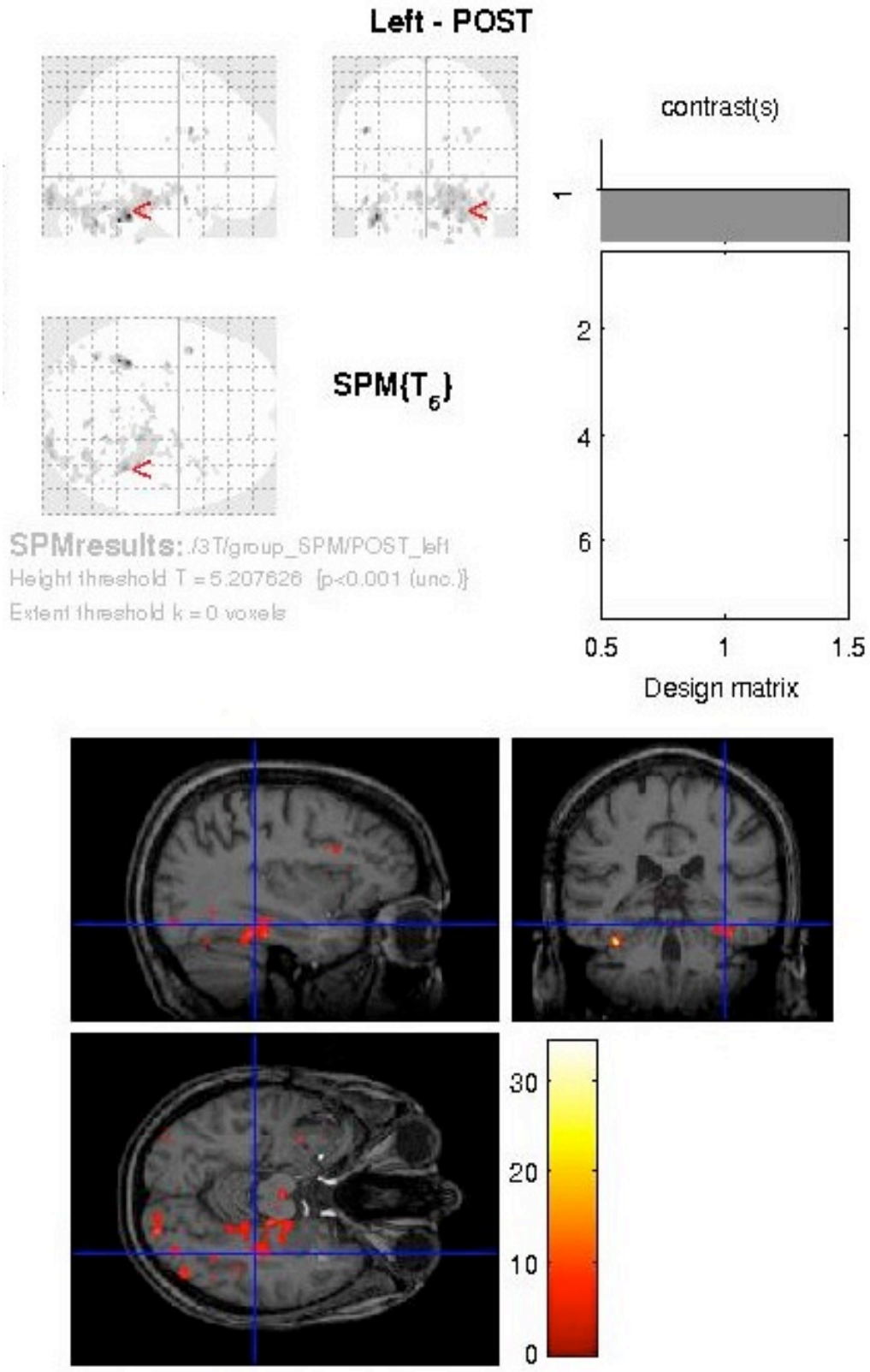


Figure 11

Second post-surgical: whole brain activation maps for subjects with left-side seizure

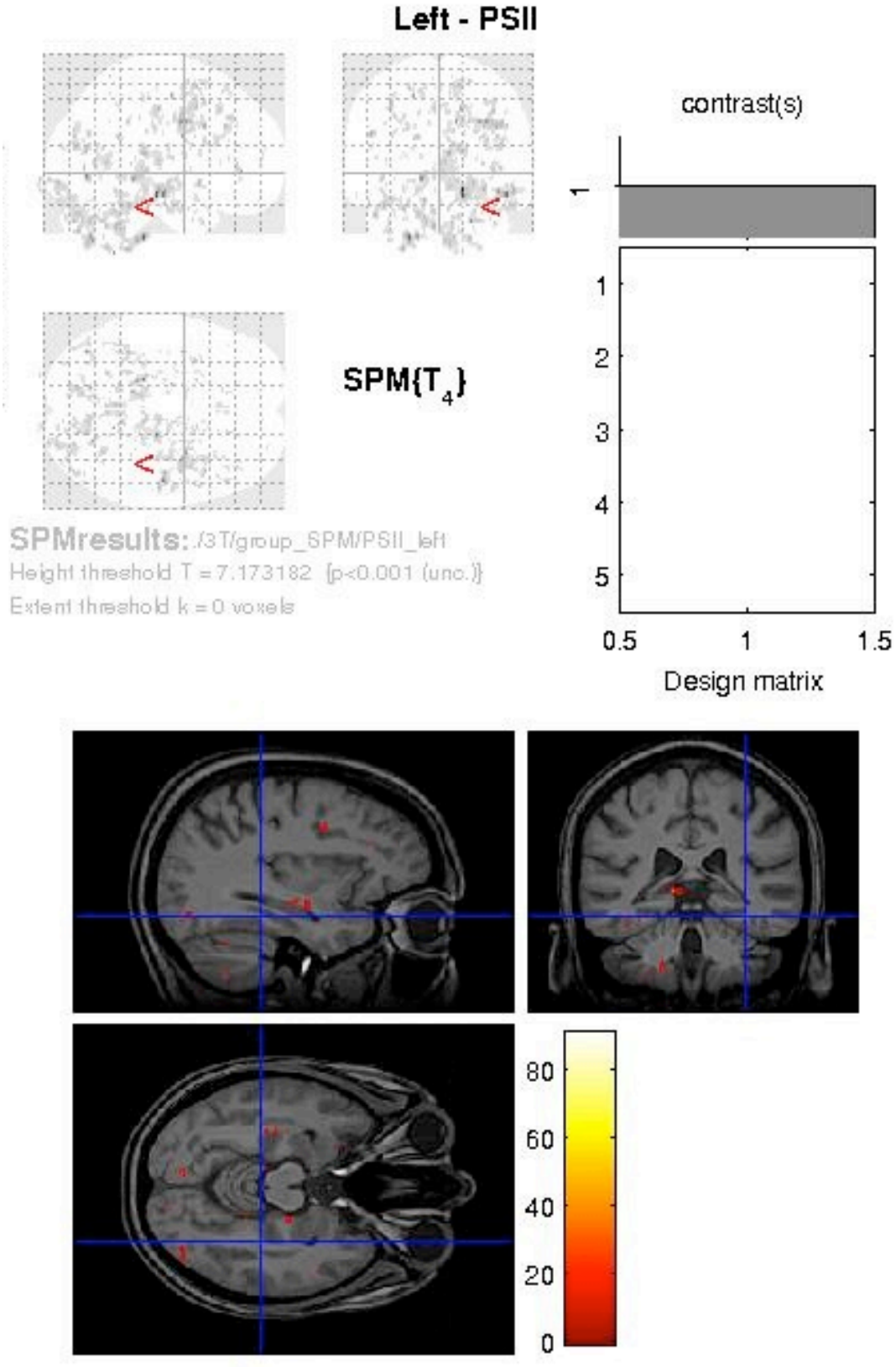


Figure 12

Pre and 1st Post-Surgical Scan: whole brain activation maps for subjects with left-side seizure who were included in the 2nd post-surgical session

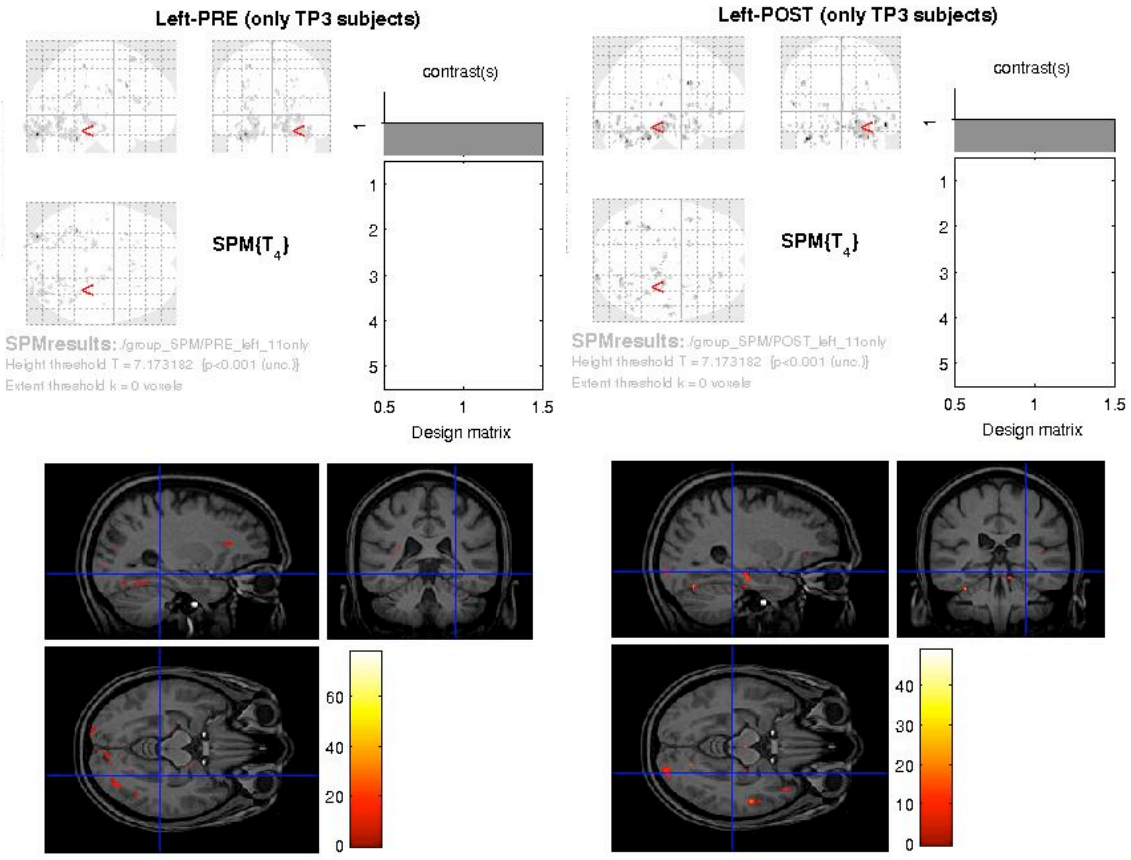


Figure 13

Pre-surgical whole brain activation maps for subjects with right-side seizure

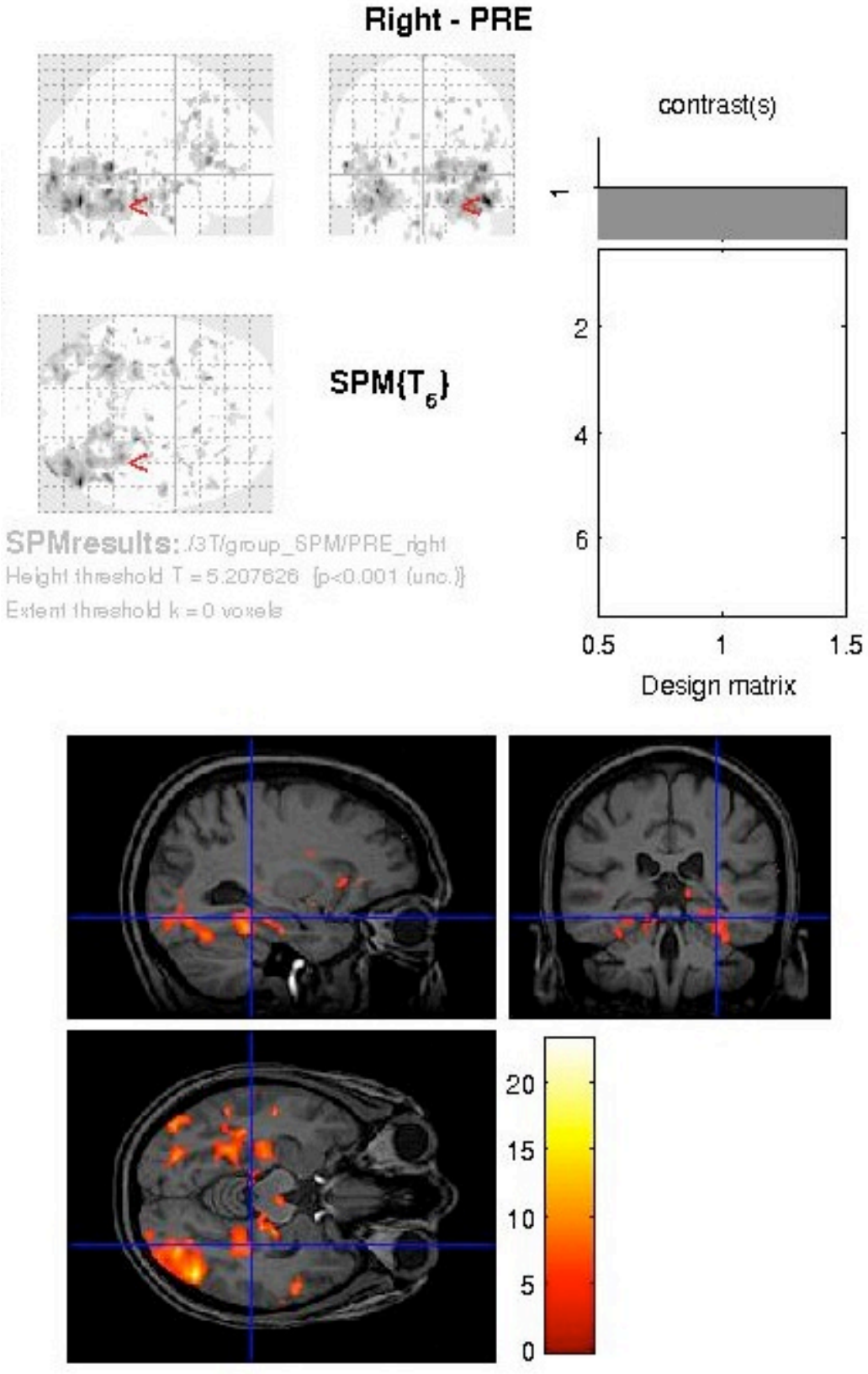


Figure 14

Post-surgical whole brain activation maps for subjects with right-side seizure

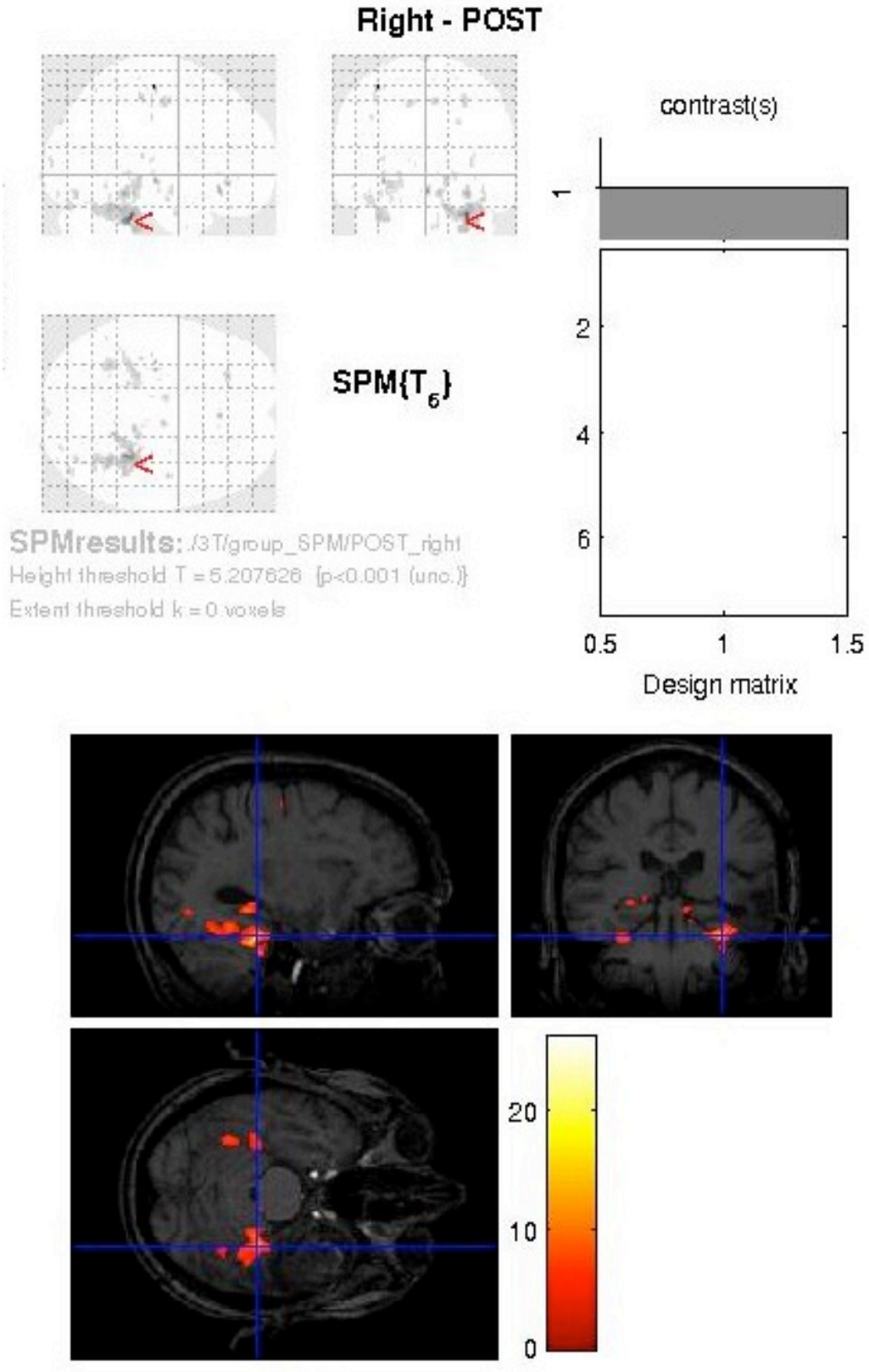
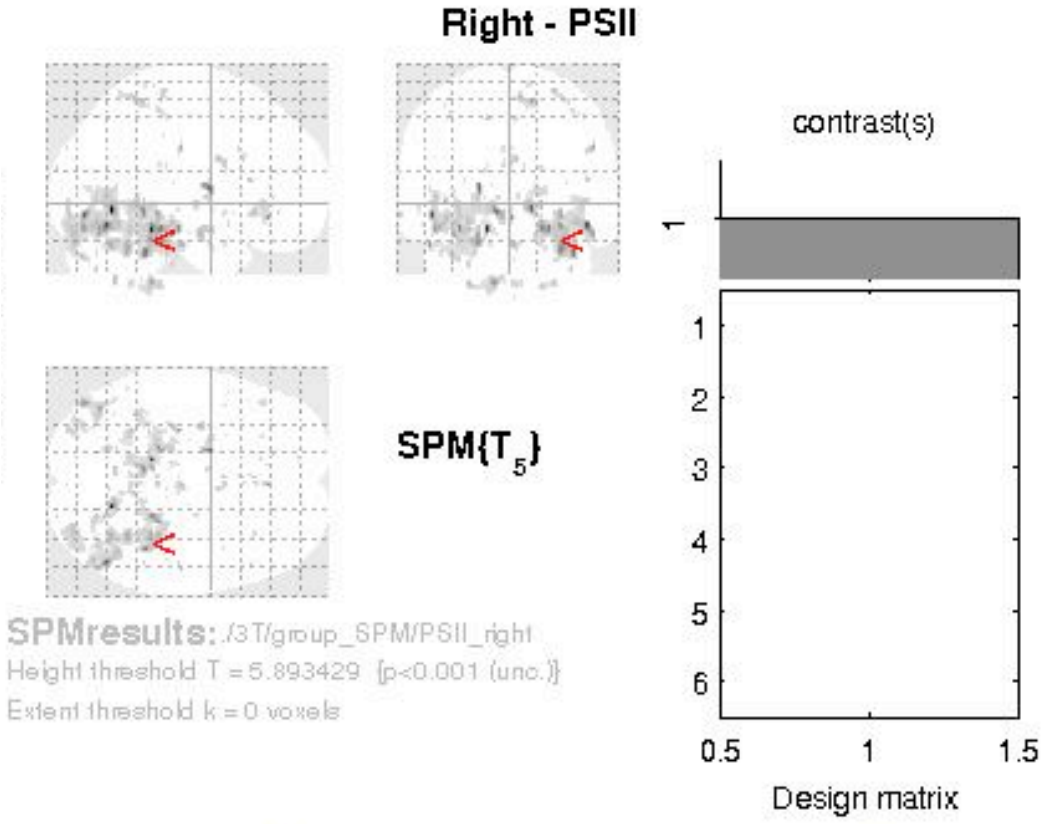


Figure 15

Second post-surgical scan: whole brain activation maps for subjects with right-side seizure



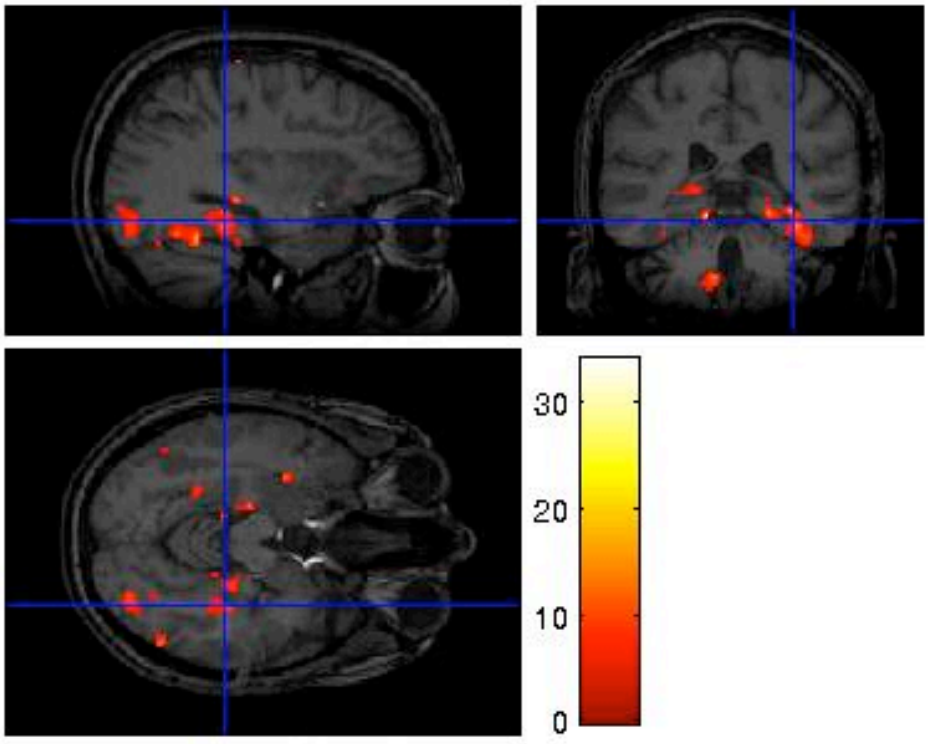


Figure 16.

Pre and 1st Post-Surgical Scan: whole brain activation maps for subjects with right-side seizure who were included in the 2nd post-surgical session

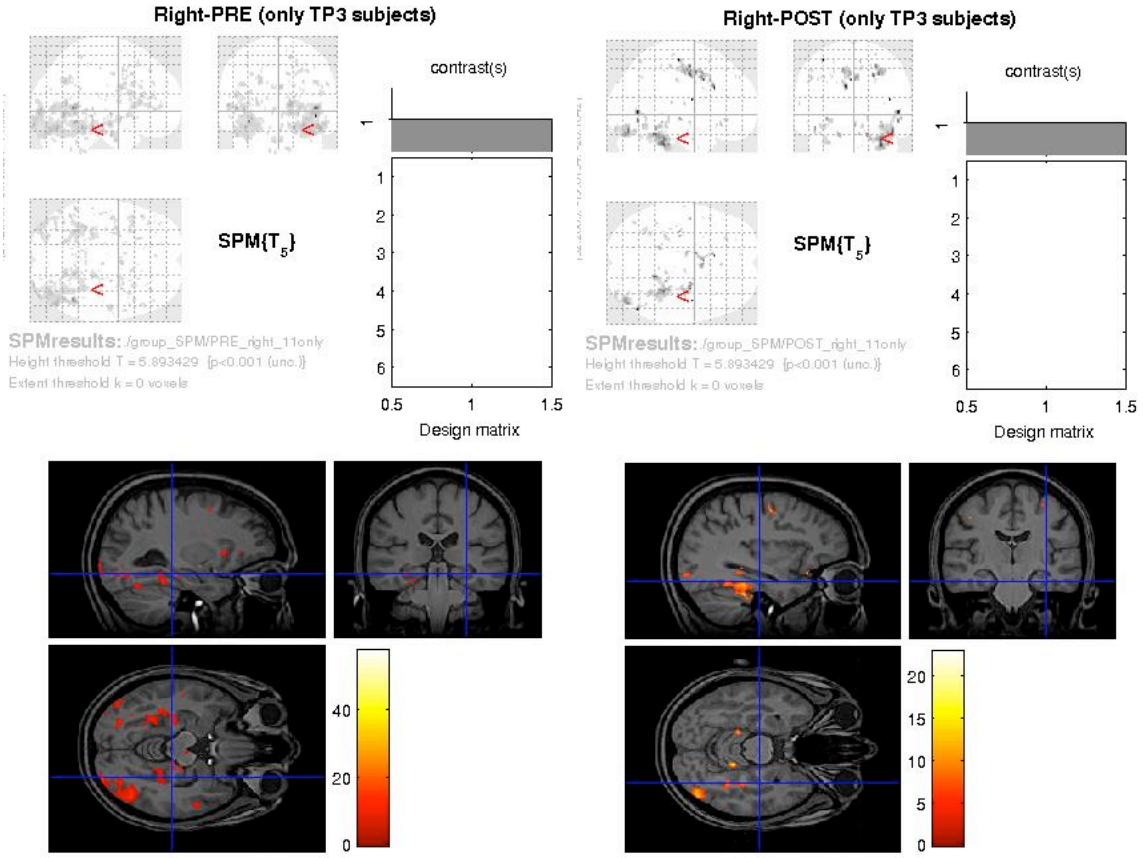


Figure 17

Pre-surgical right-side seizure group analysis, comparison of early and late onset groups

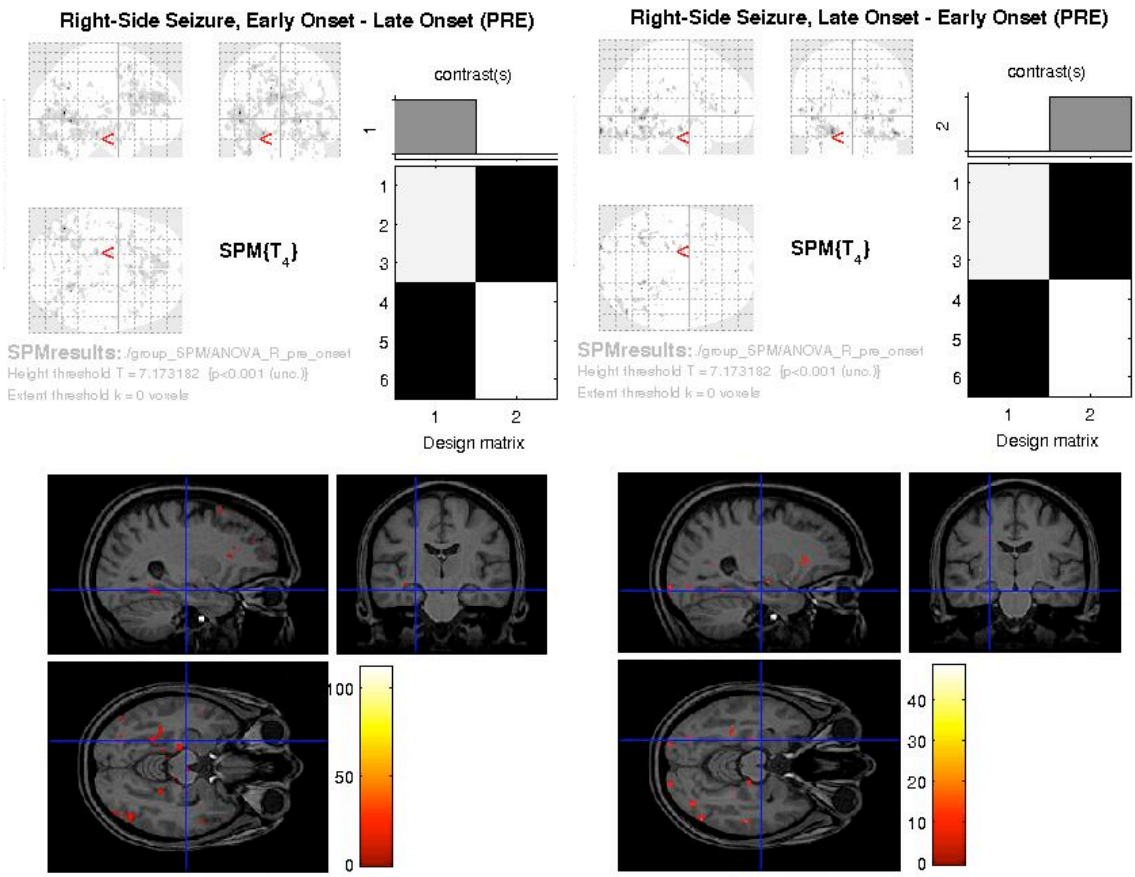


Figure 18

Post-surgical right-side seizure group analysis, comparison of early and late onset groups

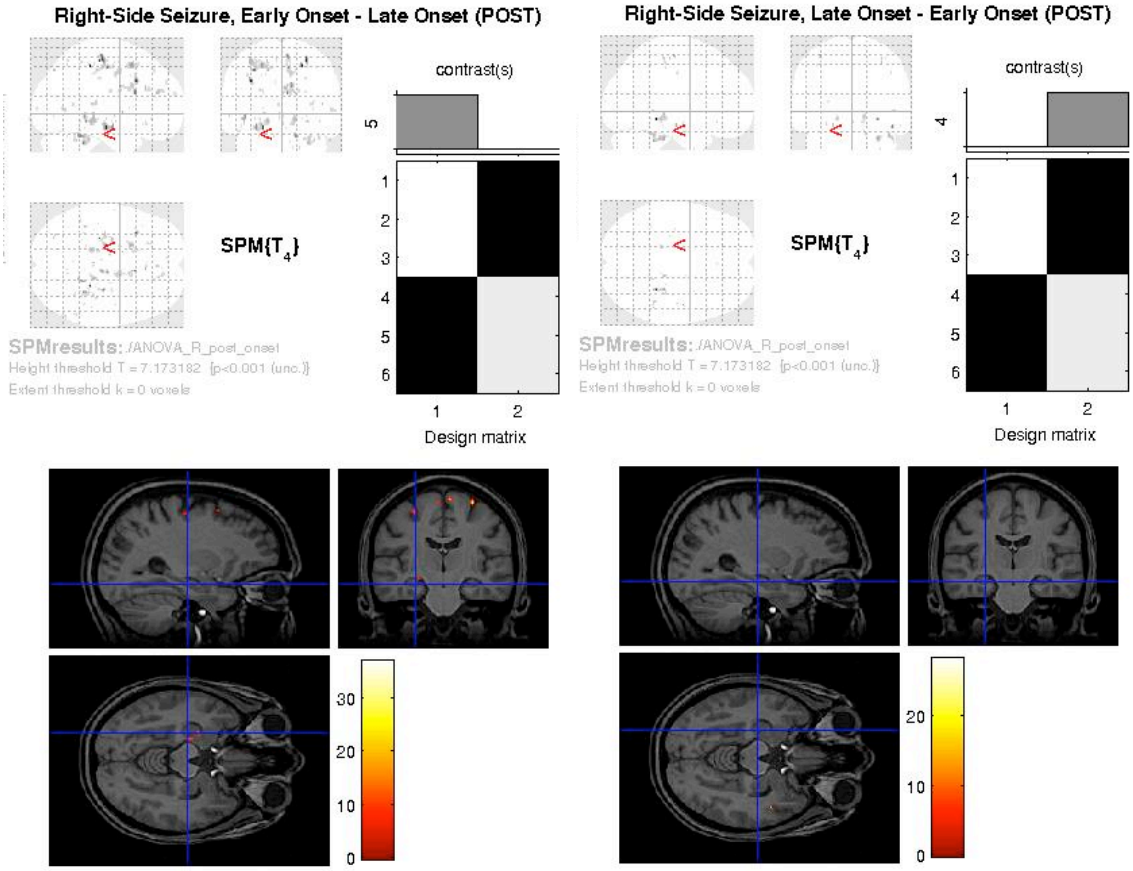


Figure 19

Pre-surgical left-side seizure group analysis, comparison of early and late onset groups

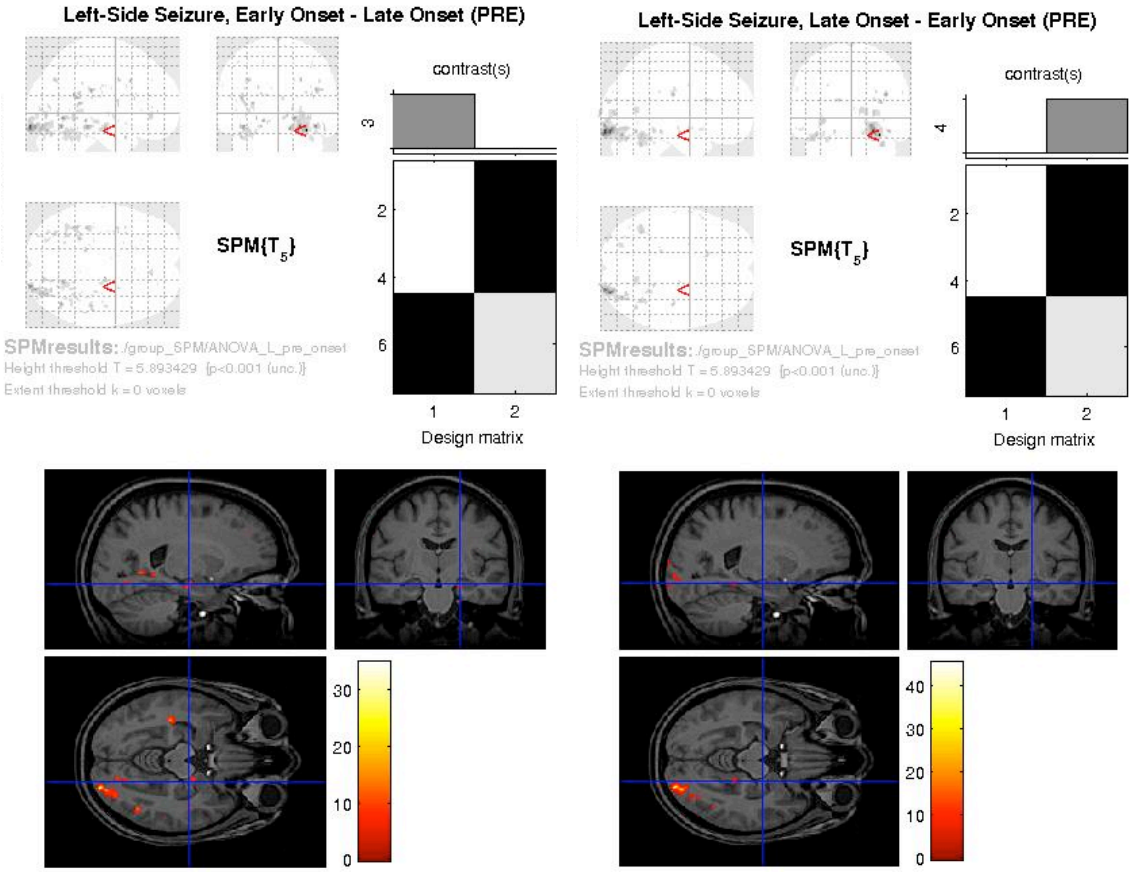


Figure 20

Post-surgical left-side seizure group analysis, comparison of early and late onset groups

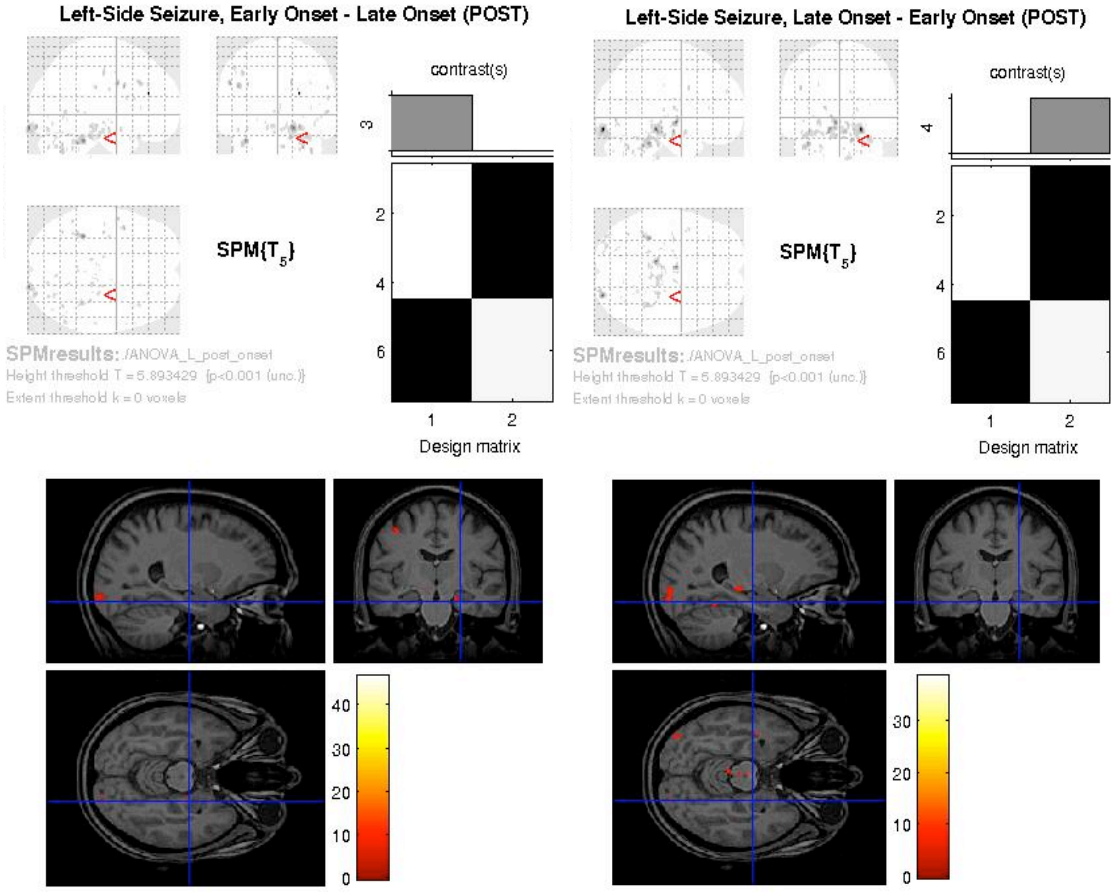
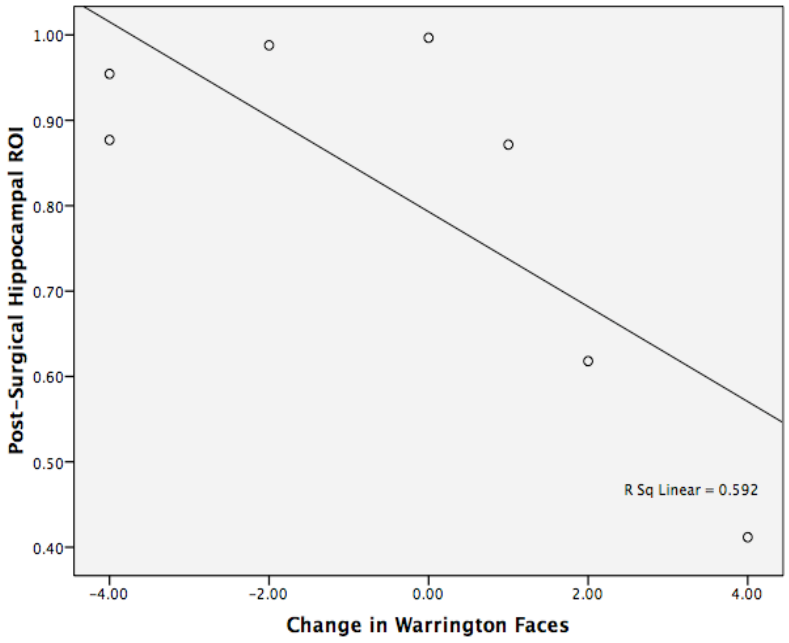


Figure 21

Right-Side Seizure: Correlation Between Change in Visual and Verbal Memory and Post-Surgical Contralateral Hippocampal Activation



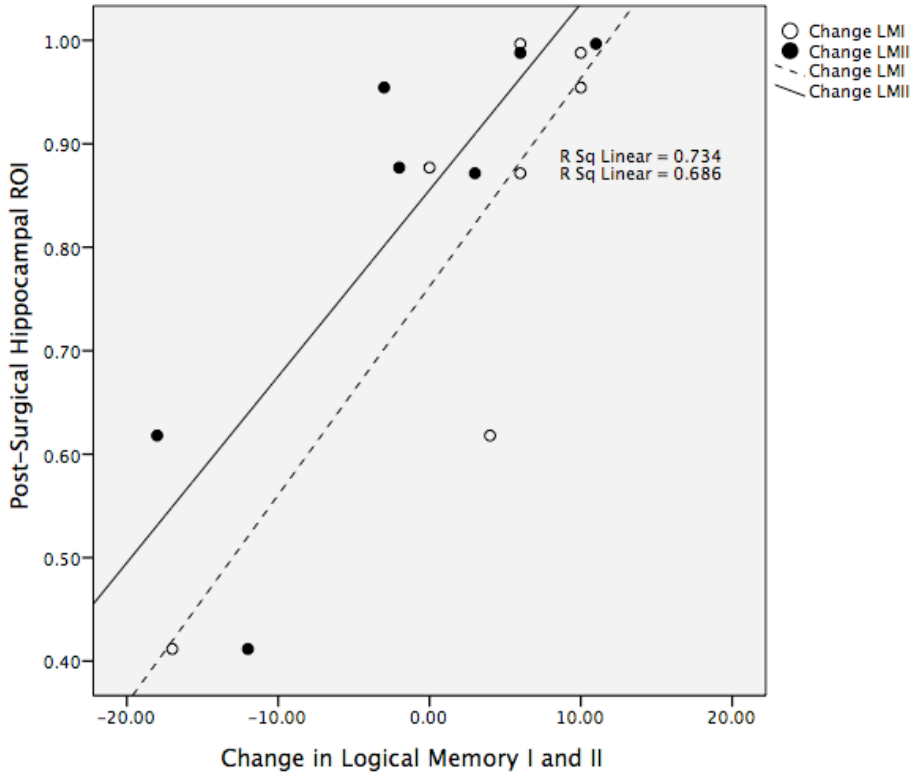
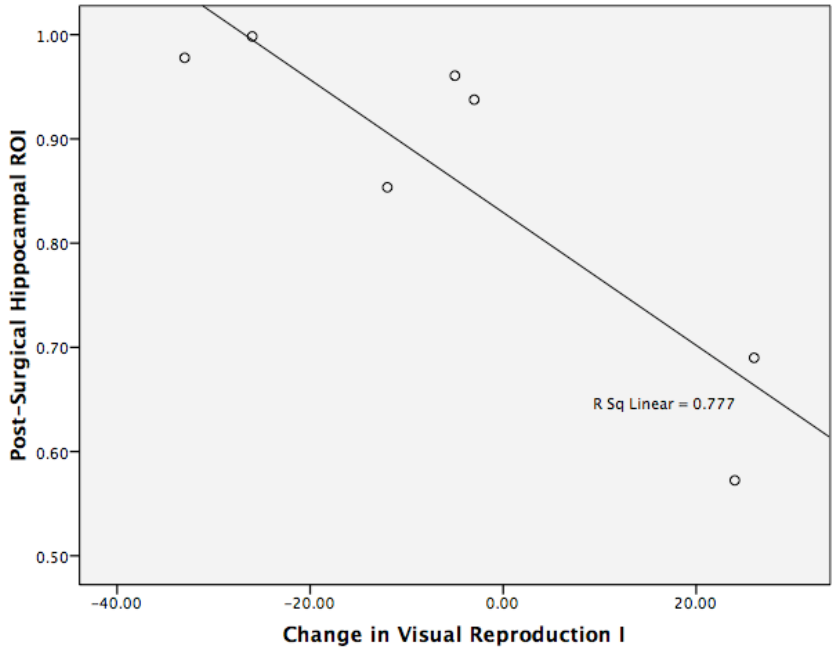
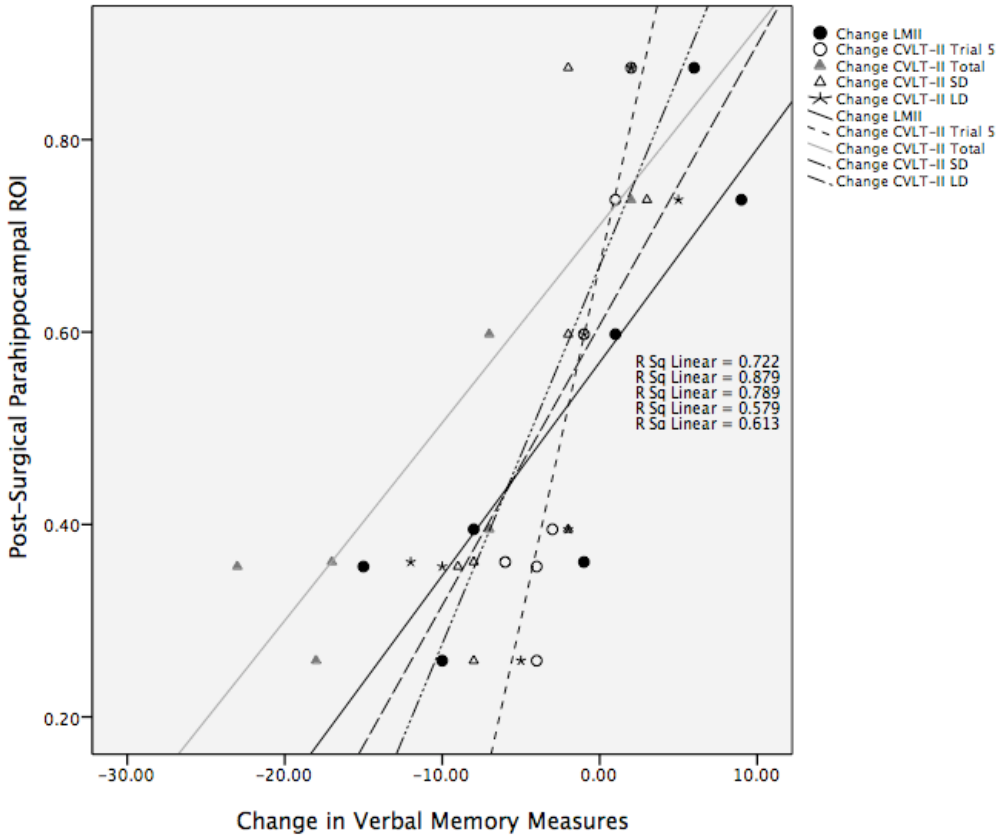


Figure 22

Left-Side Seizure: Correlation Between Change in Visual and Verbal Memory and Post-Surgical Contralateral Hippocampal and Contralateral Parahippocampal Activation





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