Language Outcome After Left Temporal Lobectomy in Patients with Discordant fMRI and Sodium Amobarbital Testing Results

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by

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ABSTRACT

LANGUAGE OUTCOME AFTER LEFT TEMPORAL LOBECTOMY IN PATIENTS WITH DISCORDANT fMRI AND SODIUM AMOBARBITAL TESTING RESULTS

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The rationale for this study was to examine 1) language lateralization discordance rates between fMRI and the IAT in pre-surgical epilepsy patients and 2) naming outcome after left ATL in a group of patients for whom IAT and fMRI language LIs were discordant. Participants were 229 consecutive pre-surgical epilepsy patients who underwent the IAT and fMRI. IAT LIs (% correct inject right –% correct inject left condition) were calculated based on performance on comprehension, naming, repetition and reading language tasks. The fMRI LIs [(L-R)/(L+R) where L = number of activated left hemisphere voxels and R = number of activated right hemisphere voxels) were calculated for lateral, angular gyrus, temporal, and frontal regions of interest (ROIs) using a published semantic decision task. Discordance was determined using cut scores and difference scores for each method. Regression analyses were performed to investigate predictors of discordance. Additionally, regression formulas developed from a separate sample for predicting language outcome using fMRI and IAT LIs were applied to the discordant cases so that observed and predicted outcome scores could be compared with each method. Discordance rates ranged from 14-17%, depending on ROI. Atypical language dominance on fMRI was most predictive of discordance. Of discordant cases who underwent left ATL, language outcome was more accurately predicted by each method in approximately half the cases. When fMRI indicates left language dominance, IAT LI concordance is high. However, when fMRI indicates atypical language dominance, concordance rates with the IAT decrease. Post-operative language outcome data suggests that the IAT and fMRI each predict outcome in certain cases, suggesting some error variance with each mapping method.

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CHAPTER 1: Statement of the Problem

Epilepsy is the third most prevalent chronic neurological disorder worldwide and affects approximately 2.7 million people in the United States (Epilepsy Foundation of America, 2008). It is estimated that 30-40% of individuals with epilepsy have medically intractable seizures despite treatment with anti-epileptic medications (AEDs). Of these, 30% are considered good candidates for epilepsy surgery. Favorable candidates typically have localized seizures in brain regions that are not essential for cognitive functions such as memory and language (Binder & Raghavan, 2006; Engel & Shewmon, 1996). The objective of surgical intervention is to remove the seizure focus while minimizing risk for cognitive morbidity. Patients who undergo epilepsy surgery, particularly dominant temporal lobectomy, are at risk for decline in language functions and verbal memory (Hermann, Wyler, Somes, & Clement, 1994; Langfitt & Rausch, 1996; Sabsevitz et al., 2003). As such, the assessment of hemispheric representation of language is a standard component of the pre-surgical evaluation for epilepsy surgery candidates.

The “gold standard” method for lateralizing cognitive functions such as language and memory has traditionally been the intracarotid sodium amobarbital test (IAT) (Loring, Meador, Lee, & King, 1992; Wada & Rasmussen, 1960). The IAT is a procedure in which an anesthetic agent is injected into the anterior and middle cerebral arteries that supply one cerebral hemisphere via the internal carotid artery, which temporarily inactivates the hemisphere so that the cognitive functions of the contralateral hemisphere may be tested. The procedure is then typically repeated so that both cerebral hemispheres may be assessed.

In 1993, over 95% of epilepsy surgery centers worldwide were using the IAT to assess all surgical candidates (Rausch et al., 1993). The results of a more recent survey (Baxendale, Thompson, & Duncan, 2008) suggested that many epilepsy centers no longer use the IAT for all pre-surgical evaluations. This decline in the prevalence of intracarotid amobarbital testing is likely related to the limitations of this method (e.g., invasive, costly, patient complications, methodological concerns) and the increased use of functional neuroimaging and cortical mapping techniques such as functional magnetic resonance imaging (fMRI) to lateralize and localize language functions.

Over the past 15 years, fMRI has been increasingly used to lateralize language functions; fMRI is less costly than IAT, noninvasive, may be safely repeated if necessary, and has the potential to provide not only lateralization, but also more specific information about localization of language processes (Binder & Raghavan, 2006; Binder et al., 1996). In this procedure, cerebral activation is detected by examining blood flow changes that occur in association with performance of a cognitive task while in the MRI scanner. In recent years, there has been a trend among epilepsy centers to replace the standard IAT with fMRI for the assessment of language lateralization (Baxendale et al., 2008). However, it has been suggested that an appropriate evidence base has not yet been developed to establish post-operative risks for cognitive decline based on fMRI language maps (Loring, 2008), though several studies have been published recently showing that fMRI language lateralization scores can predict both language and memory outcome after left anterior temporal lobectomy (Binder, Sabsevitz, et. al., 2008; Sabsevitz et al., 2003). At present, there is no universally accepted, validated fMRI language lateralization protocol; a variety of tasks and methods of data analysis are used. Moreover, because

IAT/fMRI discordance has been reported in approximately 1 out of every 10 cases of language lateralization, further examination of discordance rates and predictors of discordance, as well as post-surgical outcome in discordant cases is needed.

A number of studies have been conducted comparing IAT and fMRI language lateralization results. A review of these studies indicated reported concordance rates ranging from 55-100% (Swanson et al., 2007). The wide variability in concordance rates may be attributed to small sample sizes (n > 30 in only two studies) that contain limited numbers of patients with atypical language dominance, different probe tasks (e.g., semantic, covert fluency, story listening), different control tasks (e.g., rest or visual fixation vs. a perceptual control), and different regions of interest (ROIs) (e.g., frontal, whole brain, temporal, parietal). Despite the rates of discordance, fMRI has the potential to be an alternative to IAT for the determination of language lateralization in epilepsy patients. However, further investigation of the rates and potential causes of discordance between these two functional mapping methods is needed, including concordance and correlation differences by ROI and employing a large sample with a wide range of language dominance scores (Swanson et al., 2007). Additionally, further investigation of language outcome is needed, as only one study to date has examined the predictive validity of fMRI with regard to post-operative language morbidity (Sabsevitz et al., 2003).

Rationale for the Study

Functional magnetic resonance imaging is a potential alternative to the IAT for the lateralization of language functioning in epilepsy surgery candidates. However, further examination of discordant cases between fMRI and IAT is needed so that factors affecting the concurrent and predictive validity of fMRI can be understood. Specifically, further investigation is needed to compare the IAT and fMRI using a tightly controlled language/control task protocol with a large sample of epilepsy patients whose language dominance ranges across the continuum. Most studies to date have relied on small samples (N < 30), with even fewer individuals with atypical language dominance, even though those with atypical dominance have frequently been the participants who have had discordant findings. Many of these comparison studies used an inadequate control task (e.g., rest, fixation), which further limited findings. Moreover, many previous studies have used a covert fluency task that results in more frontal than temporal activation, although temporal activation has been more highly correlated with naming outcome (Benke et al., 2006; Sabsevitz et al., 2003; Spreer et al., 2002).

Differences in correlations and rates of concordance can be investigated across different ROIs (e.g., frontal, temporal, angular gyrus, lateral). Additionally, closer examination of factors that may contribute to finding discordant results between fMRI and IAT is necessary. Finally, language outcome should be examined post-operatively in cases with discordant results to assess which method was more predictive of naming outcome. At present, most findings related to language outcome refer anecdotally to the absence of post-operative aphasia, but no formal studies have examined the predictive value of IAT vs. fMRI in cases with discordant language lateralization prior to surgery. As such, a study that would provide additional information regarding the concurrent and predictive validity of fMRI by comparing IAT and fMRI procedures for language lateralization has important clinical implications regarding the selection of pre-surgical language assessments for intractable epilepsy patients.

Research Questions

As previously indicated, although IAT/fMRI comparison studies have investigated the concordance of language lateralization scores between the two procedures, the proposed study, which would closely examine causes and cognitive outcome in discordant cases, may lay to rest any remaining doubts about replacing IAT with fMRI. Therefore, the primary research questions of this study are as follows:

Question One: What is the correlation between language lateralization scores measured by the IAT and fMRI in a large sample (N = 229) of intractable epilepsy patients?

One of the criticisms of the IAT/fMRI comparison studies has been the small sample sizes, which have typically been less than 30. Such a small number of participants may not include a large enough group of individuals with atypical language dominance. The sample of the proposed study was comprised of 229 consecutive patients in the comprehensive epilepsy program at the Medical College of Wisconsin. Examination of the correlation between the two measures allowed a direct comparison of language lateralization scores along a continuum, and provided valuable information regarding the concurrent validity of fMRI.

Question Two: What is the rate of discordance between the language lateralization scores measured by the IAT and fMRI?

Rates of discordance have differed in past reports, which may be related to methodological differences (e.g., task differences, inclusion criteria, data analysis). In particular, researchers have defined "discordance" in different ways, which is likely related to the discrepancy. We examined concordance using both a pre-determined threshold for categorization of left, right and "bilateral language" as well as a difference score between the LIs of the two measures, which provided greater accuracy than a cut score alone. The rate of discordance is important, as it has clinical implications for the validity of the fMRI and IAT LIs. Equally important is the ROI, which has been shown to alter rates of concordance. In the proposed study, we plan to make comparisons between fMRI LIs based on activation in the frontal, temporal, angular gyrus, and lateral ROIs.

Question Three: What factors predict discordance?

It is necessary to closely examine the discordant cases and the variables associated with each method (fMRI and IAT) that predict discordance. As fMRI replaces IAT, these factors will serve as indicators that language may not be accurately assessed by one procedure, and that both should be performed in certain circumstances. Furthermore, these factors may provide information that leads to improvements in fMRI protocol design. Factors that were hypothesized to predict discordance included methodological limitations of the IAT (e.g., obtundation, vascular abnormalities, duration of drug effect) and methodological limitations of fMRI (e.g., motion artifacts, behavioral performance). Additionally, subject characteristics such as structural abnormalities (e.g., mesial temporal sclerosis or atrophy), handedness, age at seizure onset, and baseline cognitive functioning (IQ) were hypothesized to predict discordance.

Question Four: In discordant cases, is the IAT or fMRI more predictive of post-operative language outcome?

Examination of the discordant cases with regard to post-operative functioning provided preliminary evidence, which is quite limited in the extant literature, of the predictive validity of each procedure. This data has the potential to inform clinician decision-making regarding which procedure may be of greater clinical use in specific situations.

CHAPTER 2: Review of the Literature

This literature review will provide an overview of the epidemiology of epilepsy, classifications of epileptic seizures and epilepsy syndromes, a review of surgical treatment for intractable epilepsy and post-surgical outcome considerations, and findings regarding language organization in both neurologically normal individuals and epilepsy patients. These sections will provide context for the description and evaluation of the IAT and fMRI procedures, their utility for lateralizing language in epilepsy patients, and their ability to predict post-surgical language outcome. The literature review will conclude with a critical evaluation of studies that have compared language lateralization IAT and fMRI, examining concordance rates, outcome predictions, the limitations of each method, and the proposed study that will be designed to address some of the limitations of this body of literature.

Definitions

Angiography: A procedure used to visualize the inside of blood vessels and organs in the body. A contrast agent is injected into a blood vessel, and then is viewed using an x-ray technique.

Angular gyrus: A region of the inferior parietal lobe that is involved in the processing of auditory and visual input and in the comprehension of language.

Aphasia: Inability to express and/or comprehend language.

Atypical language dominance: Characterized as language represented primarily in the right hemisphere or bilaterally.

Complex partial seizures: Characterized as seizures arising from one part of one cerebral hemisphere in which consciousness is impaired.

Contralateral: Occurring on, affecting, or acting in conjunction with the opposite side of the body.

Cortical stimulation mapping: Administering stimulation directly to a part of a neural circuit in the brain and measuring the consequences.

Crossflow: The occurrence of anesthetic crossing over to the cerebral hemisphere being tested during the IAT.

Deoxyhemoglobin: The form of hemoglobin without oxygen; the predominant protein in red blood cells.

Electroencephalogram (EEG): A procedure that records the electrical activity in the brain produced by the firing of neurons within the brain.

Epilepsy: A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.

Epileptic seizure: A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epileptic syndrome: A cluster of symptoms and signs that occur together but do not have a single known etiology.

Functional Magnetic Resonance Imaging (fMRI): A type of MRI scan that measures the hemodynamic response related to neural activity in the brain. This is one of the two measures used to assess language lateralization in the proposed study.

Generalized seizures: Characterized as seizures in which initially involvement from both hemispheres is observed.

Hypsarrythmia: Abnormal interictal high amplitude waves and a background of irregular spikes seen in electroencephalogram, mostly in infants prior to age two.

Inferior frontal gyrus: An area of the frontal lobe of the brain, that has been associated with language functioning, particularly expressive language.

Intracarotid Sodium Amobarbital Test (IAT): A procedure in which one hemisphere of the brain is anesthetized at a time and neuropsychological testing is performed in order to determine cerebral dominance for various cognitive functions. This is one of the two measures used to assess language lateralization in the proposed study.

Intractable epilepsy: failure to achieve seizure remission despite compliance with appropriate anti-epileptic medications.

Lateralization index (LI): A method of computing the asymmetry of cognitive functions as they are represented in the brain.

Mesial temporal sclerosis (MTS): loss of neurons and scarring of tissue in the temporal lobe (typically the hippocampus).

Mesial temporal lobe epilepsy (MTLE): The most common form of epilepsy, associated with MTS.

Obtundation: A dulled or reduced sense of alertness or consciousness.

Oxyhemoglobin: The oxygen-loaded form of hemoglobin, the predominant protein in red blood cells.

Positron emission tomography (PET): A nuclear medicine imaging procedure that requires injection of a short-lives radioactive tracer isotope, which then produces a three-dimensional image of functional processes in the body when an individual is scanned.

Motion artifacts: Movement by individuals while in a scanner that distorts the image that is obtained.

Magnetic resonance imaging (MRI): A procedure that uses a magnetic field to visualize the internal structure and function of the body.

Simple partial seizures: Characterized by seizures arising from one area of one cerebral hemisphere, in which consciousness is not impaired.

Status epilepticus: A state of persistent seizure which is not self-limited and must be stopped by medical intervention.

Superior temporal gyrus: An area in the temporal lobe that has been associated with language and processing.

Voxel: A “volume pixel” which represents a quantity of three-dimensional data, and is the unit of measurement used in fMRI.

Epidemiology of Epilepsy

Epidemiological studies of individuals with epilepsy provide critical information about the incidence, prevalence, etiology, and prognosis of epilepsy. It has been suggested that information about incidence and prevalence is necessary for the evaluation of etiologic factors, and that incidence cohorts are the most appropriate group in which to evaluate prognosis (Hauser, Annegers, & Rocca, 1996). As such, the incidence, prevalence, etiology and risk factors, and prognostic indicators of the epilepsies are outlined below.

Incidence and Prevalence

Epilepsy is one of the most common chronic neurological disorders, yet there is significant variance in reported incidence and prevalence rates. These differences are related to the geographic location of the study, variable inclusion criteria (e.g., febrile seizures, single seizures), different age groups (i.e., the highest incidences of epilepsy are found in children and the elderly), and a lack of standardized definitions of key terms such as “active epilepsy” (Bell & Sander, 2001). Annual incidence rates reportedly range from 11 per 100,000 in Norway to 230 per 100,000 in Ecuador. Prevalence studies have been carried out in more than 25 countries, and the reported prevalence rates range from 1.5 per 1,000 to 57 per 1000 (Sander & Shorvon, 1996). Overall, the incidence of epilepsy is generally accepted as 50 cases per 100,000 persons per year in developed countries, and between 100 and 190 cases per 100,000 persons per year in developing countries. Across studies, the prevalence of epilepsy is accepted as 5 to 10 cases per 1000 persons, with lifetime prevalence of seizures between 2 and 5% (Bell & Sander, 2001; Sander, 2003). In the United States, it is estimated that 200,000 new cases of epilepsy are diagnosed each year, and that epilepsy affects approximately 2.7 million individuals (Epilepsy Foundation of America, 2008).

Etiology and Risk Factors

The current epidemiological data indicate that epilepsy is a ubiquitous disorder, but that it does not affect individuals equally, which raises questions of etiology (Jallon, 2002). The etiology of epilepsy is thought to be related to the interaction of numerous contributing factors. The main causes and risk factors of epilepsy that have been identified are genetic factors, acquired conditions (e.g., traumatic brain injury), geographic location, age, and sex.

Genetic factors. According to Ottman (1997), the best estimates of the increased risk of having epilepsy among family members of epilepsy patients relative to the population were reported in the classic Rochester Epidemiology Project, which provided the proportions of all documented cases of epilepsy in Rochester, Minnesota between 1935 and 1984 (N ~ 2600) that were attributable to various causes (Annegers, Rocca, & Hauser, 1996). Annegers and colleagues (1996) reported an idiopathic cause, which they defined as either of genetic origin or presumed symptomatic with an unknown cause, in 68% of all cases of epilepsy. The findings of this project indicated an increased incidence (approximately two to four times as likely) of epilepsy in siblings and children of individuals with epilepsy, suggesting the possibility of a genetic contribution to the disorder. Additional evidence of a genetic factor is indicated by the following findings: (1) higher concordance rates have been reported in monozygotic twins than dizygotic twins, (2) seizures are often associated with genetic disorders (3) animal studies have indicated several genes which raise seizure susceptibility, (4) in certain epilepsy syndromes, human epilepsy susceptibility genes have been localized to specific chromosomal regions (e.g., autosomal dominant cortical myoclonus epilepsy), and (5) causative genes have been identified some types of epilepsy (e.g., autosomal dominant nocturnal frontal lobe epilepsy) (Abad, Vilaplana, & Fernandez, 2007; Ottman, 1997). This evidence suggests a genetic predisposition for the development of some types of epilepsy, but the specific genes that may be responsible for the most common forms of epilepsy with a genetic origin are still largely unknown. Furthermore, nongenetic factors are likely involved in the expression of epilepsy in individuals with a genetic susceptibility.

Acquired factors. The Rochester Epidemiology Project (Annegers et al., 1996) also provided estimates of the proportions of various acquired causes of epilepsy. Cerebrovascular disease, the leading cause of acquired epilepsy in adults, accounted for 11% of the cases. Other etiological factors included developmental disabilities (in 5 % of cases), traumatic brain injury (in 4% of cases), brain tumor (in 4% of cases), degenerative central nervous system disease (in 3% of cases), and perinatal factors and febrile seizures (in 5% of cases). Other factors that have more recently been associated with the development of seizure disorders are infectious diseases, the contraction of pneumonia or meningitis in early childhood, extremely low birth weight (less than 1000g/27 weeks), and alcohol and drug use (Berg, Testa, Levy, & Shinnar, 1996; Sander & Shorvan, 1996).

Geographic location. Certain risk factors are specific to particular geographic locations or settings. For example, cystercicosis, a parasitic disease that affects the nervous system, is the most commonly identified cause of epilepsy in parts of Latin America but is exceedingly rare in Europe. Other risk factors such as race, SES, or type of setting (e.g., rural vs. urban) have not been conclusively linked to the development of epilepsy. While these factors have been associated with an increased incidence of epilepsy, they are likely confounded by the differences in nutrition, prenatal care, and medical services that exist in different geographic locations, both internationally and within the United States (Sander & Shorvan, 1996).

Age. In developed countries, the incidence of epilepsy is highest in children and the elderly, a finding that has not been observed in developing countries (Jallon, 2002). Still, approximately 50% of cases of epilepsy start in childhood or older adulthood, and of those, half occur prior to age one (Bell & Sander, 2001). These age-related incidence rates have the potential to fluctuate with medical advances. As medical care improves, increasing numbers of at-risk children survive and people are living longer. Subsequently, improvements in treatment for epilepsy and for causal conditions (e.g., cerebrovascular disease) are necessary to maintain and/or decrease the incidence of epilepsy (Bell & Sander, 2001; Berg et al., 1996).

Sex. It has been suggested that men have a slightly higher incidence of epilepsy than women (Sander & Shorvon, 1987). This finding may be related to the higher incidence of traumatic brain injury among men, but this relationship has not been substantiated. However, further evidence that men may be at higher risk for epilepsy is related to the higher incidence of nonepileptic seizures observed in women, which have the potential for misdiagnosis, thus possibly artificially inflating the incidence rates of epilepsy among females (Sander & Shorvon, 1996).

Prognosis

The prognosis for full seizure control is quite good; more than 70% of individuals with epilepsy achieve long-term remission within five years of diagnosis (Bell & Sander, 2001; Berg et al., 1996; Sander, 2003). The prognosis of epilepsy depends on a number of factors, including etiology, age at onset, number of seizures at onset, history of the condition, and the influence of treatment (Sander, 2003). Generally, starting treatment closer to the onset of the seizures is associated with better prognosis, and most patients whose seizures remit do so during the first two years of treatment. Seizure type and syndrome may also be predictors of recurrence; partial seizures have been shown to have a poorer prognosis for remission than generalized seizures (although this has not always been a significant finding), as have symptomatic or cryptogenic epilepsies (Bell & Sander, 2001).

Epilepsy is, then, a widespread disorder that affects a significant number of individuals in every country throughout the world. Etiology varies, but risk factors include genetic susceptibility, acquired factors that influence the structural integrity of the brain, age, and sex. Knowledge of these causal factors assists in the classification of seizure types and syndromes, which is necessary for prognostic assessment and optimal treatment planning.

Classifications of Epileptic Seizures and Syndromes

The epilepsies are a heterogeneous group of disorders, and their complexity necessitates a universal classification of epileptic seizures and syndromes. This allows communication and exchange of information between epileptologists, which furthers the advancement of treatment and research. The terms epileptic seizure, epilepsy, and epileptic syndrome are not interchangeable. The definitions epileptic seizure and epilepsy have recently been published by the International League Against Epilepsy (ILAE; Fisher et al., 2005). An *epileptic seizure* has been defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.” *Epilepsy* has been defined as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition” (p. 471). An *epileptic* *syndrome* is considered to be a cluster of symptoms and signs that occur together but do not have a single known etiology (Benbadis, 2001). This distinction is an important one, as it provides the most basic foundation for a universal dialogue between epilepsy clinicians and researchers.

The ILAE Task Force on Classification and Terminology has been in existence since 1997, with the objective of revising the currently accepted 1981 International Classification of Epileptic Seizures (Commission of ILAE, 1981) and the 1989 International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders (Commission of ILAE, 1989). In response to criticisms of the clinical usefulness of the current classification systems, the Commission published reports that clarify concept classification and proposed a 5-axis diagnostic scheme for individuals with epileptic seizures and epilepsy; however, a new classification proposal has not yet been accepted (Engel, 2001; 2006).

The 1981 International Classification of Epileptic Seizures

In 1981, the Commission on Classification and Terminology of the ILAE proposed a revised classification of epileptic seizures that, although criticized almost since its inception, remains widely accepted (Commission on Classification and Terminology of the ILAE, 1981; Engel, 2006). The 1981 classification revision recommended two significant changes from the previous 1969 version. First, the seizure classification system provided descriptive information in three domains (reduced from six): (1) clinical seizure type, (2) electroencephalographic (EEG) seizure type, and (3) EEG interictal expression. Seizure semiology during the ictal (during seizure) and interictal (between seizures) period is described. Secondly, descriptive accuracy was further improved by the addition of the separation of partial seizures into simple and complex, depending on whether or not consciousness is disturbed. Most broadly, seizure types were classified as partial (also referred to as focal or localization-related), generalized, and unclassified.

Partial seizures. Partial seizures are “those in which, in general, the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to one part of the cerebral hemisphere” (Commission on Classification and Terminology of the ILAE, 1981, p.493). Partial seizures can further be distinguished as simple or complex based on the status of consciousness. Simple partial seizures, sometimes referred to as auras, are those in which consciousness is not impaired. In contrast, complex partial seizures denote a state of impaired consciousness, defined as the inability to respond normally to external stimuli due to altered awareness/responsiveness. Partial seizures, then, can be classified as one of three types: (1) simple partial seizures, (2) complex partial seizures, and (3) partial seizures evolving to generalized tonic-clonic seizures.

Simple partial seizures are indicated when the EEG seizure type and interictal expression are characterized by local, contralateral discharge starting over the corresponding area of cortical representation for the given symptom. Consciousness remains intact during simple partial seizures. This seizure type is further described as follows: (1) with motor signs, such as focal motor with or without march, versive, postural, vocalization or arrest of speech, (2) with somatosensory or special-sensory symptoms that may be somatosensory, visual, auditory, olfactory, gustatory, or vertiginous, (3) with autonomic symptoms or signs, including epigastric sensation, pallor, sweating, flushing, piloerection and papillary dilation, and (4) with psychic symptoms, which may be dysphasic, dysmnesic, cognitive, affective, illusions, or structured hallucinations.

Complex partial seizures have an EEG seizure type that may have unilateral or bilateral discharge, diffuse or focal, often in temporal or frontotemporal regions. EEG interictal expression is unilateral or bilateral, generally asynchronous in focus, and usually in the temporal or frontal regions. Complex partial seizures are distinguished from simple partial seizures by the impairment of consciousness that occurs either at onset or following a simple partial onset. The simple partial features described above (i.e., motor signs, somatosensory/special sensory symptoms, autonomic symptoms, psychic symptoms) may be present, as well as automatisms, which are defined as “more or less coordinated adapted involuntary motor activity occurring during the state of clouding of consciousness either in the course of, or after an epileptic seizure, and usually followed by amnesia for the event” (Commission on Classification and Terminology of the ILAE, 1981, p. 497). Automatisms may be of the following types: (1) eating automatisms (e.g., chewing, swallowing), (2) automatisms of mimicry, (3) gestural automatisms, (4) ambulatory automatisms, and (5) verbal automatisms.

The third type of partial seizure is classified as partial seizures evolving to secondarily generalized seizures. In this case, the EEG reveals discharges of either the simple or complex partial seizure type that become secondarily and rapidly generalized. The evolution may be directly from either partial or complex seizures to generalized seizures, or a progression from simple, to complex, to generalized seizures.

Generalized seizures. Generalized seizures are “those in which the first clinical changes indicate initial involvement of both hemispheres” (Commission on Classification and Terminology of the ILAE, 1981, p. 494). Consciousness may be impaired, and motor signs tend to be bilateral. EEG patterns are bilateral, at least initially, which is thought to indicate widespread neuronal discharge in both hemispheres. Generalized seizures are classified as one of the following types: (1) absence seizures, (2) myoclonic seizures, (3) clonic seizures, (4) tonic seizures, (5) tonic-clonic seizures, and (6) atonic seizures.

Absence seizures are associated with EEG discharges that are regular and symmetrical 2-4 Hz spike-and-slow-wave complexes with bilateral abnormalities. EEG interictal expression usually shows normal background activity, although regular and symmetrical paroxysmal activity may occur. The distinguishing feature of an absence seizure is the sudden interruption of ongoing activities, a blank stare, and sometimes an upward rotation of the eyes. Absence seizures may occur with impairment of consciousness only, with mild clonic, tonic, or atonic components, or with automatisms. Absence seizures may also be atypical, which are distinguished by changes in tone that are more pronounced and a more gradual onset and/or cessation.

Myoclonic seizures have ictal and interictal EEG patterns that are polyspike-and-wave, spike-and-wave, or sharp and slow waves. These seizures are characterized myoclonic jerks (single or multiple), which are sudden muscle contractions that may be repetitive or isolated. Myoclonic seizures may frequently occur just before falling asleep or awakening, and may be exacerbated by volitional movement.

Clonic seizures have an ictal EEG pattern that reveals fast activity and slow waves, as well as the occasional spike-and-wave pattern. EEG interictal expression is spike-and-wave or polyspike-and-wave discharges. Clonic seizures are characterized by repetitive clonic jerks, which are the rapid contraction and relaxation of muscles and/or muscle groups, the absence of a tonic component, and a relatively short post-ictal phase.

Tonic seizures have ictal EEG patterns of low voltage, fast activity or a fast rhythm of 9-10 c/sec or more, decreasing in frequency and increasing in amplitude. Interictal EEG reveals rhythmic discharges or sharp and slow waves, sometimes asymmetrical, with abnormal background. Tonic seizures are characterized by a rigid muscular contraction resulting in a straining of limbs. Often, deviation of the eyes, distortion of features, rotation of the body, movement of the head toward one side, and pupil dilation occurs. The face often becomes pale, then flushed as the contractions interfere with respiration. Tonic-clonic seizures, the most frequently occurring type of generalized seizure (previously referred to as “grand mal”), involve both muscle rigidity and muscle contractions of the tonic and clonic types.

Atonic seizures are characterized by an ictal EEG that depicts polyspike-and-wave, flattening, or low-voltage fast activity. The interictal EEG reveals a polyspike-and-slow-wave pattern. Atonic seizures consist of a loss of muscle tone, which may lead to a head drop with slackening of the jaw, dropping of a limb, or slumping to the ground. These seizures may be very brief, in which case they are referred to as “drop attacks.”

Unclassified epileptic seizures. This category was developed to capture all seizures that do not fit into the previously outlined categories. Many seizures observed in infants are deemed unclassified until EEG characterization can provide information that is necessary for classification. In other cases, there is sometimes inadequate or incomplete data, which makes it impossible to classify the seizure type in the established categories.

The 1989 International Classification of Epileptic Syndromes

In addition to classification of seizure type, the Commission on Classification and Terminology of the ILAE also proposed a classification of the underlying condition, or epileptic syndrome. Information regarding the epileptic syndrome is useful for predicting prognosis and determining an optimal course of treatment (Bancaud, 1989; Dreifuss & Henriksen, 1992). The ILAE distinguished between idiopathic (primary) epilepsy, symptomatic (secondary) epilepsy, and cryptogenic epilepsy, with cryptogenic epilepsy referring to presumed symptomatic epilepsy with an unknown etiology.

Idiopathic epilepsy. Idiopathic epilepsies are typically attributed to genetic causes. Often, idiopathic epilepsies are observed in individuals with a family history of epilepsy. The condition typically begins in the first few years of life, but not as early as symptomatic epilepsies, intellect is intact, and there are no signs of structural neuronal damage. EEG background is generally normal without excessive slow activity and the condition is generally self-limited (i.e., when seizures occur, they are stopped without medical intervention). Idiopathic epileptic syndromes may be localized and/or generalized

Symptomatic epilepsy. The symptomatic epilepsies are those which occur as the result of a structural neurologic disease or identifiable metabolic disturbance (Commission on Classification and Terminology of the ILAE, 1989). These epilepsies are associated with neurological and intellectual impairment and an EEG background that is slow and disorganized. Prognosis is typically poor, response to medication is often less favorable, and spontaneous remission is less likely than in cases of idiopathic epilepsy. Symptomatic and cryptogenic localization-related epilepsies are the most common type of adult-onset epilepsy. The most common localization-related epilepsy in adults is mesial temporal lobe epilepsy (MTLE), whereas neocortical epilepsy is more common in infants. Hippocampal sclerosis is the most common cause of MTLE, which is usually characterized by complex partial seizures with automatisms, often preceded by a simple partial phases with sensory symptoms, or auras (commonly epigastric or psychic).

The 2001 Proposed Diagnostic Scheme for Epileptic Seizures and Epilepsy

Dissatisfaction with the accepted classification systems prompted a new proposal by the ILAE for a diagnostic scheme rather than a fixed classification system (Engel, 2001). The diagnostic scheme relies on five axes that are used to provide a description of individual patients and may be as brief or detailed as necessary. Axis 1 consists of a description of ictal semiology. Axis 2 is the epileptic seizure type, which includes self-limited epileptic seizures such as generalized, partial, and neonatal seizures, and status epilepticus, which is characterized by the failure of biological seizure-suppressing mechanisms to terminate seizure activity. Axis 3 is the syndromic diagnosis, which may be categorized as idiopathic focal epilepsies of infancy and childhood, familial focal epilepsies, symptomatic (or likely symptomatic) focal epilepsies, idiopathic generalized epilepsies, reflex epilepsies, epileptic encephalopathies, progressive myoclonus epilepsies, and seizures not necessarily requiring a diagnosis of epilepsy. Axis 4 will specify etiology when it is known. Axis 5 is an optional designation of the degree impairment caused by the epileptic condition (Engel, 2006; Engel, 2001). This diagnostic scheme is still a work in progress, as it proposes new concepts that are under discussion, but it represents the direction that the classification of the epilepsies is heading. It is hoped that this diagnostic scheme will be more descriptive than the previously accepted categories (e.g., partial, generalized), provide more clarity (e.g., the terms cryptogenic and idiopathic are often misunderstood and misused), and will be more useful for treatment planning (Engel, 2001).

Seizures, then, can broadly be described as partial (or localization-related, focal) or generalized, depending on the focus of the seizure. They can be distinguished in terms of impairment of consciousness (i.e., simple, complex), symptoms (e.g., motor, sensory), and type (e.g., absence, tonic-clonic). Moreover, the distinction of idiopathic, cryptogenic, and symptomatic syndromes indicates a broad etiological type. These classification systems provide the foundation for the proposed flexible 5-axis diagnostic scheme, which has the potential to provide the most individualized description of seizures and epileptic conditions.

Overview, Treatment, and Outcome of Intractable Epilepsy

One subgroup of individuals with epilepsy, those with intractable epilepsy, poses a significant burden at both the societal and the individual level. In a recent survey conducted in the United States, individuals with intractable epilepsy comprised 35% of all epilepsy patients, yet this group was responsible for 79% (8.5 billion dollars) of the lifetime costs of the entire epilepsy population (Begley et al., 2000). The individual costs in terms of disability and decreased quality of life are also significant (Taylor, 1993), which indicates the need for a curative treatment. It is widely accepted that approximately 30-40% of epilepsy patients do not achieve seizure remission despite appropriate pharmacological treatment (Sander, 2003; Starreveld & Guberman, 2006). As such, much research has focused on the predictors of intractability, treatments, and predictors of outcome for individuals with intractable epilepsy.

Criteria for Intractable Epilepsy

Individuals with intractable epilepsy comprise a poorly defined group, often broadly referred to as individuals who fail to achieve seizure remission, which likely overestimates true intractability due to factors such as medication noncompliance or inappropriate medication regimens (Farrel, Wirrell, & Whiting, 2006). A common set of criteria that define intractable are important, as this aids in early recognition, prognosis, outcome prediction, and treatment planning (Starreveld & Guberman, 2006). Proposed components of intractability are (1) anti-epileptic drug (AED) failures, (2) seizure occurrence, (3) the time period of observation, and (4) the time period during the course of the disorder (Berg, 2006).

A treatment plan that includes all possible combinations and doses of AEDs would be impractical, and unlikely to be beneficial. The number of AED failures that constitute a designation of intractability varies, but the minimum number is typically two to three, as two unsuccessful AED trials have consistently been predictive of subsequent failed drug trials (Berg, 2006). Criteria for seizure frequency differs, but all definitions include a minimum seizure frequency that is required for a categorization of intractability or a minimum period of seizure remission that is specified as disqualifying an individual from having intractable seizures (e.g., 6-12 months of complete remission, two seizures in a four month time period). In addition to seizure frequency, definitions of intractability generally specify an amount of time during which the patient is to be observed while taking AEDs (e.g., two years). Finally, the course of the disorder is considered; some consider intractability to be an appropriate classification following two years of treatment after the initial diagnosis without a six-month remission period, others consider seizure frequency during the amount of time since last follow-up, regardless of the total length of time of the disorder (Berg, 2006; Berg, 2003; Dlugos, 2001).

Predictors of Intractable Epilepsy

A number of factors have been found to predict intractable epilepsy, including neurological deficits, epilepsy syndrome and seizure type, earlier age at onset, history of febrile seizures, perinatal asphyxia, central nervous infection, status epilepticus, serious head trauma, and a lack of response to the first AED (Andrade, Zumsteg, Sutula, & Wennberg, 2006; Berg, Levy, Novotny, & Shinnar, 1996; Chawala, Aneja, Kashyap, & Mallika, 2002; Dlugos, 2001). As such, it has been suggested that early intervention may be appropriate for individuals who have neurologic impairment such as cerebral palsy or mental retardation, those with seizure onset before one year of age, and those who do not respond to AEDs (Andrade et al., 2006; Dlugos, 2001). Furthermore, certain epilepsy syndromes such as West Syndrome (characterized by infantile spasms, an EEG that indicates hypsarrythmia, and mental retardation) and Lennox-Gastaut Syndrome (characterized by seizure onset prior to age four, varied seizure types, impaired intellectual functioning and possible developmental delay and/or behavioral disturbance), as well as specific seizure types such as complex partial seizures are likely to predict intractability (Chawala et al., 2002).

Treatment of Intractable Epilepsy

When epilepsy is intractable, surgical resection of the area of seizure focus is currently the most effective means of achieving seizure control; patients have reportedly been seizure-free in 50-80% of cases, depending on the type and location of seizure focus (Al-Kaylani, Konrad, Lazenby, Blumenkopf, & Abou-Khalil, 2007; Bonilha et al., 2007; Wiebe, Blume, Girvin, & Eliasziw, 2001). In the one randomized, controlled clinical trial to date comparing the efficacy of temporal lobe epilepsy surgery with medical therapy (AEDs), it was found that 58% of the surgical patients were seizure free at one year follow-up, compared to 8% of the medical group. However, neurological deficits were significantly greater in the surgically treated group (Wiebe et al., 2001), although this finding is potentially misleading, as the cognitive deficits that are sometimes associated with AED use or continued seizure activity may take longer than one year to develop. These findings are consistent with those of Tellez-Zenteno and colleagues (2005), who conducted a meta-analysis of post-surgical outcome studies; 66% patients who underwent temporal resection in a sample of 40 studies were seizure-free at long-term follow-up ($\geq$ 5 years). Seizure freedom was less common after other resections, but findings should be interpreted with caution, as they were based on a relatively small sample of nine studies; 46% of patients were reportedly seizure-free after occipital and parietal resections (based on two studies), as were 27% following frontal resections (based on seven studies). These findings indicate preferable seizure outcomes after resective surgery compared to the medical therapy group described by Wiebe and colleagues (2001). As such, when post-surgical risks are predicated to be minimal, surgery appears to be preferable to palliative treatments (e.g., AEDs, vagus nerve stimulators). Surgical procedures include focal cortical resection, anatomical lobectomy, lesionectomy, corticectomy, multiple subpial transections, corpus callosotomy, and hemispherectomy (Kuzniecky & Devinsky, 2007). Temporal lobe epilepsy (TLE) surgery is by far the most commonly performed type of surgical procedure for the treatment of epilepsy (more than all other types combined), followed by frontal lobe epilepsy (FLE) surgery (Jeha et al., 2007; Sperling, O'Connor, Saykin, & Plummer, 1996). However, epilepsy surgery is not a viable option for all patients with intractable epilepsy, as the benefits (e.g., seizure control, reduced cognitive morbidity, improved quality of life) do not always outweigh the risks (e.g., cognitive decline, mood or personality disturbance), and must therefore be evaluated on a case-by-case basis.

In order to evaluate candidacy for surgery, it is necessary to conduct a comprehensive pre-surgical assessment designed to predict post-operative functioning. This assessment procedure varies by epilepsy center, but generally includes an EEG evaluation, structural and functional imaging, and neuropsychological assessment. Measures such as EEG, positron emission tomography (PET), single photon emission tomography (SPECT), magnetic resonance imaging (MRI), fMRI, IAT, neurological examination, and neuropsychological assessment are used, with the goals of determining the cortical areas responsible for the generation of seizures, structural abnormalities, the functional integrity of the brain, and predicting the outcome of the resection of a specified section of cortical tissue (Berkovic, Newton, Chiron, & Dulac, 1993; Henry, Chugani, Abou-Khalil, Theodore, & Schwartz, 1993; Jones-Gottman, Smith, & Zatorre, 1993; Luders, Engel, & Munari, 1993; Kuzniecky et al., 1993; Quesney, Risinger, & Shewmon, 1993).

Post-surgical Outcome Assessment

Prediction of post-surgical functioning is a central goal of the pre-surgical assessment described above. Outcome assessment is primarily concerned with seizure control, cognition, and quality of life (Engel, Van Ness, Rasmussen, & Ojemann, 1993). Post-surgical prognosis is estimated relative to pre-surgical seizure status, cognitive level, and quality of life, which are closely interrelated (Steven & Wiebe, 2006).

Seizure status. A widely used outcome classification system was proposed by Engel (1987), which categorizes patients based on post-operative seizure status. Class 1 indicates complete seizure freedom or auras only for at least two years post-surgery, some seizures two years or more after surgery, or atypical generalized convulsion with AED withdrawal only. Class 2 is given to patients who were initially seizure free, but currently have rare seizures (i.e., 90% or greater seizure freedom compared to preoperative seizure frequency/status), those who had more than rare seizures after surgery (the exact time is unspecified), but then have rare seizures for at least two years, or nocturnal seizures which cause no disability. Class 3 is reserved for patients who have worthwhile seizure freedom (i.e., 75-90% seizure freedom compared to preoperative seizure frequency/severity), or seizure-free intervals amounting to greater than half the follow-up period, but not less than two years. Finally, Class 4 indicates no worthwhile improvement (i.e., 25% seizure freedom compared to preoperative seizure frequency/severity), no change, or a worsening of seizure frequency and/or severity.

Cognitive functioning. Cognitive outcomes have been addressed frequently in the literature (Vickrey, Hays, Hermann, Bladin, & Batzel, 1993). General intellectual ability, as well as language and memory are typically assessed, as the temporal lobe is believed to contribute heavily to language and memory functions (Rausch, 1991). Pre-surgically, individuals with epilepsy, particularly TLE, are at risk for cognitive deterioration; often patients with right-hemisphere TLE are impaired in visuospatial retention tasks, while those with left-hemisphere TLE may have impaired language and verbal memory (Aldenkamp, 1997; Hokeit & Ebner, 2002). Following surgery, particularly anterior temporal lobectomy, language and verbal memory deficits are possible following dominant hemisphere resection, whereas nonverbal memory deficits are more likely after nondominant hemisphere resection, although outcome is related to factors such as resection site, pre-surgical cognitive ability, and hippocampal integrity (Chelune et al., 1998; Clusmann et al, 2002; Seidenberg et al., 1998). Various measures of language and memory are used to assess lateralization and localization such as IAT, fMRI, and neuropsychological assessment. Neuropsychological assessment is typically repeated pre- and post-surgically in order to monitor cognitive changes, particularly in the domains of verbal and non-verbal memory, verbal fluency, comprehension, and confrontation naming. (Davies, Bell, Bush, & Wyler, 1998; Hermann et al., 1999; Sass et al., 1994; Suchy, Sands, & Chelune, 2003).

Quality of life. Individuals who have epilepsy often report a decrease in their quality of life due to the restrictions that are typically imposed by seizure activity. A review of the extant research revealed six areas that represent quality of life domains (Batzel & Fraser, 1993). These include the following: (1) interpersonal relationships, (2) vocational adjustment, (3) level of functional dependence, (4) perceived impact of seizures on everyday functioning, (5) personal adjustment in terms of self-image, sexual functioning, and personal initiative, and (6) overall psychosocial functioning. These areas are typically assessed with a self-report inventory, such as the Washington Psychosocial Seizure Inventory (WPSI) and the Quality of Life in Epilepsy (QOLIE – 31) (Dodrill, Batzel, & Fraser, 1991).

Predictors of Post-surgical Outcome

A number of predictors of post-surgical outcome have been identified in the literature. Age at seizure onset, seizure frequency, seizure type, pre-operative cognition scores, lateralization of memory and language functions, presence of mesial temporal sclerosis and hippocampal status, functional integrity of the hemisphere contralateral to the resection, and side of seizure (i.e., side of resection) have all been shown to be predictive of outcome. These predictors are important factors to consider when evaluating post-operative prognosis in terms of seizure control, cognition, and quality of life (Bell, Devies, Haltiner, & Walters, 2000; Chelune, Maugle, Luders, & Awad, 1991; Dinner, 1991; Dodrill, Wilkus, & Ojemann, 1992; Sabsevitz et al., 2003; Strauss, et al. 1995).

Seizure onset, frequency, type and focus. Seizure variables have been shown to be predictive of post-operative outcome. Earlier seizure onset and a history of febrile seizures have been associated with better seizure control (Clusmann et al., 2002; Holmes, Dodrill, Ojemann, Wilensky, & Ojemann, 1997) and better language outcome (Hermann, Davies, Foley, & Bell, 1999; Ruff et al., 2007) after surgery. A low seizure frequency and the absence of status epilepticus was also related to better seizure control (Clusmann et al., 2002; Hardy et al., 2003). Furthermore, localized epileptic discharges in one hemisphere have been associated with better outcome, as it is more likely that surgical resection will be able to remove the entire seizure focus (Radhakrishanan, 1998).

Structural integrity of the brain. The structural integrity of both the resected and nonresected brain tissue, as well as the surgical procedure used to remove the seizure focus has been shown to be predictive of outcome. There are two main histological categories of temporal lobe epilepsy; the most common is mesial temporal lobe epilepsy (MTLE), which comprises 66% of individuals with temporal lobe epilepsy (Wiebe, 2000), and the other is neocortical epilepsy (Wieser, Engel, Williamson, Babb, & Gloor, 1993). MTLE is associated with primary limbic pathology, typically mesial temporal sclerosis (MTS), and has been shown to have good surgical outcome (65% are seizure free following temporal resection), whereas neocortical epilepsy is generally associated with cortical lesions that are not limited to the temporal lobe. MTS is characterized by a loss of neurons in the hippocampus, and sometimes includes secondary involvement of other mesial temporal structures such as the amygdala or extratemporal structures. Individuals with MTLE, when compared to non-MTLE patients, have been shown to have significantly less post-surgical cognitive decline, particularly in verbal memory, confrontation naming, and verbal conceptual ability after left-hemisphere resections, as well as less decline in visual-spatial learning following right-hemisphere resection (Davies et al., 1998; Hermann et al., 1995; Seidenberg et al., 1998; Trenerry et al., 1993). In one study of individuals with TLE, less post-operative verbal memory decline was observed in left TLE patients with more severe hippocampal atrophy (likely because they lost less functional cortex), whereas patients with right TLE demonstrated better verbal memory performance following resection, regardless of the condition of the resected area (Sass, 1994). The integrity of the hemisphere contralateral to the resection is important as well; individuals with a structurally normal hippocampus contralateral to the resected hippocampus have been shown to have better seizure outcome and better verbal memory outcome (Baxendale, Thompson, & Kitchen, 2000; della Rocchetta et al., 1995; Radhakrishnan, 1998; Trenerry, Westerveld, & Meador, 1995). The findings from these studies indicate that a severely atrophic hippocampus (particularly in the left hemisphere) contributes less to pre-operative functioning, and as such, will have less of an impact on post-surgical cognitive functioning than if a fully functional hippocampus were resected. Cognitive decline is even less likely if the contralateral hippocampus is structurally normal.

Surgical procedure. The relationship between resection type and post-surgical outcome has also been investigated. Both standard en bloc resections (i.e. removal of approximately 4-6 cm of the anterior lateral temporal neocortex and removal of all or most of the amygdala and hippocampus) and limited resections have been shown to result in similar rates of seizure control. However, limited resections, such as selective amygdalohippocampectomy may have a lesser impact on cognitive functioning (Hamberger & Drake, 2006; Steven & Wiebe, 2006), particularly at one-year follow-up (Gleissner, Helmstaedter, Schramm, & Elger, 2002; Gleissner, Helmstaedter, Schramm, & Elger, 2004), and when collateral damage of surrounding brain tissue is minimized (Helmstaedter et al., 2004).

Pre-operative cognitive functioning. It has been suggested that individuals with low IQ scores have diffuse seizure foci, and therefore poorer post-surgical outcomes (King, Olivier, Spencer, & Wyllie, 1993). However, this finding may be dependent on the structural integrity of the brain; as much as a fourfold increase in risk for continued seizures was found for those with IQ scores ≤ 75, but only when structural lesions in the brain were also present (Chelune et al., 1998). Therefore, low IQ should be considered in the pre-surgical evaluation, but should not necessarily exclude individuals from surgery. Another important consideration is hemispheric dominance for language and memory functions. Verbal abilities such as language and verbal memory are often more affected by a left temporal lobectomy, although some individuals with atypical dominance (i.e., right hemisphere or bilateral) may have language function preserved after a left hemisphere resection. Furthermore, greater post-surgical deficits have been observed in individuals with greater language and memory abilities prior to surgery (Chelune, Naugle, Luders, & Awad, 1991; Ivnik, Sharbrough, & Laws, 1988). Therefore, to predict individual outcome, language dominance and memory asymmetry are assessed prior to surgery; those with language and memory lateralized to the hemisphere contralateral to the seizure focus and resection site have been shown to have better seizure control and cognitive outcomes following surgery, although better pre-operative functioning may result in relatively greater decline (Bell, Davies, Haltiner, & Walters, 2000; Sabsevitz et al., 2001; Sabsevitz et al., 2003).

Language Organization in Neurologically Normal Individuals and Epilepsy Patients

Language processes are conceptually complex, which makes it difficult to identify the neural basis of language. Traditional views of language organization based on lesion-deficit models have evolved over the past 150 years, and current hypotheses regarding the neural substrates of language are based on more recent functional imaging studies (Binder, et al, 1997; Grabowski & Damasio, 2000; Wise & Price, 2006). The localization of language is critically important for epilepsy patients who undergo cortical resection, particularly dominant temporal lobectomy, because they are at risk for post-operative language decline. As such, the identification of cortical areas that are involved language processes is a standard part of the pre-surgical evaluation and much research has focused specifically on the language development and organization of neurologically normal individuals as well as epilepsy patients.

Language Organization

"Language" incorporates a number of interrelated processes, including the expression and reception of sounds (phonetics), words (morphology), the grammatical structure of phrases and sentences (syntax), and meaning (semantics) (Kutas, Federmeier, Staab, & Kluender, 2007). Furthermore, language processing is a function of various other cognitive systems such as the attention, memory, visual, auditory, and motor systems (Wise & Price, 2006). Although the neural substrates of language have been the subject of much research, they are still not well understood. However, the theoretical trend has been toward an understanding of language organization as being less localized than originally thought, and greater emphasis is now being given to the functional connectivity of a number of different regions of the brain (Grabowski & Damasio, 2000).

Classical models of language organization, although not entirely accurate, provided valuable information about language processing and became the foundation for subsequent research. Specifically, classical language organization models suggested that the left cerebral hemisphere is typically dominant for language, that there is a link between language and handedness, and that two brain regions (Broca's area and Wernicke's area; See Appendix A) have a critical role in language processing (Damasio & Damasio, 2000). In the mid-19th century, Paul Broca suggested that part of the left inferior frontal gyrus (Broca's area) was associated with the articulation of written and spoken language (Broca, 1861). A decade later, Carl Wernicke proposed that the left superior temporal gyrus (Wernicke's area) was responsible for the reception and comprehension of linguistic sensory information, and also postulated a connection with Broca's area via the arcuate fasciculus that was also necessary for language processing (Wernicke, 1874). These hypotheses were extended to include essential "concept centers" (e.g., auditory and written word centers) that worked in concert with Broca's area and Wernicke's area and were also an integral part of language production and comprehension (Lichtheim, 1885). Although these ideas received a fair amount of criticism at the time, they later served as the foundation for more progressive theories, which proposed that a network of brain regions support language functions (Geschwind, 1971; Luria, 1966), which is consistent with current views of language organization based on more sophisticated brain mapping and imaging techniques (Binder et al., 1997; Liotti, Gay, & Fox, 1994; Ojemann, 1979).

The advancement of brain mapping and imaging techniques allowed researchers to decrease their reliance on individuals with lesions and language deficits, and to manipulate proposed essential and non-essential language areas in the brain. For example, electrical stimulation mapping allowed researchers to temporarily incapacitate specific areas of the brain and test naming ability. These studies have shown that there is considerable variability between individuals in the localization of naming sites in the left lateral cortex (Ojemann, 1979). Positron emission tomography (PET), which indicates changes in blood flow, oxygen use, and metabolism that occur with activation of brain regions, permitted researchers to go a step beyond the lesion method, which revealed essential, but not supporting language areas. Research findings based on PET scans have suggested that a functionally connected neural network is involved in language processing (Liotti et al., 1994). Similarly, fMRI has been used to investigate the neural correlates of language, and has indicated typical left hemisphere lateralization with right hemisphere participation, with a diffuse network of activated regions in the frontal, temporal, and parietal lobes, as well as subcortical limbic structures (Binder et al., 1997; Grabowski & Damasio, 2000; Wise & Price, 2006). These findings suggested that there is individual variance in language organization, both intra- and inter- hemispherically, but that in most neurologically normal individuals certain brain regions appear to be essential areas (i.e., the left inferior frontal gyrus and/or surrounding areas; the left superior temporal gyrus and/or surrounding areas), as well as a number of other brain regions and cognitive systems (Ojemann, 1991).

Factors Related to Language Development

Language dominance has been specifically investigated in both neurologically normal individuals and epilepsy patients using both deactivation (e.g., IAT, cortical stimulation mapping) and activation (e.g., fMRI) paradigms (Frost et al., 1999; Galliard et al., 2007; Spreer et al., 2001; Springer et al., 1999). In healthy right-handed individuals, language has been found to be strongly left lateralized (Frost et al., 1999), whereas healthy non-right-handed people have a higher incidence of atypical language (i.e., bilateral or right hemisphere dominance) (Szaflarski, et al., 2002). Approximately 10% of neurologically normal individuals have atypical language dominance, compared to approximately 25% of epilepsy patients (Helmstaedter, Kurthen, Linke, & Elger, 1997; Knake et al., 2006; Springer et al., 1999). In a comparison of normal individuals and epilepsy patients, Springer and colleagues (1999) observed significantly greater atypical language dominance in the epilepsy group. Additionally, factors such as early brain injury/seizure onset, atypical handedness, and structural and functional factors associated with epilepsy (i.e., seizure focus, site of lesion, and seizure activity) have been related to language reorganization and atypical language dominance in epilepsy patients (Gaillard et al., 2007).

Age of seizure onset. Research suggests that the development of the neural substrates that underlie language processes occurs early in life (Duchowny, 2007). In a comparison of healthy individuals and pediatric epilepsy patients (ages 8-18), Yuan and colleagues (2006) reported that in healthy individuals, language lateralization tended to increase with age, whereas this was not the case in the epilepsy group. Examining a broader age group, Szaflarski and colleagues (2006) reported similar findings; they investigated language lateralization in 170 neurologically normal individuals ages 5 - 67 and found that the strength of language lateralization to the dominant hemisphere increased until age 20 – 25, then decreased with age. Epilepsy patients more often experienced a rightward shift in language organization, which has been shown to have different effects on language functioning. For example, epilepsy patients (not limited to those with early seizure onset) with left-sided seizure foci and atypical language dominance were found to have poorer verbal and nonverbal abilities than those with right-sided seizure foci, which may be indicative of crowding of right hemisphere functions (more likely associated with earlier seizure onset) or insufficient language reorganization (more likely associated with later seizure onset) (Helmstaedter et al., 1997). In contrast, Thivard and colleagues (2005) reported better productive and perceptive language performance in a group of adult epilepsy patients with atypical vs.

typical language lateralization. These findings suggest that language reorganization may be an adaptive, compensatory mechanism, although they should be interpreted with caution due to the small sample size (N = 36, of whom 7 had atypical language). One factor which may partially account for the discrepant findings is age of seizure onset, which appears to be related to language reorganization and subsequent language abilities. Studies that have limited their samples to pediatric patients have found no difference in language production of children with right vs. left-sided brain trauma, and better performance than their adult counterparts (Bates et al., 2001; Max, 2004). These findings suggest that organization and lateralization of language naturally takes place within the first 5-10 years of life; during this time, it may be disrupted and reorganized by early seizure activity with minimal cognitive consequences due to the neuroplasticity of the developing brain.

Although age of seizure onset was not associated with lateralization in a number of studies (Bartha, Benke, Bauer, & Trinka, 2005; Knake et al., 2006; Liegeois et al., 2004; Sabbah et al, 2003; van der Kallen et al., 1998; Yuan et al., 2006), this may be due to limited sample sizes (N < 25) and heterogeneous patient samples in terms of seizure focus and pathology. These findings may also reflect the results of a recent study by Kadis and colleagues (2007) who reported intrahemispheric reorganization following early seizure onset; this type of reorganization would not be atypical according to the usual categorization of atypical language. In contrast, a number of larger studies (N > 100) have consistently found that age at onset of seizures (typically < 5 years of age) is associated with atypical language (Gaillard et al., 2007; Helmstaedter et al., 1997; Rassmusen & Milner, 1977; Springer et al., 1999), a finding that has been replicated with smaller samples (N = 44, N = 23, respectively) of left temporal lobe epilepsy patients (Brazdil, Zakopcan, Kuba, Franfrdlova, & Rektor, 2003) and individuals with mesial temporal sclerosis (Pataraia et al., 2004).

Atypical handedness. Left-handedness is found in approximately 8-15% of the general population (Hardyck & Petrinovich, 1977). Handedness may be influenced by a number of factors, such as genetics, hormones, environmental influence, and left-hemisphere injury, referred to as “pathological left-handedness.” In particular, pathological left-handedness has been associated with right hand motor deficits and atypical language dominance (Yeo, Thoma, & Gangestad, 2002). It is generally accepted that approximately 95% of right-handed individuals have left hemisphere language dominance (Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999). However, the incidence of atypical language dominance was found to be much higher (22-24%) in a group of left-handed and ambidextrous neurologically normal individuals (Pujol et al., 1999; Szflarski et al., 2002). Moreover, epilepsy patients, particularly with left-sided seizure foci, have a higher degree of atypical handedness than the general population, which has been associated with atypical language dominance in a number of studies (Adcock et al., 2003; Gaillard et al., 2007; Helmstaedter et al., 1997; Janszky et al., 2003; Rassmusen & Milner, 1977; Sveller et al., 2006; Thivard et al., 2005). These findings likely reflect a greater incidence of pathological left-handedness and subsequent reorganization of both manual and language dominance in epilepsy patients as compared to neurologically normal individuals.

Sex. There are conflicting reports regarding the relationship between sex and language lateralization. Some studies have found that women were more likely than men to have bilateral language lateralization (Pugh et al., 1996). However, these findings were often observed within specific populations such as individuals with a left-sided seizure focus, during particular tasks (e.g., story comprehension), or only in certain brain regions (e.g., superior and middle temporal gyri) (Helmstaedter et al., 1997; Kansaku, Yamaura, & Kitazawa, 2003). In numerous other studies, no difference in language lateralization between men and women was observed in neurologically normal individuals (Frost et al., 1999; Knecht et al., 2000; Pujol et al., 1999; Springer et al., 1999) or epilepsy patients (Janszky et al., 2003; Springer et al., 1999; van der Kallen, 1998). These discrepant findings may be attributed to differences in language lateralization tasks or ROIs.

Seizure focus, site of lesion, and seizure activity. Certain features of epilepsy, such as the side of seizure focus, location of lesion, and seizure activity influence the reorganization of language. A left hemisphere seizure focus has consistently been linked to atypical language dominance compared to a right hemisphere seizure focus, particularly for individuals with early seizure onset (Adcock et al., 2003; Berl et al., 2005; Brazdil et al., 2003; Helmstaedter et al., 1997; Rassmusen & Milner, 1977; Sabbah et al., 2003). Right hemisphere dominance, although rare, has been more commonly associated with left temporal lobe epilepsy than right temporal lobe epilepsy, whereas the atypical dominance associated with right temporal lobe epilepsy is most often bilateral (Helmstaedter et al., 1997; Rassmusen & Milner, 1977). Additionally, lesion characteristics may influence language organization. Specifically, the impact of lesions that encroach upon eloquent cortex (i.e., Broca's and Wernicke's area and surrounding cortex) vs. those located in the temporal region (e.g., MTS) has been investigated. A number of studies have reported an association between temporal lesions, such as hippocampal sclerosis or developmental tumors, and atypical language (Briellmann et al., 2006; Pataraia et al., 2004; Weber et al., 2006), and have shown that MTS is more commonly associated with atypical language lateralization than other temporal or frontal lesions (e.g., tumor, dysplasia, vascular malformation) (Gaillard et al., 2007). In studies conducted with left-sided mesial temporal lobe epilepsy patients, the location and duration of seizure activity has been associated with atypical language dominance. Specifically, higher spike frequency and seizure activity in the lateral temporal region as opposed to the limbic region was associated with atypical language lateralization (Janzsky et al., 2003; Janzsky et al., 2006). These findings are consistent with reports from comparison studies, which indicated that temporal lesions are more often associated with atypical language than frontal lesions (Liegeois et al., 2004; Thivard et. al, 2005). Frontal lesions have been associated with atypical language lateralization to a comparatively lesser extent; however, they have been associated with intrahemispheric reorganization in the surrounding cortex, which may partially account for less frequent atypical lateralization (Anderson et al., 2006; Kadis, 2007; Liegeois et al., 2004; Thivard et al., 2005).

The extant literature regarding language development, organization, and lateralization in neurologically normal individuals and epilepsy patients reveals a number of factors that are often associated with atypical language lateralization. These factors include early age of seizure onset, atypical handedness, being female, the presence of lesions either in or around the temporal lobe, and a high seizure frequency, with activity in the lateral temporal region (Helmstaedter et al., 1997; Janzsky et al., 2006). Despite the associations that have been reported between these variables and language lateralization, language organization remains a highly individualized process that is not yet well understood. Moreover, unexpected language lateralization has been observed, which has been highlighted in a number of case studies. For example, cases have been reported of right-handed individuals with late seizure onset, with either left-sided seizure focus and right hemisphere dominance (Boatman et al., 2000; Spreer et al., 2001), and right-sided seizure focus with right hemisphere dominance (Cunningham, Morris, Drea, & Kroll, 2008). This significant variability of language organization, and the greater incidence of atypical language dominance, necessitates the use of reliable procedures, such as IAT and fMRI, to lateralize and localize the neural substrates of language for all epilepsy patients who are candidates for resective surgery.

Intracarotid Sodium Amobarbital Test

The IAT has traditionally been the “gold standard” for language lateralization (Loring et al., 1992; Wada & Rasmussen, 1960). The IAT is a procedure in which an anesthetic agent is injected into the anterior and middle cerebral arteries via the internal carotid artery (See Appendix B), which inactivates eloquent cortex in one cerebral hemisphere, while the expressive and receptive language functions of the contralateral nonanesthesized hemisphere are tested (memory testing is also typically performed during this procedure). Prior to the sodium amobarbital injection, an angiography is typically performed to determine vascularlization patterns; after the injection, EEG is used to monitor activity in each hemisphere. After recovery of neurological function, the procedure can be repeated on the other side so that each hemisphere’s contribution to language functioning can be assessed. Initially, aphasia (the inability to express or comprehend language) or paraphasic errors (substitution of a sound or related word) served as an indication of language lateralization. Currently, tasks such as counting, comprehension, naming, and repetition are typically used to assess language lateralization, with the assumption that language lateralized to the side of proposed surgery poses a greater risk for post-operative language decline (See Appendix C for a language protocol). The IAT has been widely used to determine language dominance, which has provided valuable information regarding the risks of surgery and assisted with surgical planning. (Dinner, 1991; Loring et al., 1992; Rausch et.al, 1993; Snyder & Harris, 1997). Despite the benefits of IAT, and although it has been shown to be predictive of post-surgical naming decline in epilepsy patients who underwent left temporal lobectomy (Sabsevitz et al., 2003), the procedure is associated with a number of risks and limitations.

Brief History of IAT

In the 1940's, W. James Gardner, an American neurosurgeon, and Juhn A.Wada, a Japanese neurologist, independently performed procedures that resembled what is currently known as the IAT (Gardner, 1941; Wada, 1949). Both Gardner and Wada used slightly different procedures, for very different reasons, which anesthetized cortical language areas in only one cerebral hemisphere. Interestingly, although it was Gardner who originally intended to lateralize language, whereas Wada was attempting to arrest an episode of status epilepticus in a patient, it was Wada's work that led to the development of the IAT (Snyder & Harris, 1997).

Gardner (1941) first noted the occurrence of speech and language deficits following hemispherectomy of the language dominant hemisphere, and later became particularly concerned with atypical language lateralization in left-handed individuals. In an attempt to determine language dominance, he injected anesthetic (procaine hydrochloride) directly into cortical areas presumed to be necessary for language (e.g., Broca's area or the corresponding area in the right hemisphere) prior to hemispherectomy in two left-handed individuals. One patient received a right-sided injection and the other had a left-sided injection, which corresponded to the side of their tumors. Neither injection produced aphasia and although this did not necessarily mean that language was not represented in the hemisphere in question, neither individual demonstrated language deficits following hemispherectomy. Although it preceded that of Juhn Wada, Gardner's work was not replicated, and it is typically not associated with the development of the IAT (Harris & Snyder, 1997).

In contrast, Wada (1949) first injected sodium amytal into the left carotid artery of a man with status epilepticus to anesthetize the cortical area that is supplied by the middle cerebral artery, in an attempt to stop his seizure activity. He was successful, but noted that the man became temporarily mute and hemiplegic. Wada then went on to use this procedure to lateralize speech and language functions, first to aid in the placement of electrodes in the nondominant hemisphere during electroconvulsive therapy. Later, the IAT, or Wada test, became routinely used to determine not only language lateralization, but also memory lateralization and the seizure focus of epilepsy patients at the Montreal Neurological Institute (Milner, Branch, & Rasmussen, 1962; Wada & Rasmussen, 1960), and remains a widely used procedure used to assess language lateralization as part of the pre-surgical evaluation for individuals with intractable epilepsy.

Evolution of the Use of IAT for Language Lateralization

In 1960, Wada and Rasmussen conducted clinical trials of the IAT, first in primates, then with 20 epilepsy patients using variable amounts of sodium amytal (100-200mg), which was injected into the common carotid artery. Resections guided by IAT results were carried out in 17 of these patients who subsequently displayed either no aphasia or transient aphasia, which provided preliminary evidence of the correctness of the IAT lateralization findings. Since that time, the IAT has been widely used and validated, the protocols and definitions of language have evolved, and although the IAT may soon be replaced by noninvasive methods of language lateralization, it continues to be considered the gold standard for language lateralization by a number of clinicians (Baxendale et al., 2008; Jones-Gotman, 2008; Loring, 2008).

Studies from the Montreal Neurological Institute. The first large-scale studies of language lateralization were conducted at the Montreal Neurological Institute (Branch, Milner, & Rasmussen, 1964; Milner, Branch, & Rasmussen, 1966; Rasmussen & Milner, 1975; Rasmussen & Milner, 1977; Wada & Rasmussen, 1960). These studies progressively added patients to their series and provided the earliest estimates of language representation, using the IAT with a sample of nearly 400 epilepsy patients, many of whom had early brain injury. Language lateralization was characterized as “left” when aphasic errors were observed after left hemisphere injection only, “right” when aphasic errors were observed after right hemisphere injection only, and “bilateral” when some degree of aphasic errors were observed after both injections. Rasmussen and Milner (1977) reported that 96% of right-handed epilepsy patients without early left hemisphere damage were left hemisphere dominant for language, while the remaining 4% were right hemisphere dominant for language. Left-handed or ambidextrous patients without early neurologic injury had left hemisphere language dominance in 70% of cases, bilateral language dominance in 15% of cases, and right hemisphere dominance in 15% of cases. For individuals with early left hemisphere injury, the prevalence rates differed; 81% of right-handed individuals were left hemisphere dominant, 7% had bilateral dominance, and 12% had right dominance. Of the left-handers with early left hemisphere injury, 28% had left hemisphere dominance, 19% had bilateral dominance, and 53% had right hemisphere dominance. Combined, this series of patients had left hemisphere language dominance in approximately 70% of cases, bilateral language dominance in 10% of cases, and right dominance in 20% of cases. Overall, the results of these studies indicated that atypical handedness and early seizure onset/injury were associated with a higher incidence of atypical language dominance. Although the results of these studies represent valuable first estimates of language lateralization using the IAT, a number of limitations were associated with these findings, including the use of unilateral injections for a number of patients in the sample, lack of angiography to determine individual differences in vasculature, and a biased sample that included only patients who were suspected of having atypical language (Loring et al., 1992; Woods, Dodrill, & Ojemann, 1988).

Dissemination of the IAT. Subsequently, a number of other studies examining language lateralization using the IAT were conducted, still relying on a trichotomous (i.e., left, right, bilateral) categorization of language. Estimates of left hemisphere language dominance ranged from 57-90%, estimates of right hemisphere language dominance ranged from 5-23%, and bilateral language was observed in 5-36% of cases (Mateer & Dodrill, 1983; Rausch & Walsh, 1984; Strauss & Wada, 1983; Woods, Dodrill, & Ojemann, 1988). This variability may reflect a number of factors. For instance, amobarbital dosage ranged from 75-200mg both between centers and within series of patients, as centers changed their IAT protocols. Over time, pre-IAT angiography became included as standard in many epilepsy centers, as did the use of EEG monitoring during the procedure, which had not always been the case. These changes allowed for detection of abnormal vasculature and distribution of sodium amobarbital within the brain. Another procedural difference between studies was the amount of time between injections, which ranged from approximately 30 minutes (Rausch, Gregory, & Walsh, 1984) to consecutive days (Strauss & Wada, 1983). Additionally, differences in language assessment protocols and scoring criteria influenced estimates of language lateralization. Initially, only interruption of counting and the presence of paraphasic responses during serial speech or oral spelling were used to determine language dominance, which largely neglected the assessment of comprehension. Moreover, a number of epilepsy patients experienced transient speech arrest immediately following injection of the nondominant hemisphere, lasting approximately 25 seconds, but then displayed normal language functions. As a result, assessments of comprehension and confrontation naming were eventually added to the language protocol, and some institutions required impairment in multiple areas to determine language representation (Loring et al., 1992). Finally, differences in patient selection influenced estimates of language dominance; some centers performed IAT on consecutive pre-surgical candidates, while others used the procedure only in cases of suspected atypical dominance, which inflated estimates of bilateral and right hemisphere dominance relative to the population.

Conceptualization of language as a continuous variable. In 1990, Loring and colleagues at the Medical College of Georgia introduced a continuous method of classifying language, when they compared discrete hemispheric language representation (i.e., left, right, bilateral) to relative hemispheric language dominance using the IAT (i.e., L>R; R>L). They first classified patients based on linguistic errors following each hemispheric injection, with errors following both injections resulting in a categorization of bilateral language dominance. These same patients also received laterality ratios based on their language ratings for each hemisphere (i.e., L-R/L+R). Using this method, only patients with laterality ratings between 0.15 and -0.15 were categorized as having bilateral language. Loring and colleagues (1990) suggested that this measurement technique provided a more sensitive assessment of language lateralization, and that conceptualizing language dominance as a continuous variable provided a more accurate assessment of right and bilateral language dominance, which had likely been overestimated by previous studies that had relied on a trichotomous categorization of language dominance.

Validity of the IAT. As the IAT became more widely used, questions were raised about its validity. Specifically, researchers cited the lack of a standardized protocol and the inconsistent criteria by which language representation was being defined (particularly bilateral language representation) as significant problems with the procedure (Snyder, Novelly, & Harris, 1990). Snyder and colleagues (1990) surveyed 55 epilepsy centers regarding their practices; they asked about the way each administered anesthetic, conducted language components of the examination, and interpreted language representation data. The reported incidence of bilateral language was quite varied, which was attributed to the use of different doses of sodium amobarbital and the absence of standardized criteria for assessing language dominance, particularly for determining what constitutes bilateral language. Most centers (78%) required a display of aphasic errors prior to determining language lateralization and reported that they did not infer bilateral language when no aphasic errors were observed (Snyder et al., 1997). Language criteria also influenced the incidence of reported bilateral language; programs reported a low incidence of bilateral language (0-6%) when they did not consider the production of partial phonemes, serial rote speech, or the expression of familiar words as being indicative of speech control in the hemisphere contralateral to injection. Given the procedural differences between centers, the surveyors suggested the need for clear, empirically supported IAT guidelines, a set of which were published shortly thereafter (Loring et. al, 1992; Loring, 2008).

Despite these methodological differences, the IAT has been validated by two primary means: (1) by confirming IAT results with cortical stimulation mapping, which has shown a high rate of concordance, particularly when IAT indicates left hemisphere dominance and (2) by observing post-operative language functioning in patients with resections in the language dominant hemisphere (Dinner, 1991; Loring et al., 1992). In one study, a 96% concordance rate was found between IAT lateralization and cortical stimulation mapping for patients with left hemisphere language dominance. However, of the seven patients with right hemisphere language dominance according to the IAT, cortical stimulation mapping indicated speech in the left hemisphere in two cases (Wyllie et al., 1990). This finding suggested that when right hemisphere language is indicated by IAT, it may be useful to have patients undergo cortical mapping prior to left hemisphere resection, a practice which has been adopted by numerous epilepsy centers. In terms of post-operative language functioning, IAT language lateralization has been correlated with post-surgical language outcome in a number of studies (Branch, Milner, & Rasmussen, 1964; Epstein et al., 2000; Sabsevitz et al., 2003; Wada & Rasmussen, 1960). Notably, most studies provided only anecdotal evidence of the predictive capability of the IAT, such as reporting the number of patients who developed aphasia following resection. Sabsevitz and colleagues (2003) conducted the only formal study examining the relationship between IAT and post-operative naming outcome. In that study of 24 consecutive left anterior temporal lobectomy candidates and a comparison group of 32 right anterior temporal lobectomy candidates, the IAT was more predictive of post-operative naming decline (i.e., a decline of 10 or more points on the Boston Naming Test) than age at seizure onset or preoperative naming performance, showing 100% sensitivity and 43% specificity.

IAT practices in 1992. In 1992, a more comprehensive survey of IAT practices was conducted, and respondents from 71 epilepsy surgery centers (of 102 that were surveyed) indicated that 68 epilepsy surgery centers were assessing language lateralization with pre-surgical IATs to assist in determining surgical parameters or approach (mean = 24.9 procedures per year) (Rausch et al., 1993). Of these, 85% performed the procedure on all surgical candidates. Many reported using both standard and selective procedures at their centers, but considerable procedural variability was reported between centers. Ninety percent of respondent centers always or almost always performed an angiography prior to IAT and 84% always or almost always injected both hemispheres. Drug dosages were variable, ranging from 60mg-200mg (most commonly

125mg), with the volume of solution injected ranging from 0.75 cc-10 cc. Injection rate was also variable, which, along with drug volume, influences the spread of the drug within the arteries. This has implications for behavioral responses; a low (or slowly injected) dose of sodium amobarbital may allow detection of subtle hemispheric effects but may not be strong enough to produce aphasic errors, whereas a higher dose (or a faster injection rate) may more closely approximate the effects of a resection but might result in obtundation (reduced awareness or consciousness). The following areas were indicated by respondents as components of their language assessment: spontaneous speech (87%), counting (85%), naming (99%), reading simple words (83%), reading complex sentences (28%), repetition of words or phrases (81%), response to verbal commands (93%), and other (23%). Most centers (97%) characterized language dominance as left or right, with 60% additionally classifying left greater than right or right greater than left, and 80% classifying bilateral speech. However, the criteria for determining bilateral language was quite varied, including the presence of some language functioning in both hemispheres (15%), no errors in language functioning (17%), arrest, impairment, or no impairment in both hemispheres (13%), equal or approximately equal representation (17%), and significant representation (37%). In terms of the clinical usefulness of the IAT, 97% of respondents indicated that they believed the IAT was effective for assessing hemispheric language function, while at the same time endorsing the importance of improving noninvasive measures of language laterality.

Current IAT practices. A brief international survey of IAT use that was conducted 15 years later with respondents from 92 epilepsy surgery centers (of 207 surveyed) revealed differences in the use of the IAT compared to what was reported in 1992

(Baxendale et al., 2008). Although the results should be interpreted with caution, given the 40% response rate, notable differences from the 1992 survey results emerged. Compared to 85% of respondents in the 1992 survey, only 12% of respondents in the 2007 survey reported always performing an IAT on pre-surgical patients, and approximately 50% of respondents indicated that they rarely to never performed the IAT. Eighty-six percent of respondents reported that the resections they performed in the language dominant hemisphere were less extensive, whereas the other 14% used a standardized resection technique. Sixty-six percent of respondents indicated that they would feel confident allowing a patient to proceed to surgery without IAT language lateralization data (this included the 14% who used standardized resections, and were significantly more confident as a group). Some respondents noted specific instances when they would require IAT language lateralization data, such as for left-handed patients with non-concordant pre-operative data, inconclusive fMRI, and bilateral temporal lesions or EEG spikes. These responses indicate that many centers are using the IAT on a more selective basis, while relying on other less invasive means to determine language lateralization when possible.

Limitations of the IAT

The IAT is an invasive, expensive procedure with significant risks and methodological limitations. Specifically, concerns have been raised regarding morbidity and mortality, the ability to monitor drug effects, the sensitivity and specificity of the procedure, and methodological differences. As such, there has been much interest in the development of alternative, less invasive measures of language lateralization (Baxendale, 2008; Rausch et al., 2003; Snyder et al., 1990).

Morbidity/Mortality. Although infrequent (typically in <1-2% of cases, although rates as high as 11.6% have been cited), patients who undergo intracarotid amobarbital testing are at risk for transient and/or permanent complications (Abou-Khalil, 2007; Loddenkemper et al., 2004; Rausch et al., 1993). A recent chart review of 677 patients revealed a complication rate of 10.9%, which included encephalopathy, seizures, strokes, transient ischemic attacks, localized hemorrhage at the site of injection, carotid artery dissection, allergic reaction, bleeding from the catheter insertion site, and infection (Loddenkemper, 2008). A recent survey of 16 European epilepsy centers in which a total of 1421 IATs were performed between 2000 and 2005, reported a complication rate of 1.09% (0.36% with a permanent deficit) for that time period (Haag et al., 2008). The complications reported included prolonged somnolence, blurred vision, psychotic reaction, groin hematoma, thrombosis of arteria dorsalis pedis, internal carotid artery dissection, and microembolic brainstem infarction. Complications causing permanent deficits included partial middle cerebral artery infarction, brainstem and thalamus infarction, posterior inferior cerebellar artery infarction, and retinal thrombosis. Although these complications occurred very infrequently, they demonstrate the significant risks that may be associated with the IAT.

Drug effects. Almost since the IAT's inception, researchers have expressed concern about the distribution of anesthetic within the brain and the effect that this has on behavioral performance (Serafetinides, Hoare, & Driver, 1965; Subirana, 1964). Widespread diffusion of anesthetic may result in bilateral perfusion (i.e., crossflow), and varied drug doses and injection rates may cause obtundation, or alternatively, inadequate sedation. Furthermore, different drug doses, rates of injection, and solution volume result in variable durations of anesthesia, which are not always readily apparent based on sensory and motor observations (Bouwer, Jones-Gotman, & Gotman, 1993; Loring, Meador, & Lee, 1992; Rausch et al., 1993).

A number of studies have investigated the effects of these drug-related phenomena on consciousness, which has implications for language assessment. Serafetinides and colleagues (1965) reduced the rate of injection after observing bilateral filling of the anterior cerebral arteries, but they still found a positive correlation between cerebral dominance for speech and what they determined to be cerebral dominance for consciousness. That is, they found that consciousness was more impaired after injection of the language dominant hemisphere, which was more frequently the left hemisphere. This finding was consistent with the observation that left hemisphere injection has been associated with a depressive emotional reaction, whereas euphoria has been observed more frequently after the right hemisphere injection (Ahern et al., 1994; Loring et al., 1992; Perria, Rosadini, & Rossi, 1961). These findings are contrasted by observations of intact consciousness following both hemispheric injections, which have also been reported (Fedio & Weinberg, 1971; Rosadini & Rossi, 1967). Other studies have suggested that when injections are completed on the same day rather than over the course of two days, as was originally the case, residual medication effects may have an impact on awareness when the second hemisphere is injected (Glosser et al., 1999; Grote et al. 1999). Moreover, due to individual differences in vasculature, variable drug dosage, and different injection rates, crossflow and variable intrahemispheric filling (e.g., posterior cerebral artery, thalamic or mesencephalic branches) have been observed in a number of patients, which has the potential to decrease attention and therefore negatively impact behavioral performance (Hong et al., 2000; Jeffrey et al., 1991; Malmgren et al., 1992; Perrine, Devinsky, Luciano, Choi, & Nelson, 1995). Typically, EEG and behavioral observation are used to monitor drug effects, but it can be difficult to determine exactly when hemispheric anesthetization ends. For instance, slow waves as measured by EEG have been found to dissipate prior to the return of motor and sensory functions (Bouwer et al., 1993), which suggested that IAT accuracy may be compromised if evaluations are based on the return of these functions. In other cases, bilateral sedation after a single injection has also been inferred by the presence of bilateral slow waves measured by EEG (Bouwer et al., 1993; Jones-Gotman, Bouwer, & Gotman, 1994).

Alternative anesthetics, such as brevital and pentobarbital have recently been compared to sodium amobarbital, and were found to be similarly useful in terms of language lateralization. The results of some studies have indicated that brevital results in reduced sedation compared to sodium amobarbital, although it may elicit seizure activity in some patients (Buchtel, Passaro, Selwa, Deveikis, & Gomez-Hassan, 2002; Loddenkemper, Moddel, Schuele, Wyllie, & Morris, 2007). In another comparison study, the incidence of drowsiness or confusion after injection was significantly lower in the pentobarbital group when compared to the sodium amobarbital group (Kim et al., 2007). These alternative drugs have the potential to reduce the obtundation that has been associated with IAT, but more research needs to be done to fully investigate the effects of using alternative anesthetics.

Sensitivity. Typically, concerns about the sensitivity of the IAT have been related to memory assessment, whereas most clinicians have reported confidence in the ability of the IAT to correctly lateralize language functions (Lancman, Benbadis, Geller, & Morris, 1998; Rausch et al., 1993). Language-related findings are questioned primarily when IAT reveals right hemisphere or bilateral language dominance; it is in these cases that electrical stimulation mapping is often used in one hemisphere to confirm results prior to resection. Occasionally, cortical mapping does not confirm IAT findings in cases of atypical dominance for reasons that are not entirely known, but are likely related to the methodological limitations of the IAT (Kho et al., 2005; Wyllie et al., 1990). A limitation that is more frequently cited is the inability of the IAT to localize language, which would be useful for planning resections (Abou-Khalil, 2007; Baxendale et al., 2008; Kloppel & Buchel, 2007).

Methodological limitations. A number of methodological concerns have been raised with regard to the IAT. As have been previously discussed, the lack of a standardized protocol across epilepsy centers, various methods of scoring, and different anesthetic agents and injection amounts have been cited as limitations of the IAT (Loring et al., 1992; Rausch et al., 1993; Trenerry & Loring, 1995). Additionally, the short amount of time (less than 10 minutes) during which the anesthetic is maximally effective has been citied as a limitation, as well as the inability to safely determine test-retest reliability due to the risks associated with the procedure (Bouwer et al., 1993; Malmgren et al., 1992). Furthermore, individual variations in response to the anesthetic, recency of seizures, incidence of hypoglycemia, interaction with current medications, abnormal neurovascular patterns, as well as variations in criteria for hemispheric anesthetization and behavioral stimuli across sites may also limit the interpretability of results (Rausch et al., 1993).

In summary, the IAT has a long history and has been widely used to determine language as part of the pre-surgical evaluation for almost 50 years. It is the only inactivation procedure that is routinely used bilaterally, and its validity for accurately determining language lateralization has been well-established. However, in light of the invasive nature, potential complications, and methodological limitations of the IAT, less invasive methods of language lateralization and localization procedures have been developed, and may soon be able to replace the IAT in the pre-surgical evaluation of patients with intractable epilepsy (Baxendale et al., 2008).

Functional Magnetic Resonance Imaging

Over the past 15 years, fMRI, a method which has the capacity to measure changes in regional blood flow during the performance of a task, has been increasingly used to lateralize language function in epilepsy patients (Baxendale et al., 2008; Swanson et al., 2007). The development of this procedure offers a non-invasive alternative to the IAT that is safer, less costly, replicable, and has the potential to not only lateralize language function, but to localize it as well (Binder & Raghavan, 2006; Binder et al., 1996). A fundamental difference between the IAT and fMRI is that IAT is an inactivation procedure that is intended to mimic the effect of a resection, while fMRI uses an activation paradigm to determine which parts of the brain are activated during various language tasks. However, as with the IAT, the use of fMRI for language lateralization has some limitations. Although it has been preliminarily suggested that preoperative fMRI data is able to predict post-operative naming decline in patients who undergo left temporal lobectomy (Sabsevitz et al., 2003), the current evidence base is not sufficient to evaluate post-operative risks of language decline, nor to support widespread use of this method (Abou-Khalil, 2007; Loring, 2008). Limited sample sizes and the lack of standardized probe and control tasks make it difficult to evaluate the effectiveness of fMRI for language lateralization (Swanson et al., 2007), however, this method has been increasingly used to assess the location of language processes.

Brief Description of fMRI

A relationship between changes in brain circulation (i.e., metabolism, blood flow) and neural activity has been theorized for over a century (Raichle, 2006). Functional magnetic resonance imaging was introduced in 1990, with the discovery that the signal intensity of some magnetic resonance images was decreased in the presence of paramagnetic deoxygenated blood; that is, deoxygenated hemoglobin distorts a magnetic field and subsequently decreases signal intensity. This signal, known as blood-oxygenation-level-dependent (BOLD) contrast, provides an indirect measure of neural activity, which is the basis for most fMRI studies (Song, Huettel, & McCarthy, 2006). The BOLD contrast is seen because the oxygen content of the blood increases at the site of an increase in brain activity (more oxyhemoglobin is present) and decreases in areas of less brain activity (more deoxyhemoglobin is present). Since neural activity is associated with a decrease in deoxyhemoglobin, a stronger signal intensity of magnetic resonance images is thought to indicate neural activity (Lee, Jack, & Riederer, 1996). That is, greater brain activity is associated with less deoxyhemoglobin, which disturbs the magnetic field to a lesser degree, and therefore produces a stronger signal on MRI (Raichle, 2006). These changes in deoxyhemoglobin levels are temporally linked (i.e., temporal resolution of 1-2 seconds) to the presentation of stimuli, onset of motor function, or cognitive task response, and spatially mapped (i.e., spatial resolution of about

3-5mm) onto an image of the brain (Wise & Price, 2006). Notably, it is the moment-to-moment change in the ratio of oxyhemoglobin to deoxyhemoglobin results in a signal, rather than an absolute level of oxygen in the blood, which has implications for the design of probe and control tasks used in functional imaging studies. For instance, if control tasks require neural activity in the ROI, the change in blood oxygenation between the probe task and the control task may be artificially decreased. Over the past 15 years, thousands of fMRI studies have provided evidence of a correspondence between the BOLD contrast signal and neural activity, yet the details of this relationship are not well-defined (Song et al., 2006). Although fMRI has a significantly shorter history than IAT, this method has provided valuable preliminary data that suggests diffuse neural networks, rather than discrete brain regions, work together to contribute to cognitive functions. To date, the most widely studied clinical application of fMRI with epilepsy patients has been the in the area of pre-surgical language lateralization (Detre, 2004).

Functional Magnetic Resonance Imaging and Language Lateralization

Functional magnetic resonance imaging has been widely used to investigate language processes in neurologically normal individuals as well as epilepsy patients. In contrast to the IAT, fMRI is noninvasive, safe, and replicable. Moreover, fMRI has the potential to not only lateralize hemispheric language dominance, but also to localize language functions. Rates of language dominance for right-handed neurologically normal individuals based on fMRI findings have been reported as 94-100% left hemisphere dominant, 0-6% right hemisphere dominant, and 0-6% bilateral dominance (Gaillard et al., 2002; Hund-Georgiadis, Lex, & Yves von Cramon, 2002; Springer et al., 1999). However, these rates differed when left-handed individuals were examined. Pujols and colleagues (1999) examined language dominance in 50 left-handed neurologically normal individuals, and categorized 76% as left hemisphere dominant, 10% as right hemisphere dominant, and 14% as having bilateral language. In contrast, similar language dominance rates have been investigated with samples of right-handed epilepsy patients (78% left hemisphere dominant; 6% right hemisphere dominant; 16% bilateral dominance) and left-handed patients (78% left hemisphere dominance; 8% right hemisphere dominance; 14% bilateral) (Springer et al., 1999; Szaflarski et al., 2002).

Language dominance rates based on fMRI were consistent with IAT findings, which provided evidence that epilepsy patients, particularly those with left-sided seizure foci, have a higher rate of atypical dominance than neurologically normal right-handed individuals, which is similar to rates observed with normal left-handers (Berl et al., 2005). It is notable that, even in cases of left-lateralized language dominance, some degree of right hemisphere activation was seen in most instances, suggesting an inter-hemispheric language network. Recently, many epilepsy surgery centers have begun using fMRI to localize language as a part of their pre-surgical evaluation (Baxendale et al., 2008), and there is a growing body of literature that has explored the utility of this method. Many researchers have investigated various ways to calculate the language lateralization index (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2005; Jansen et al., 2006; Seghier, 2008), the adequacy of particular language probe and control tasks (Baciu, Juphard, Cousin, & Le Bas, 2005; Gaillard et al., 2004; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), and the validity and reliability of different language protocols (Harrington, Buonocore, & Farias, 2006; Rutten, Ramsey, van Rijen, & van Veelen, 2002; Swanson et al., 2007).

Calculation of the lateralization index. A number of methods have been used to calculate the lateralization index (LI), but the following formula is generally used: LI = (A_L – A_R/A_L + A_R), where A_L and A_R refer to quantities of fMRI-measured brain activity within equal ROIs in the left and right hemispheres (Jansen et al., 2006). An alternative to this classical lateralization method has been proposed by Baciu and colleagues (2005), who directly compared left and right hemisphere activity to determine if the difference in hemispheric activity was statistically significant. Brain activity is processed in units called voxels, or "volume pixels," which represent a quantity of three-dimensional data. LI values typically range continuously from -1 or -100 (indicating pure right hemisphere dominance) to 1 or 100 (indicating pure left hemisphere dominance). To categorize dominance, the LI is often compared to a pre-defined threshold ($LI_{TH)}$; generally $LI>LI_{TH}$ indicates left hemisphere dominance, $LI< -LI_{TH}$ indicates right hemisphere dominance, and the absolute value of LI is less than or equal to LI_{TH} in cases of bilateral language. LI_{TH} is generally set to 0.2, but this value has varied across studies (e.g., 0.1, 0.15, 0.25, and 0.3) (Seghier, 2008).

Significant variability has also been observed in the way "brain activity" is measured and relatedly, with the way activation thresholds (i.e., the volume of significant brain activation above a given statistical threshold) are determined. Jansen and colleagues (2006) recently compared combinations of common procedures used to calculate brain activation in two domains: (1) based on either the number of active voxels in the ROI or based on the magnitude of signal change, and (2) using either fixed or variable statistical thresholds for activation. They reported that lateralization was most robustly and reproducibly calculated by comparing signal intensity changes in voxels in the ROI that exceeded a predefined level of activation for small ROIs, whereas examining the total number of active voxels may still be appropriate for large ROIs. In a more specific investigation of optimal threshold levels, Adcock and colleagues (2003) demonstrated that setting the activation threshold at different rates has an influence on lateralization indices; in that study, higher thresholds appeared to be more reliable. Others have attempted a direct comparison of left- and right- hemisphere activation, which allows a direct comparison of activated voxels. Clearly methodological variation in the calculation of LI such as differences in LI formula, the definition of brain activation, the selection of ROIs, and the statistical threshold may compromise the meaningfulness of the LI. Therefore, further investigations are needed to establish one unified, validated protocol for LI assessment in each cognitive domain of interest (Seghier, 2008).

Development of probe and control tasks. Different neural substrates have been shown to underlie various aspects of language in neurologically normal individuals. Specifically, different parts of the brain are involved in concrete and abstract processing, semantic and syntactic processing, and phonemic processing (Binder, Westbury, McKiernan, Possing, & Medler, 2005; Binder et al., 2003; Liebenthal, Binder, Spitzer, Possing, & Medler, 2005). Observations that different regions of the brain are activated during different types of languages tasks have implications for the development of fMRI language protocols. Many language protocols have been developed to assess specific language processes with a wide variety of probe tasks that were designed to isolate components of language functioning and different control tasks, and to allow "subtraction" of all cognitive processes other than the one of interest. The activation of different brain regions that has been observed during those different language and control tasks clearly indicates that the nature of the tasks has a great influence on the location of hemispheric activation and language lateralization (Baciu, Juphard, Cousin, & Le Bas, 2005; Gaillard et al., 2004; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003).

Numerous probe tasks have been designed to assess aspects of language functioning and subsequently lateralize and localize expressive and receptive language areas. Specific tasks have included semantic decision, verbal fluency, verb generation, object naming, number counting, sentence repetition, synonym judgment, rhyme detection, and story comprehension (Baciu et al., 2005; Berl et al., 2005; Binder et al., 1997; Brennan et al., 2007; Fernandez et al., 2003; Gaillard et al., 2002; Lehericy et al., 2000; Szaflarski et al., 2008). Although language processing is not confined to localized areas as previously thought, frontal language areas are one of the regions that are typically activated during expressive language tasks (e.g., verb generation). Many probe tasks are designed to activate the inferior frontal gyrus, as LIs based on activation in this area have been shown to have a high correlation with the IAT (Lehericy et al., 2000). Activation of the temporal lobe, which has been theoretically associated with semantic processing or receptive language functions, has proven more difficult, as most language tasks do not result in the isolation of activation to the temporal region (Vingerhoets et al., 2004). The aforementioned probe tasks have been examined singularly (e.g., Binder et al., 1996; Desmond et al., 1995), combined in the hopes of improving the detection of language-related brain regions (Gaillard et al., 2004; Ramsey, Sommer, Rutten, & Kahn, 2001), and compared with one another to determine if some tasks more accurately map language cortex and therefore better predict language lateralization (e.g., Baciu, 2005;

Brennan, 2007; Binder, Swanson, Hammeke, & Sabsevitz, 2008; Harrington, Buonocore, & Farias, 2006; Hund-Georgiadis, Lex, & Yves von Cramon, 2001).

A review of a number of fMRI studies that used different probe and control tasks revealed activation in prefrontal, temporal, and parietal-occipital regions (Swanson et al., 2007). A number of specific regions have been associated with aspects of language functioning: the inferior frontal gyrus has been linked to the planning and execution of speech; the prefrontal cortex, which has been described as an “orchestrator for integrating other cortical areas”(Mesulam, 2000, p.48), has been activated in many language tasks; the temporal gyrus has been involved in language comprehension and production; the inferior parietal lobe has been activated in phonological tasks (supramarginal gyrus) as well as semantic processing (angular gyrus); and activation in motor areas has been observed in tasks requiring verbal output (Seghier et al., 2004). The activation that is observed is heavily dependent on the task design, and the processing during the perception, comprehension, and expression of speech generally recruits a network of brain regions. Researchers have attempted to isolate the systems that are responsible for object identification, word retrieval, expressive speech, word meaning, and syntactic processing (Binder & Raghavan, 2006; Wise & Price, 2006). However, activation is often distributed throughout the frontal, temporal, and parietal lobes because tasks involve complex systems that include not only the language processes in question, but also working memory, remote memory, attention, motor systems, and visual or auditory information processing (Wise & Price, 2006).

Stimulus modality and task difficulty have also been shown to influence activation. In one study, visual input activated parts of the inferior frontal gyrus that were not activated by auditory input, whereas auditory input activated part of the superior temporal gyrus in the right hemisphere. This resulted in fMRI language lateralization scores that were stronger when a visual presentation of information was used (Carpentier et al., 2001), although this has not been a consistent finding (Hund-Georgiadis et al., 2001). Task difficulty and task performance have also been associated with brain activation. Specifically, increased task difficulty has been related to an increase in parietal activation (Draeger et al., 2004), while better task performance has been correlated with increased activation levels in temporoparietal areas (thought to be due to more extensive conceptual processing and greater semantic retrieval) and a decrease in inferior frontal areas (thought to be due to less neuronal demands) (Weber et al., 2006). Furthermore, variation has been observed in the modality of task responses, which also influences the location of brain activation. For example, some task designs rely on a motor response (e.g., pushing a button), some rely on covert word generation or comprehension, and others require audible verbal responses (e.g., Binder et al., 1997; Gaillard et al., 2004). Regardless of the chosen input and response modalities, it is important for the control task to be matched as closely as possible to the probe task in order to minimize activation that is not directly related to the language task.

A well-designed control task will require the use of all the same cognitive functions as the language task except for language processing. The optimal control task is similar enough to the probe task to allow the "subtraction" of all activation that is not related to language processes, yet distinct enough that the activation associated with language is not lost. Many control tasks have been designed, including rest, perceptual control (e.g., tone discrimination task), fixation (e.g., on a line or shape), visual control, reverse speech, and covert counting. Rest has been shown to be a poor control for cognitive processes because certain brain regions are consistently active during rest (Wise & Price, 2006). It has been hypothesized that this is because “rest” provides the opportunity for ongoing, unmonitored, cognitive processing (Binder et al., 1999). In fact, more activation has been observed during rest than during a tone discrimination task (McKiernan et al., 2003; McKiernan, D’Angelo, Kaufman, & Binder, 2006). The brain regions associated with “rest” are the midline cortex and bilateral posterior parietal cortex; any activity in these regions during rest would be “subtracted” from the activation during the probe task, which interferes with language lateralization calculations (Wise & Price, 2006). In one comparison study of two different control tasks, Hund-Georgiadis and colleagues (2001) observed bilateral activation of eloquent and noneloquent cortex when rest was used as the control condition, but when a perceptual encoding task was used (i.e., presentation of words with and without space between the letters), the activation patterns were only observed in the anterior inferior frontal gyrus. These findings indicate that activation patterns that are observed during tasks which use rest as a control condition should be interpreted with caution.

Other control tasks have been developed that require a similar level of attention and working memory, have a similar level of difficulty, and use the same input and response modalities as the probe task. One such task was developed by Binder and colleagues (1995; 1997), who evaluated a semantic decision probe task and a tone decision control task with 30 neurologically normal right-handed individuals. During the semantic decision task, individuals listened to a list of animal names and were instructed to press a button if the animal was both found in the United States and used by humans.

During the tone discrimination task, individuals listened to series' of high- and low-pitched tones, and were instructed to press a button if they heard two high-pitched tones in a series. The overlapping components of the semantic decision task and the tone discrimination task that were subtracted out included attention, working memory, auditory processing, and motor response, leaving activation from semantic and phonetic processing, resulting in strongly left-lateralized language, consistent with expectations for neurologically normal right-handed individuals.

Some researchers have combined tasks in an attempt to produce a better protocol for language lateralization. Ramsey and colleagues (2001) found that the combined analysis of three tasks: (1) covert verb generation, (2) categorical semantic decision, and (3) covert antonym-generation, improved detection of language-related brain areas compared to analysis based on a single task. The control conditions for these tasks were fixation on a small dot for the verb and antonym tasks, and a button-press response when a dot was presented for the semantic decision task. Their use of combined task analysis yielded strongly left-lateralized language, which was consistent across different statistical thresholds, despite the use of a fixation control task and the inability to monitor task performance in covert word generation tasks. These findings were replicated by Rutten and colleagues (2002), using similar tasks (i.e., verb generation, antonym generation, and picture naming, with a fixation control). Similar findings were also reported by Gaillard and colleagues (2004), who observed that a panel of language tasks including verbal fluency with a silent rest control, reading comprehension with a dot fixation control, and auditory comprehension with a silent rest or reverse speech control more accurately determined language dominance than any single task. Using a slightly different task panel, Seghier and colleagues (2004) combined a phonological task and a semantic language task, using a perceptual control (i.e., identification of identical Greek letter-strings). Their findings suggested that the combination was suitable for language mapping and lateralization, although the semantic task produced stronger lateralization data based on activation in the inferior frontal gyrus and prefrontal cortex. Notably, the use of fixation as a control task in many of these studies was problematic, as rest has been associated with increased bilateral activation and may have influenced the findings that a single task yielded weaker lateralization (Binder, Swanson, et al., 2008).

Probe and control tasks have also been compared with one another to identify which tasks are better able to lateralize language functions in children and adults (Binder, Swanson, et al., 2008; Brennan et al., 2007; Wilke et al., 2006). Wilke and colleagues (2006) compared two new tasks (letter identification and animal decision) for language lateralization with children to two previously developed tasks that have been used with adults (synonym decision and verb generation). The letter identification task required individuals to identify a phoneme within the name of a visually presented object and was paired with a visual control task. In the animal decision task, individuals were presented with a picture of an animal and required to answer an aurally presented question about the animal, which was paired with an auditory and visual control. These tasks were compared to a previously developed synonym task (decision about whether two visually presented words have the same meaning) with a perceptual control (decision about whether two meaningless letter strings are identical), and a verb generation task (covert generation of words that are associated with an aurally presented noun) with a rest control. They reported that in their sample of 23 children, ages 6-15, the previously developed tasks activated a number of frontal areas that were not directly involved in language areas, and presented a challenge because behavioral monitoring could not be conducted in the synonym task. With regard to the new tasks, the animal decision task did not result in activation of frontal language regions, but the letter task was useful, as it resulted in robust language lateralization, allowed for behavioral monitoring, and was appropriate even for children as young as six years old. In another preliminary study with seven adults (Brennan et al., 2007), object naming was reported to better lateralize language than number counting. The results were confirmed with cortical stimulation mapping, although these findings may be limited by the small sample size or the task design, which utilized a combination of fixation and perceptual controls.

Recently, Szaflarski and colleagues (2008) compared two frequently used language tasks: a covert verb generation task with a motor/auditory control (bilateral finger tapping in sync with an aurally presented tone) and a semantic decision task with a tone decision control. Findings indicated that both are useful for lateralizing language, but the semantic decision/tone decision task showed greater agreement with previously established language lateralization techniques (e.g., IAT, cortical stimulation mapping). This may have been due to the better match between the cognitive processes required in the probe and control task, and ability to monitor performance.

To specifically investigate receptive language, Binder and colleagues (2008) compared five protocols that had been designed and previously used to assess language comprehension in a sample of 26 adults. The participants underwent seven fMRI scans, comparing different passive (i.e., simply listen) and active (i.e., requiring a response) probe and control tasks. The tasks included rest (i.e., instructions to remain relaxed and motionless), passive tone (i.e., listen to tones), passive word (i.e., listen to words), semantic decision (i.e., listen to animal names, and press a button if the animal was both found in the United States and used by humans), and phoneme decision (i.e., listen to triplets of consonant-vowel pairs and press a button if the triplet contained both the consonants b and d). Upon comparison of these conditions, the semantic decision paired with the tone decision task as a control produced the most strongly left-lateralized activation, particularly in regions that have been associated with language comprehension deficits, including the angular gyrus, dorsal prefrontal cortex, and ventral temporal lobe. Notably, this activation was not observed when the semantic decision task was paired with rest, once again suggesting that semantic processing likely occurs during the resting state.

Reliability and validity. The reliability and validity of language protocols have been the subject of much study. Unlike with the IAT, test-retest studies are permissible, as fMRI is noninvasive and relatively safe (Fernandez et al., 2003; Harrington et al., 2006; Jansen et al., 2006; Rutten et al., 2002). One potential problem with reliability studies is that excessive task repetition may result in an artificial increase in bilateral activation, as was observed in a case study in which a covert word generation task paired with rest was repeated 10 times over the span of two months (Lohmann, Deppe, Jansen, Schwindt, & Knecht, 2004). These results should be interpreted with caution, as they have not been confirmed in a larger sample or with different language protocols, such as those which do not use rest as a control and/or allow for performance monitoring. Moreover, reliability studies typically do not involve such a high degree of task repetition. Nevertheless, the findings of Lohmann and colleagues (2004) suggested that the effect of task repetition on cortical activation may warrant further investigation.

In terms of reliability, there have been a number of investigations of the reproducibility of language protocols. Rutten and colleagues (2002) had nine neurologically normal individuals perform the same three language tasks (i.e., verb generation, antonym generation, and picture naming) on two separate occasions, approximately five months apart. Only the verb generation task and a combined analysis of all three tasks yielded reproducible findings, most robustly when calculated from pre-defined language regions in frontal and temporal regions rather than within a whole hemisphere. Fernandez and colleagues (2003) evaluated the within-test reliability of a language protocol with 34 consecutive pre-surgical epilepsy patients and the between-test reliability of the same protocol (using different synonyms) with 12 patients who were examined twice in one day. The protocol consisted of alternating blocks containing a synonym judgment task and a letter-matching control task. The reliability observed both within- and between-sessions was adequate in both cases, although reliability was higher for global and frontal regions than for temporoparietal areas. High within-session reliability was calculated for the whole hemisphere ($r = .898$, $p < 0.0001$), Broca's area ($r = .715$, $p < 0.0001$), remaining prefrontal cortex ($r = .781$, $p < 0.0001$), and temporoparietal region ($r = .794$, $p < 0.0001$). Across sessions, reliability was also high for the whole hemisphere ($r = .815$, $p < 0.001$), Broca's area ($r = .837$, $p < 0.001$), remaining prefrontal cortex ($r = .982$, $p < 0.0001$), and adequate in the temporoparietal region ($r = .695$, $p < 0.05$).

Jansen and colleagues (2006) conducted another investigation of reproducibility based on two scans done the same day approximately two hours apart with a sample of 10 neurologically normal adults. Participants performed three language tasks, including covert phonemic word generation paired with covert repetition of a visually presented nonsense word, a synonym decision task paired with identification of identical letter strings, and picture naming paired with fixation. The authors calculated the lateralization index in a number of ways, using different statistical thresholds, and found that the word generation task was more reliable than the synonym decision and the picture naming task (equivalent to a combined task analysis) when activation was measured in a pre-defined ROI with a pre-defined activation threshold. Similarly, Harrington and colleagues (2006) found the most reliable results with a verb generation task. They compared activation of inferior frontal and temporparietal areas based on 6 language tasks (i.e., verb generation, confrontation naming, semantic decision, visual sentence comprehension, auditory sentence comprehension, and story listening) in a sample of 10 neurologically normal adults. Findings indicated that verb generation was the most reliable language task in both ROIs ($r = \geq .90$); this was also the case for combined task analysis in both regions and the story listening task in the temporoparietal area. The results of these studies indicate that the use of fMRI for language lateralization is reliable, but is heavily influenced by task choice and method of data analysis.

The concurrent validity of fMRI language protocols has been investigated by comparing lateralization scores from fMRI with those obtained using a more well-established method. Xiong and colleagues (1998) reported that 92% of the activation observed in positron emission tomography was also seen during a verb generation task paired with a fixation control task. However, fMRI also identified 64% more activation than positron emission tomography, which the authors attributed to the greater spatial resolution of fMRI compared to positron emission tomography, the differences in the underlying physiological mechanisms of each method, or perhaps greater sensitivity or motion artifacts (image irregularity due to movement while in the scanner) that are associated with fMRI.

When fMRI has been compared with cortical stimulation mapping, there has been generally adequate agreement between the two methods. More specifically, when fMRI has been used to predict the critical language regions assessed by cortical stimulation mapping, average sensitivity has been reported from 81-92%, with average specificity between 53-61% (Binder & Raghavan, 2006). These findings were consistent with one of the limitations of fMRI; because this method relies on an activation paradigm, the activated areas do not necessarily represent essential language cortex. Additionally, there have been a number of comparisons of the lateralization indices obtained using fMRI and IAT, the current “gold standard” for language lateralization in pre-surgical epilepsy patients. These studies, which will be reviewed in detail in the following section of this paper, have reported concordance rates between fMRI and IAT language indices from 55-100%, although most studies report rates of approximately 80% or higher (Swanson et al., 2007). These concordance rates provided additional evidence of the concurrent validity of fMRI language lateralization methods.

The predictive validity of fMRI in terms of post-surgical language functioning is an area that should be examined in future research, but has been the subject of one study to date (Sabsevitz et al., 2003). In this study, 24 consecutive epilepsy patients who were planning to undergo a left anterior temporal lobectomy performed a semantic decision task paired with a tone decision control task prior to surgery. They also were given a confrontation naming task (i.e., the Boston Naming Test) prior to and following surgery to assess language outcome. Pre-operative fMRI showed 100% sensitivity and 73% specificity for predicting postoperative naming decline. This study provided preliminary evidence of the predictive validity of at least one fMRI language lateralization protocol.

Limitations of fMRI

Although the use of fMRI to lateralize language processes has become increasingly popular among epilepsy centers in the past 15 years, some would argue that this method does not yet have a sufficient evidence base to replace the IAT (Jones-Gottman, 2008; Loring, 2008). Specifically, there are a number of limitations associated with the use of fMRI, including poorly designed language protocols, the different data analysis methods that are used to calculate the lateralization index, and other general fMRI methodological concerns. These limitations influence the ability of researchers and clinicians to interpret fMRI findings.

Language protocol design. As has been previously discussed, well-designed probe and control tasks are critically important for the interpretation of fMRI data. When a control task is developed that does not require all of the non-language-specific cognitive processes of the probe task (e.g., semantic decision paired with rest), or requires additional processing (e.g., an auditory probe task paired with a visual control), the activation less accurately reflects isolated language processes (Binder, Swanson, et al., 2008). Moreover, when probe and control tasks are not matched in terms of difficulty, a difference in parietal activation has been observed, which also limits the validity of the lateralization index (Draeger et al., 2004). Finally, task performance has been associated with differential activation in frontal and temporal regions; increased performance was associated with increased temporoparietal activation and decreased frontal activation (Weber et al., 2006). As such, task designs that do not permit performance monitoring (e.g., covert verb generation) are limited in their ability to detect potential differences in activation due to variable task performance.

Data analysis. The conceptual and procedural variation in data analysis methods, including differences in the calculation of the lateralization index, definitions of brain activation, ROIs, and statistical thresholds, influence the interpretation of fMRI maps. For instance, conceptual variations in the determination of brain activation (e.g., number of activated voxels vs. magnitude of signal intensity change) and decisions about ROIs have been shown to influence the calculation of the lateralization index (Jansen et al., 2006). Furthermore, different data analysis procedures (e.g., threshold variation, direct statistical comparison) have been shown to influence the robustness and reliability of language lateralization indices and alter concordance rates with previously established language lateralization methods (Chlebus et al., 2007; Seghier, 2008). An optimal data analysis procedure has not yet been identified, which makes it difficult to compare fMRI findings with other language lateralization procedures, as well as across studies, and therefore limits knowledge regarding the reliability and validity of specific language protocols.

Other methodological considerations. Functional resonance imaging is a relatively new procedure that is not yet well-understood (Culham, 2006). In fact, some researchers have compared it to “a modern and extraordinarily expensive version of nineteenth-century phrenology" (Nichols & Newsome, 1999; Uttal, 2001, as cited in Raichle, 2006, p.9). This concern has not been shared by all researchers, and is likely related to instances in which fMRI activation has been investigated in one discrete ROI, after which global interpretations about complex mental functions were made (Raichle, 2006). Another concern has been raised regarding the finding that activation may be more frequently observed in cortical regions with dense vascularization, which may result in misleading activation maps (Culham, 2006). More broadly, there is uncertainty regarding the interpretation of cortical activation because fMRI is an activation method, which means that activated regions may not be essential for (or even related to) language functioning, or alternatively, a task may not activate all areas involved in language processing. In particular, it is difficult to determine the role of the right hemisphere in cases of bilateral activation, which is significant, as some degree of right hemisphere activation is frequently observed in fMRI language studies (Pelletier, Sauerwein, Lepore, Saint-Amour, & Lassonde, 2007). Moreover, individual differences and sources of error can also limit the interpretability of findings, including variations in attention and effort, cognitive ability, head movement, and vocal responses. While fMRI is relatively safe compared to invasive language lateralization procedures such as the IAT, it is unsuitable for individuals with claustrophobia and those who are significantly overweight, and certain tasks have cognitive demands that are too high for some patients. Additionally, medical and technical issues prohibit the use of fMRI, such as pacemakers, cochlear devices, surgical clips, metal devices (e.g., braces), and CNS active medications (Swanson et al., 2007).

The use of fMRI for language lateralization in the pre-surgical evaluation of epilepsy patients has been embraced by some as a replacement for the IAT (Baxendale et al., 2008; Loddenkemper, 2008). There is preliminary evidence of the reliability and validity for fMRI language protocols, particularly when verb generation or semantic decision/tone decision tasks have been used, and when the inferior frontal gyrus is one of the ROIs. However, the absence of a standardized protocol, validated data analysis procedure, and the limited understanding of the mechanisms that underlie fMRI procedures themselves limits the interpretability of activation data. As such, while many agree that fMRI is preferable to invasive methods for the determination of language lateralization and localization, it appears that the methodological limitations warrant further study before replacement is advisable.

Comparison Studies: IAT and fMRI

Some have suggested that fMRI may soon replace the IAT in the pre-surgical evaluation of intractable epilepsy patients (Abou-Khalil, 2007; Baxendale et al., 2008; Pelletier, et al., 2007). However, most agree that incongruities between the IAT and fMRI procedures have yet to be sufficiently addressed. Swanson and colleagues (2007) recently reviewed a number of studies that directly compared the assessment of language dominance for patients who had both IAT and fMRI, and reported concordance rates of 55-100%. This discrepancy likely reflects the methodological differences between the procedures, small sample sizes, and the absence of standardized fMRI language protocol across studies.

Concordance between IAT and fMRI

As the body of IAT/fMRI comparison literature has evolved over the past 15 years, concordance rates have been investigated in a number of contexts. Specifically, researchers have examined the effects of different language tasks, combinations of language tasks, ROIs, sample characteristics (e.g., atypical dominance, extratemporal epilepsy), methods of analysis at different magnetic strengths, and individual differences in language organization (e.g., dissociation of language functions) on rates of concordance. Concordance rates between IAT and fMRI for language lateralization have been reported from 55-100%; this discrepancy is likely due to paradigm differences (deactivation vs. activation), different ROIs, small sample sizes, and individual differences in language organization. In terms of outcome, some reports have offered anecdotal evidence of the absence of post-operative aphasia (e.g., Worthington et al., 1997), but only one study to date has examined the predictive validity of the IAT and fMRI with regard to post-operative language morbidity (Sabsevitz et al., 2003).

Early comparison studies. The first IAT/fMRI comparison study was conducted by Desmond and colleagues (1995). Seven patients underwent both the IAT procedure and had functional imaging to determine language lateralization. The language protocol consisted of a semantic encoding task with a perceptual control. Participants were shown words, half abstract (e.g., love) and half concrete (e.g., chair), half upper case (e.g., LOVE) and half lower case (e.g., chair). During the semantic encoding condition, participants were instructed to squeeze a ball depending on whether a visually presented word was abstract or concrete, while in the control condition they were to squeeze the ball depending on whether the word was upper- or lower-case. In all seven cases (four left hemisphere dominant; three right hemisphere dominant), the IAT and fMRI lateralization indices were in agreement (100% concordance). Only the frontal regions of the brain were imaged, and activation was limited to the inferior frontal gyrus. A limitation of this study was that the participants had already undergone surgical intervention for seizures. The authors noted that including only frontal ROIs was a limitation of this study, as semantic tasks are also likely to engage temporal structures. Notably, one participant with left hemisphere dominance had considerable activation in the right inferior frontal gyrus, and one participant with right dominance had bilateral activation. These findings were consistent with those of many subsequent studies in which activation was not limited to the dominant hemisphere, which indicates that language may be better conceptualized as continuous (i.e., -100 to + 100), rather than categorical (i.e., left, right, bilateral).

Binder and colleagues (1996) conducted the first IAT/fMRI comparison study in pre-operative epilepsy patients. They used a semantic decision task with a tone decision control task. In the language task, 22 participants heard names of animals and were instructed to press a button if the animals were found in the United States and used by humans. In the control task, participants heard series' of high and low-pitched tones and were asked to press a button every time they heard a series with two high-pitched tones. In contrast to the study by Desmond et al. (1995), Binder and colleagues (1996) imaged the whole brain, and found activation in the lateral frontal and temporo-parietal-occipital areas. They also reported 100% concordance between IAT and fMRI language lateralization (18 left hemisphere dominant, one right hemisphere dominant, three with bilateral dominance). Examination of language along a continuum also resulted in a high correlation between IAT and fMRI lateralization indices ($r = .96$, $p < 0.0001$). Similar findings were observed by Yetkin and colleagues (1998), who reported a correlation of .93 ($p < 0.0001$). They compared the IAT and fMRI language lateralization indices of 13 patients who performed a covert fluency task (silent word generation). Concordance was reported in the 12 cases of left language dominance. However, in the case of right dominance according to IAT (laterality score of -100), the fMRI laterality score was -10, which indicates considerably more bilateral activation.

Worthington and colleagues (1997) reported the lowest concordance between IAT and fMRI lateralization indices, at 55%. Twelve participants performed a covert verbal fluency task, in which they silently generated as many words as possible that started with a given letter in one minute. The control condition for this study was one minute of rest. Agreement between the IAT and fMRI was observed in five cases, in four cases there was disagreement, and in the remaining three, fMRI was indeterminate due to motion artifacts or unclear activation. This low concordance rate may be attributed to the task design (use of rest for control), small sample size (nine with usable data), or methodological difficulties with fMRI (e.g., motion artifacts, lack of performance monitoring). Of note, two patients with discordant IAT and fMRI data who had resections after the completion of this study also underwent cortical mapping to confirm language lateralization, which confirmed IAT findings. Furthermore, neither of these patients developed post-operative aphasia, which suggested that the fMRI procedure used in this study was inadequate for lateralizing language functions.

Similar studies were subsequently conducted with adults (Baciu et al., 2001; Bahn et al., 1997) and children (Hertz-Pannier et al., 1997). Seven adult participants performed a covert fluency task paired a rest control (as in Worthington et al., 1997), and also a covert rhyming task in which they were instructed to silently generate words that rhymed with a given word (e.g., cat, door, bag) with a rest control. Once again, all cases were concordant (five left hemisphere dominant, two right hemisphere dominant). The authors found that although both frontal and temporoparietal activation was observed, asymmetric activation of the inferior frontal gyrus was a better predictor of language dominance than temporal activation. One-hundred percent concordance between IAT and fMRI was also observed in a sample of six children who performed a covert verbal fluency task (i.e., generating words starting with a certain letter; generating words of a certain category, such as animals, foods, etc.). Once again, activation in frontal regions was consistent with IAT findings in all cases (five left hemisphere dominant, one with bilateral dominance).

Baciu and colleagues (2001) proposed a different rhyme detection task in which paired words were presented and participants were required to press a button if they rhymed. In the control condition, unreadable strings of text were presented, and the button was to be pressed if one of the characters overshot the others. Language dominance was concordant in all eight cases (seven left dominant, one with bilateral dominance). The authors noted that a number of these patients had resections that included fMRI activated cortical areas, but did not have post-operative aphasia, which suggested that fMRI, at least this instance, detected non-essential language areas.

Comparison of fMRI language tasks. Several studies have examined IAT and fMRI concordance while comparing different fMRI tasks (Benson et al., 1999; Lehericy et al, 2000; Szaflarski et al., 2008). Using a variation of the covert verbal fluency task, Benson and colleagues (1999) compared IAT and fMRI with 23 participants using a covert verb generation task (i.e., silent generation of verbs that were associated with a visually presented noun) paired with a visual fixation control (fixation on a crosshair). These authors also attempted to use object naming and word reading tasks, but they found that these did not adequately lateralize language functions. However, the verb generation task resulted in activation that was 96% concordant with IAT results; again, activation was predominantly observed in frontal areas, which was related to the supposed reason for discordance. The one participant who had discordant laterality scores (left dominance according to IAT, right dominance according to fMRI) had a large left frontal tumor, which likely limited the left-hemisphere task-related activation, as the verb generation task has been shown to activate mainly frontal areas. The authors omitted the area of the tumor and the homologous contralateral region from the fMRI analysis, which then resulted in concordant language lateralization with IAT.

Lehericy and colleagues (2000) observed language lateralization using a covert semantic fluency task (i.e., name as many word from a given category as possible, such as animals, fruits, or furniture) paired with a rest control condition in a sample of 10 participants. Using the semantic fluency task, frontal regions ($r = .88$, $p < 0.001$), but not temporal regions, were correlated with IAT lateralization indices. However, neither covert sentence repetition with a rest control, nor story listening with a control condition in which participants listened to the same story backward, adequately lateralized language.

Recently, Szaflarski et al., (2008) compared the two most widely used fMRI language tasks, the verb generation task (i.e., generating verbs associated with a given noun) with a finger tapping control, and the semantic decision/tone decision task described above (Binder et al., 1996). Both were reported to have acceptable correlations with IAT laterality scores, but the semantic decision/tone task was slightly better than the verb generation task ($r = 0.735$, $p < 0.001$; $r = 0.652$, $p < 0.001$, respectively). These findings may have been related to a poorly designed control (i.e., finger tapping, which added a motor component and did not subtract out auditory processing and working memory).

Concordance based on input modality. In order to investigate whether a particular input modality had an influence on IAT/fMRI concordance rates, Carpentier and colleagues (2001) compared lateralization scores based on activation from visual and auditory fMRI tasks with IAT lateralization ratings. The visual task consisted of visually presented sentences (participants were asked to press a button if the sentences were semantically and syntactically correct) with a control task in which rows of lines were presented and subjects were instructed to determine whether they were identical. The auditory task consisted of aurally presented sentences (participants were to press a button if the sentences were semantically and syntactically correct) with a tone decision control task in which participants were presented with two tones and instructed to determine whether they were identical in pitch. The authors reported different activation patterns in the control group; the visual task activated areas in the inferior frontal gyrus that were not activated during the auditory task, whereas the auditory task activated bilateral temporal areas, which were not activated during the visual task. However, this finding was not significant in the epilepsy group, perhaps due to the greater tendency of this group to show language reorganization. In general, the visual task resulted in stronger language lateralization scores, and concordance was observed in 8 of 10 participants. The two participants with discordant data had bilateral activation according to fMRI and were left lateralized with the IAT. That finding is perhaps related to the nature of fMRI; non-essential language areas in the right hemisphere may have been activated, suggesting bilateral dominance, which would not have been observed with the IAT.

Concordance with frontal and temporal regions of interest. Given the tendency of many frequently used fMRI tasks to activate frontal areas, the inferior frontal gyrus has been the ROI in numerous studies. However, several studies have specifically compared concordance rates for both frontal and temporoparietal areas (Benke et al., 2006; Deblare et al., 2004; Galliard et al., 2002; Spreer et al., 2002). Gaillard and colleagues (2002) advocated the inclusion of a reading task (responsive naming), specifically designed to activate temporal areas. Descriptive sentences were visually presented to participants (e.g., “What is a long yellow fruit”), and they were instructed to name the object. The control condition was visual fixation on eight different patterns of dots. Activation was observed in both frontal and temporal areas, and concordance was observed in 15 of 18 (83%) cases. In the discordant cases, two participants had bilateral language according to the IAT and left dominance according to fMRI, whereas one participant had left dominance according to IAT and bilateral fMRI activation.

Spreer and colleagues (2002) investigated the activation associated with a semantic decision task paired with a novel control task. Twenty-two participants were shown a target word with four words underneath it, and instructed to choose which of the four words was a synonym for the target word. The control condition was a structurally similar color matching task. Findings indicated 100% concordance when frontal regions were analyzed, but less so when global or temporoparietal regions were considered. Lateralization indices based on activation in temporoparietal regions were discordant in two cases, which was similar to the findings reported by Gaillard and colleagues (2002), as temporal activation indicated left hemisphere dominance while IAT indicated atypical dominance (right in one case, bilateral in the other). As such, it would appear that while inclusion of tasks that activate temporoparietal areas is important, this region alone may not provide accurate laterality scores in patients who have atypical language.

These findings were consistent with those of Deblare and colleagues (2004), who tested language lateralization in a sample of 17 participants who were scanned in a less powerful magnetic field (1.0T rather than the typical 1.5T). Using a covert word chain task (participants were asked to silently generate words one after another that started with the last letter of the previous word) with a covert counting control task, they found an 88% concordance rate with IAT based on activation from temporoparietal areas, whereas the concordance was 100% when frontal areas were considered. In this study, temporoparietal activation indicated bilateral language dominance in one case of left dominance categorized by the IAT, and right dominance in two cases of bilateral dominance according to the IAT.

Most recently, Benke and colleagues (2006) used an adapted version of the semantic decision/tone decision task (Binder et al., 1996) with a sample of 68 participants, and reported concordance rates for those with right temporal lobe epilepsy and left temporal lobe epilepsy. For the right temporal lobe epilepsy group, both frontal and temporal ROIs resulted in concordance in 24 of 28 cases (86%). The frontal activation most often resulted in misidentification of atypical dominance as indicated by the IAT, whereas temporoparietal lateralization indicated right dominance when IAT indicated left dominance. However, in the left temporal lobe epilepsy group, frontal activation resulted in 11 of 40 concordant cases (72.5%), whereas the temporoparietal lateralization indices were concordant with IAT findings to a lesser degree, in 15 of 40 cases (62.5%). The comparatively lower concordance rates for the left temporal group epilepsy group may be related to the higher incidence of atypical language that is observed with this condition. Approximately half the discordant cases based on frontal ROIs were those which were classified as bilateral by IAT, whereas the discordant cases based on temporoparietal cases were more evenly distributed between left, right, and bilateral IAT cases. These findings suggested that although language lateralization indices based on fMRI activation in frontal regions were associated with IAT hemispheric language dominance in many cases, this method may fail to observe contralateral or bilateral activation in temporoparietal regions of the brain, therefore resulting in discordance with the IAT.

Improving concordance using the verbal fluency task. The covert verbal fluency task (verb generation, phonemic fluency, or categorical fluency) with a rest control, having previously been shown to have fairly high concordance rates with IAT (92-100%) (Bahn et al., 1997; Chlebus et al., 2007; Hertz-Pannier et al., 1997; Yetkin et al., 1998; Lehericy et al., 2000) was the task used in several studies designed to examine methods to further improve concordance rates (Adcock et al., 2003; Liegeois et al, 2002; Sabbah et al., 2003; Woermann et al., 2003). Liegeois and colleagues (2002) addressed a potential methodological problem with fMRI related to the functional significance of activated cortex; in many cases, a larger region of activation is assumed to have greater functional significance (i.e., a greater number of activated voxels is presumed to indicate language dominance), but this may not be the case. In this study, a direct comparison was made between activated voxels in the inferior frontal gyri to determine if the activations in the left and right hemispheres were statistically significantly different from one another. Using this method of analysis, fMRI and IAT were 100% concordant with four participants (two right hemisphere dominant, one left hemisphere dominant, and one with bilateral dominance). While this rate of concordance is similar to that which was observed with a more traditional method of comparing the extent of activation between hemispheres, it is notable that three of the four participants had atypical language dominance, which has often been the case when IAT and fMRI are discordant. Therefore, these findings provided preliminary support for the direct comparison method of calculating fMRI lateralization indices.

In order to address concerns related to the activation threshold, Adcock and colleagues (2003) examined the difference between the extent of activation in the fronto-temporo-parietal cortex at two different thresholds ($z = 2.3$, which is common in many fMRI studies and $z = 5.3$, which is higher than normal), and also the magnitude of change in the inferior frontal gyrus. Lateralization scores were concordant in 16 of 19 cases at the $z = 2.3$ threshold, 19 of 19 cases when the threshold was set at $z = 5.3$, and 17 of 19 cases when the magnitude of signal change in the inferior frontal cortex was calculated. As such, the authors suggested that the use of higher thresholds when calculating activation may be more reliable. Notably, the seven patients who had right temporal lobe epilepsy all showed 100% concordance between IAT and all methods of fMRI laterality index calculation. The discordant findings were observed among individuals with left temporal lobe epilepsy, who are more likely to have atypical language; they were characterized by IAT as right dominant in one case, having bilateral language in two cases, and left dominant in one case.

In the largest study to date, Woermann and colleagues (2003) compared IAT and fMRI lateralization indices in a sample of 94 patients, 29 of whom had atypical language. They reported a 91% concordance rate, with eight discordant cases. Of these, four had left extratemporal epilepsy, one had right extratemporal epilepsy, two had left temporal lobe epilepsy, and one had right temporal lobe epilepsy. The presence of extratemporal epilepsy, particularly in the left hemisphere seemed to be a factor that contributed to discordant categorization of language dominance by fMRI, perhaps due to the intrahemispheric language reorganization that has been observed with this condition.

Sabbah and colleagues (2003) used the covert fluency task with a rest control to examine concordance rates between the IAT and fMRI with a number of left-handed participants, a group that had often been neglected in previous samples. Nineteen of their 20 participants had concordant IAT and fMRI results, which is relatively high considering the relationship between atypical handedness and atypical language dominance and the tendency for atypical dominance to be associated with IAT/fMRI discordance. The one discordant case was a left-handed participant with left temporal lobe epilepsy who was categorized as right hemisphere dominant by the IAT and bilateral by fMRI.

Most recently, Chlebus and colleagues (2007) tested a number of new methods for calculating laterality index, such as weighting voxels and varying the statistical threshold for activation. Although the use of these methods did not produce a statistically significant advantage when compared to frequently used methods (counting the number of voxels activated in each ROI based upon a given activation threshold), 100% concordance was observed when the ROI was the inferior frontal gyrus ($r = .94$, $p < 0.0001$). However, this was not a surprising finding, as fMRI language lateralization indices based on frontal activation have consistently been more highly correlated with the IAT than other ROIs (Benke et al., 2006; Deblare et al., 2004; Galliard et al., 2002; Spreer et al., 2002).

Concordance using a panel of language tasks. With the aim of improving concordance rates with the IAT, which includes a number of tasks, such as object naming, sentence repetition, and single-word reading, two studies have provided comparisons of language lateralization indices derived from a panel of fMRI tasks and IAT (Gaillard et al., 2004; Rutten et al., 2002). Rutten and colleagues (2002) combined four tasks: (1) covert verb generation with detection of a target symbol (asterisk) as a control, (2) a covert naming task paired with the same control, (3) a phonemic verbal fluency task paired with rest, and (4) a reading task paired with a perceptual control (strings of dots occasionally containing an asterisk, and participants were to push a button when the asterisk appeared). Of the 18 participants, concordance was observed in 10 of 11 who were classified as left hemisphere dominant by IAT, three of four who were classified with bilateral dominance by IAT, and two of three who were classified as right dominant by IAT. Notably, frontal lateralization indices had the same predictive power as lateralization indices that were calculated from the activity in all the ROIs (frontal, temporal, parietal).

Gaillard and colleagues (2004) used a panel of five tasks: (1) covert verbal fluency (phonemic and categorical) paired with rest, (2) the covert responsive reading task described above (Gaillard et al., 2002) paired with a visual presentation of dot patterns, (3) a reading comprehension task (story reading) paired with a visual presentation of dot patterns, (4) an auditory comprehension task (story listening) paired with either rest or reverse speech (listening to the stories backward), and (5) covert auditory responding to clues similar to the responsive reading task (e.g., “what is a long yellow fruit?”). The IAT and fMRI lateralization indices were concordant in 21 of 25 cases (88%). The fMRI language maps were rated visually by three raters, who agreed in all cases except one, which was one of the discordant cases. Of the discordant cases, IAT categorized three participants as left hemisphere dominant that appeared to have bilateral language according to fMRI, and in one case, IAT indicated bilateral dominance while left dominance was suggested by fMRI. While combined task analysis may be of value, in its current form, it has been criticized as being an inadequate mathematical construct for the determination of language lateralization because it merges activation patterns in different ROIs to a single lateralization index, which may be misleading (Wellmer et al., 2008).

Concordance using multiple regions of interest. Wellmer and colleagues (2008) recently cautioned against relying on any one ROI to determine fMRI language lateralization. They examined three ROIs in 22 patients with atypical dominance: Broca’s area (part of the inferior frontal gyrus) and the contralateral homologous region, the remaining frontal area, and the temporoparietal area. Using a semantic decision task (identification of synonym pairs) with a perceptual control (identification of identical letter strings), fMRI was calculated for each ROI, and the least lateralized ROI was compared to IAT. The authors acknowledged that this study was not meant to be an IAT-fMRI comparison study, as only nine participants underwent bilateral IAT (rather, based on unilateral IAT, they categorized hemispheric language capacity as complete, incomplete, or insufficient). Nevertheless, findings indicated that large intra-subject differences existed in lateralization indices, based upon the ROI. In this study, only patients with fMRI lateralization indices $\pm$ .84 in the ROI with the least lateralized activation would have been correctly classified as left or right dominant in concordance with IAT categorization. That is, patients with fMRI laterality indices between -.84 and .84 would have needed to be classified as bilateral, if they were to be concordant with the IAT. This is potentially problematic, as bilateral language is categorized in most studies by fMRI laterality indices between $\pm$ .01 and $\pm$ .05. While these findings should be interpreted cautiously, given the unilateral IAT procedure and small number of participants, they suggested that dissociation of language functions in patients with atypical dominance may, in part, account for discordance between IAT and fMRI laterality indices.

Evaluation of Literature/Potential Reasons for Discordance and Discrepant Findings

There are a number of common limitations that exist throughout this body of literature, and are likely related to both the IAT/fMRI discordance rates reported within studies and discrepant findings across studies. First, findings are limited by the lack of a standardized, validated fMRI language protocol; different tasks and ROIs influence cortical activation and subsequent laterality indices. Furthermore, sample characteristics such as small size, heterogeneity in terms of the side and location of seizure focus, and limited numbers of individuals with atypical language dominance likely limited findings. Additionally, methodological differences and the inherent limitations of the IAT and fMRI may be related to rates of discordance. Finally, there is a lack of post-operative outcome data, which would provide additional needed information regarding the validity of the IAT and fMRI, particularly in discordant cases.

Task selection. Tasks differ both between the IAT and fMRI, and between various fMRI language protocols. The IAT generally relies on a number of tasks, typically comprehension of commands, object naming, sentence repetition, and sentence reading (Loring et al., 1990). In contrast, many fMRI language protocols include one task; widely used tasks have been designed to draw upon expressive and semantic language functions (e.g., verbal fluency, semantic decision) (Binder et al., 1996; Worthington et al., 1997), and when multiple tasks have been used, a significant improvement has not been confirmed (Gaillard et al., 2004; Rutten et al., 2002; Wellmer et al., 2008). Different tasks recruit different cortical areas, which may be related to the discordance between IAT and fMRI. Furthermore, many of the comparison studies used rest as a control (e.g., Adcock et al., 2003; Chlebus et al., 2007; Lehericy et al., 2000; Liegeois et al., 2002), which has been shown to be problematic (Binder et al., 1999). Other studies used control tasks that added a new cognitive process not used in the language task, such as color discrimination, covert counting, or finger tapping (Deblare et al., 2004; Spreer et al., 2002; Szaflarski et al., 2008), or failed to subtract out non-language elements of the probe task, such as when visual fixation is used as a control condition (Benson et al., 1999; Rutten et al., 2002). The use of these control tasks may have confounded findings, as cortical activation would not have been isolated to language processes. Differences in probe and control task difficulty (such as in the case of using rest and fixation controls), as well as variable levels of performance, which was not monitored in the many of the comparison studies that used covert language tasks, has also been shown to limit the accuracy of the lateralization index (Adcock et al., 2003; Bahn et al., 1997; Benson et al., 1999; Chlebus et al., 2007; Deblare et al., 2004; Draeger et al., 2004; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Liegeois et al., 2002; Sabbah et al., 2003; Weber et al., 2006; Woermann et al., 2003; Worthington et al., 1997; Yetkin et al., 1998).

Regions of interest. Specific ROIs have consistently resulted in different rates of concordance when compared with IAT. When whole brain, frontal, and temporal regions were analyzed, frontal regions produced the strongest lateralization, and frontal activation was most concordant with IAT lateralization indices (Benke et al., 2006; Deblare et al., 2004; Lehericy et al., 2000; Rutten et al., 2002; Spreer et al., 2002). In a few studies, only frontal areas were analyzed (Desmond et al., 1995; Hertz-Pannier et al., 1997; Yetkin et al., 1998), which may have limited the detection of atypical language because activation in other parts of the brain is undetected. This is problematic because some patients have dissociation of language functions which is not evident based on consideration of only one ROI (Wellmer et al., 2008).

Sample size and characteristics. In most studies, the sample size was less than 30, which limited the generalizability of the findings. Moreover, the numbers of patients with atypical dominance based on IAT were typically eight or less, with a few exceptions (Benke et al., 2006; Woermann et al., 2003; Wellmer et al., 2008). Including more patients with atypical dominance according to IAT might lower concordance rates, as these patients quite often had discordant lateralization indices, despite their small numbers (Adcock et al., 2003; Benke et al., 2006; Deblare et al., 2004; Gaillard et al., 2004; Gaillard et al., 2002; Rutten et al., 2002; Sabbah et al., 2003; Wellmer et al., 2008; Yetkin et al., 1998). Interestingly, in a number of studies, all patients who were characterized as having bilateral dominance by IAT had discordant fMRI lateralization indices (Adcock et al., 2003; Deblare et al., 2004; Gaillard et al., 2004; Gaillard et al., 2002). This may reflect a weakness of current fMRI language protocols to correctly identify diffuse, atypical language networks or dissociated expressive and receptive language functions, which have been reported in a small number of patients (Lee et al., 2008; Rutten et al., 2002). Alternatively, discordance in cases of atypical dominance may be related to the designation of "bilateral" as a discrete category within a specified range rather than examining language scores along a continuum. For example, Benke and colleagues (2006) categorized individuals with lateralization indices that were $\pm$ .39 as having bilateral language, which resulted in one case of discordance based on an IAT laterality score of .37 (bilateral) and fMRI categorization of "left dominant" (the actual score was not provided, but could theoretically have been .40, a difference of .03). In this way, making categorical distinctions of language dominance may result in greater discordance rates than would be reported when language is examined as a continuous variable.

Individual patient differences also likely influenced rates of discordance, as samples were often heterogeneous in terms of seizure side and focus, and structural pathology. Often, patients with right temporal lobe epilepsy and left temporal lobe epilepsy were included in the same study. However, those with right seizure foci are more likely to have left-lateralized language, resulting in a higher incidence of concordance in this group, as was observed in the comparison study conducted by Benke and colleagues (2006). Another factor that may influence concordance rates is the presence of extratemporal epilepsy, particularly in the left hemisphere; discordance was observed in 25% of left extratemporal epilepsy cases by Woermann and colleagues (2003), which was higher than the other groups examined in that study. Finally, structural differences may be related to discordance; in one study, a large left frontal tumor was hypothesized to be the cause of discordance (left IAT dominance, right fMRI dominance) (Benson et al., 1999).

Methodological differences. The fundamental difference between the IAT paradigm (deactivation) and fMRI paradigm (activation) can make it challenging to compare the two procedures. The IAT, which was designed to mimic the cognitive consequences of a resection, temporarily incapacitates one cortical hemisphere, thereby identifying whether or not a hemisphere is essential for language functioning. In contrast, fMRI, which has the potential to localize language functions, identifies all areas associated with a language tasks, including non-essential language areas and areas that support related cognitive functions, such as attention and working memory. Each procedure has its own set of limitations which may also be related to discordance rates. The IAT is invasive, costly, has infrequently resulted in morbidity/mortality, and may be compromised by drug effects (e.g., obtundation, insufficient anesthetization) or abnormal cerebral vasculature. Meanwhile, fMRI is relatively less well-understood, lacks a standardized, validated language protocol, and may be compromised by motion artifacts, task incompliance, insufficient statistical thresholds and analyses, and activation of non-essential language areas.

Post-operative outcome evaluation. Investigations of concordance have also been limited by a lack of post-operative data, particularly in cases of discordant patients. A few studies anecdotally reported that patients did not develop post-operative aphasia (Baciu et al., 2001; Worthington et al., 1997), which was consistent with IAT lateralization findings. Sabsevitz and colleagues (2003) reported that both IAT and fMRI were predictive of post-operative naming decline. Notably, the authors reported that with fMRI, the temporal lobe lateralization index was most correlated with naming outcome, and more predictive than the frontal region, though many of the IAT/fMRI comparison studies reported the highest concordance rates between IAT and fMRI lateralization indices based on frontal activation. This suggested that the development of fMRI tasks that produce temporal activation that is concordant with IAT may be ultimately more useful for predicting post-operative decline. Currently, there are no studies that have formally tested post-operative language functioning in discordant patients, or in patients who have undergone resections guided by fMRI localization data. Both of these types of studies would provide important information regarding potential reasons for discordance, as well as the predictive validity of the IAT and fMRI.

Conclusion/Areas for Future Research

Epilepsy, the third most prevalent chronic neurological disorder worldwide, is medically intractable in 35% of the 2.7 million epilepsy patients in the United States. Of these, 30% may be candidates for epilepsy surgery, the goal of which is to remove the seizure focus while preventing or reducing cognitive morbidity (Engel & Shewmon, 1996). In particular, patients who undergo resective surgery for epilepsy are at risk for post-operative language decline (Bell et al., 2000; Langfitt & Rausch, 1996). The traditional views of language organization (expressive language localized to Broca's area; receptive language localized to Wernicke's area) have been disproven by IAT results that indicate atypical language dominance, which has been confirmed by more recent imaging studies with neurologically normal individuals and epilepsy patients that have identified more widespread functionally connected language networks. These findings necessitate the careful assessment of language lateralization prior to the removal of cortical regions. In a large percentage of neurologically normal individuals (94-96%), language is lateralized to the left hemisphere. However, epilepsy patients have a significantly higher incidence of atypical language, particularly those with early seizure onset, which further emphasizes the need for reliable, accurate assessment of cortical regions that are essential for language processing within a potentially diffuse, yet functionally connected, language network (Frost et al., 1999; Pujols et al., 1999; Springer et al., 1999).

The IAT has traditionally been the "gold standard" for language lateralization (Loring et al., 1992; Wada & Rasmussen, 1960), but has been reportedly used less frequently by epilepsy centers in recent years due to the risks associated with the procedure and the advent of fMRI, which has the potential to both lateralize and localize language functions in a manner that is less invasive, less costly, and presents less risk to patients than does the IAT. In fact, some researchers have advocated replacing the IAT with fMRI in most pre-surgical evaluations (Baxendale et al., 2008). Although both the IAT and fMRI have been shown to be predictive of post-operative naming outcome (Sabsevitz et al., 2003), in comparison studies, concordance rates between the two methods have ranged from 55-100%. While agreement between the two procedures has been observed in some studies, concordance has not yet been consistent enough to warrant replacement of the IAT with fMRI, particularly in cases of atypical dominance as assessed by either IAT or fMRI. Moreover, there is currently no universally accepted fMRI language protocol that has been standardized and validated. As such, it has been suggested that an appropriate evidence base has not yet been developed to establish post-operative risks for cognitive decline using fMRI (Loring 2008).

Purpose of the Proposed Study

Functional magnetic resonance imaging has the potential to replace the IAT in the pre-surgical assessment of language functioning with intractable epilepsy patients. However, the appropriate evidence base has not yet been established to indicate that a complete replacement would be advisable (Loring, 2008). Additionally IAT/fMRI comparison studies with larger samples than have been commonly seen in the literature (N<30) and tightly controlled language protocols are necessary. Many comparison studies used an inadequate control task (e.g., rest, fixation), which limited findings. Moreover, individuals with atypical language dominance have been neglected in the literature, even though those with atypical dominance have frequently been the participants who have had discordant findings. As such, these individuals should be included in future studies, and if discordant, these cases should be examined more closely to determine factors that may contribute to that discordance.

Closer examination of the discordant cases is also necessary. Specifically, further investigation is needed to examine factors that are related to the discordant cases of language lateralization based on the IAT and fMRI. A number of ROIs should be considered, as concordance and correlation differences have been observed in different ROIs (e.g., frontal, temporal) relative to task selection. Furthermore, in cases of discordance, investigation of post-operative language outcome is necessary to evaluate the predictive value of each procedure. At present, most findings related to language outcome refer anecdotally to the absence of post-operative aphasia, but no formal studies have examined the predictive value of IAT vs. fMRI in discordant cases of language lateralization.

Thus, the proposed study seeks to fill a gap in the extant research regarding the concurrent and predictive validity of fMRI as compared to the IAT for the assessment of language processes in the pre-surgical evaluation for intractable epilepsy patients. Specifically, a sample of over 200 intractable epilepsy patients (the largest to date) will be examined. Correlation and concordance rates of language lateralization scores obtained with IAT and fMRI will be calculated to establish concurrent validity. Furthermore, predictors of discordance will be examined and the procedure that best predicts post-operative language functioning in discordant cases will be determined. This will provide valuable information to clinicians and assist with decision-making regarding the selection of pre-surgical language assessment procedures.

CHAPTER 3: Method

Participants

A consecutive series of 275 adults (ages $\geq$ 18) underwent both the IAT and fMRI procedures for language lateralization between 1993 and 2009. Eleven individuals were excluded due to invalid IAT testing, two of whom also had unrecoverable fMRI data. Thirty-four additional individuals had unusable fMRI data (i.e., 2 – seizure while in scanner; 1 – arm pain while in scanner; 1 – claustrophobia; 3 – incomplete sessions; 1- scanner problems; 26 – unrecoverable data). One individual was excluded because he had a previous temporal resection. The resulting sample was 229 individuals; 112 males (48.9%) and 117 females (51.1%), with ages ranging from 18-68 (*M* = 38, *SD* = 10.9). The sample was predominantly Caucasian (91.7%), but also included individuals who identified as African American (4.8%), Latino (2.6%), Asian American (0.4%) and other (0.4%). These patients were evaluated at the Medical College of Wisconsin in the Comprehensive Epilepsy Program between 1993 and 2009. During that time, 169 had temporal resections (85 left temporal; 84 right temporal). Of the group with temporal resections, 133 received both pre- and post-operative neuropsychological assessments. The consecutive series of 229 patients who underwent both language lateralization procedures comprised the sample that was used to calculate IAT/fMRI correlation and concordance rates and to investigate predictors of discordance. Of the group of discordant cases, all patients who had left temporal resective surgery (L-ATL) and completed both pre-operative and 6-month post-operative neuropsychological testing comprised the sample used to examine the predictive validity of IAT and fMRI with regard to post-operative language functioning.

Data Collection

All data used in this study was archival data, retrieved from a database at the Medical College of Wisconsin. Patients with intractable epilepsy who were being considered for resective surgery were referred to the Neuropsychology Division by the department of Neurology between 1993 and 2009. Patients were required to undergo standardized pre-operative outpatient neuropsychological testing, IAT, fMRI, and were asked to return for outpatient post-operative neuropsychological testing. The neuropsychological testing was performed by a psychometrist under the supervision of a neuropsychologist. The IAT and fMRI procedures were performed by members of the Department of Neurology at the Medical College of Wisconsin. Variables were coded by a neuropsychologist and data was entered into an SPSS database by a research assistant.

The IAT predictive factors were coded by the neuropsychologist who performed the IAT procedure, and were measured as follows: posterior carotid artery filling during IAT (yes/no); crossflow ratings (graded as 0, 1, or 2); vascular abnormalities (yes/no), duration of drug effect (as indicated by the total number of trials completed during the IAT). The presence of MTS or hippocampal atrophy (yes/no) was determined via the clinical judgment of a neuroradiologist and coded by a neuropsychologist. The fMRI predictive factors were measured as follows: behavioral performance was measured by the percentage of correct responses during scanning; signal to noise ratio was averaged over time and space, broken down by run and for the two runs concatenated, motion artifacts were measured by the degree of movement that occurred during scanning, flags were calculated as the number of “bad” image volumes detected in the time series using an automated algorithm, and the residual was the mean across space of the error terms in the regression analysis of the BOLD signal. Subject variables were coded by a neuropsychologist following the clinical interview with the patient. The full scale IQ score was obtained with either the Wechsler Adult Intelligence Scale –Revised (WAIS-R) or the updated Wechsler Adult Intelligence Scale-III (WAIS-III), a widely used measure of general ability and intelligence. Neuropsychological measures of interest, IAT, and fMRI procedures are described in detail below.

Measures

Intracarotid Sodium Amobarbital Test. The IAT used at the Medical College of Wisconsin was modeled after the procedure that was developed at the Medical College of Georgia (Loring, 1992; See Appendix C). The IAT has been widely used for the pre-surgical assessment of language lateralization for over 50 years (Baxendale et al., 2008; Branch, Milner, & Rasmussen, 1964; Milner, Branch, & Rasmussen, 1966; Rasmussen & Milner, 1975; Rasmussen & Milner, 1977; Wada & Rasmussen, 1960) and has been validated using electrical stimulation mapping and post-operative language assessment (Branch, Milner, & Rasmussen, 1964; Epstein et al., 2000; Sabsevitz et al., 2003; Wada & Rasmussen, 1960; Wyllie et al., 1990). Baseline testing was performed 2 hours before the procedure. Amobarbital (75-125mg) was injected into the internal carotid artery ipsilateral to the seizure focus and language functions of the contralateral cerebral hemisphere were tested. The procedure was then repeated so that each hemisphere was tested separately. Language was assessed using measures of counting, comprehension of commands, naming, phrase repetition, and sentence reading during the period of hemianesthesia. Return of motor function and EEG monitoring were used to determine the duration of anesthesia. Scoring of language functioning ceased when motor return in the contralateral upper extremity was noted. The scores for each language task ranged from 0-3, with lower scores indicating a greater degree of impairment. Lateralization indices (LIs) were calculated as the difference between the percent of correct responses in the inject right/test left condition minus the percent of correct responses (i.e., counting, comprehension, naming, repetition, and sentence reading; see Appendix C) in the inject left/test right condition. LIs ranged from +100 (indicating complete left hemisphere dominance) to -100 (indicating complete right hemisphere dominance). The exact number of items administered varied according to the duration of drug effect and ranged from 9 to 33.

Functional Magnetic Resonance Imaging. The language activation protocol was a semantic decision/tone decision task developed by Binder and colleagues (1995), which has well documented reliability for activating the semantic language network (Binder et al., 1996; Binder et al., 1997; Frost et al., 1999; Sabsevitz et al., 2003; Springer et al., 1999). Individuals were trained to perform the tasks outside of the scanner prior to the imaging session. During the semantic decision task, individuals listened to a list of animal names and were instructed to press a button if the animal was both found in the United States and used by humans (e.g., for food, recreation). During the tone decision task, individuals listened to tone trains containing three to seven either high-pitched (750 Hz) or low-pitched (500 Hz) tones. They were instructed to press a button if they heard two high-pitched tones in a series. Tasks were alternated in a block design (i.e., participants listened to a block of series' of tone trains followed by a block of series' of animal names). For each individual, brain activation recorded during the tone task was subtracted from the activation recorded during the semantic decision task. Therefore, the overlapping components of the semantic decision task and the tone discrimination task that are in essence subtracted out included attention, working memory, auditory processing, and motor response, leaving activation from semantic and phonetic processing to be calculated as the LI. The semantic decision task has been shown to produce left-lateralized language activation in frontal, temporal, and parietal areas (Binder et al., 1997; Frost et al., 1999; Springer et al., 1999).

Imaging was conducted on commercial 1.5-T and 3T G.E. Signa scanners (General Electric Medical Systems, Milwaukee, WI). High-resolution, T1-weighted anatomic reference images were obtained throughout the entire brain using a three-dimensional spoiled-gradient-echo sequence (echo time = 5, repetition time = 24, pixel matrix = 256 x 128, slice thickness = 1.2 mm). Functional imaging used a gradient-echo T2*-weighted echoplanar sequence (echo time = 40 ms, repetition time = 3,000 ms, field of view = 24 cm, pixel matrix = 64 x 64, voxel sixe = 3.75 x 3.75 x 7 mm). Echoplanar image volumes were acquired as 19 contiguous, 7-mm sagittal slices covering the whole brain.

Image processing and statistical analyses were performed using AFNI software. All analyses were performed at the individual subject level. Volumetric image registration was used to reduce the effects of head movement. Task-related changes in MRI signal were identified using the cross correlation approach. This method compares the time series of MRI signal values in each image voxel with a reference vector representing an idealized hemodynamic response to the task alternation. The idealized response was modeled by convolving a gamma function with a time series of impulses representing each task trial. Correlation was performed using analysis of covariance, with movement vectors (computed during image registration) and a first-order linear term included as covariates of no interest. Voxels with a correlation coefficient corresponding to $p < 0.001$ were counted for each patient in each of the ROIs. LIs, reflecting the interhemispheric difference between voxel counts in the left and right homologous ROIs were calculated for each ROI using the formula: (L-R)/(L+R). LIs were calculated according to the following formula: LI = (L-R)/(L+R), where L equals the number of activated voxels in the left hemisphere and R equals the number of activated voxels in the right hemisphere. The scores range from +1 (complete left hemisphere dominance) to -1 (complete right hemisphere dominance). The ROIs included the left and right temporal lobe, left and right frontal lobe, left and right angular gyrus, and whole left hemisphere and whole right hemisphere.

Boston Naming Test. The 60-item BNT was administered to individuals prior to L-ATL and again 6-months post-operatively. The test consists of 60 black and white line drawings of objects that are relatively easy at the beginning (e.g., tree) and become increasingly more difficult (e.g., abacus). Individuals are asked to state the name of the pictures they are shown and one point is given for each picture that is correctly named spontaneously or in response to a semantic cue.

The Boston Naming Test (BNT) is a widely used neuropsychological measure of confrontation naming (Kaplan, Goodglass, & Weintraub, 1983), which has been used as a measure of language functioning in previous studies of individuals with intractable epilepsy (Bell et al., 2000; Sabsevitz et al., 2003). It has also been identified as a measure that may be used in serial examinations to document the recovery or decline of language functions, particularly for individuals with intractable epilepsy or Alzheimer's disease (Franzen, 2000; Spreen & Strauss, 1998). In 1999, as an addition to the Boston Diagnostic Aphasia Examination (Third Edition), BNT standardization data was derived from a sample of 85 aphasic individuals and 15 elderly non-aphasic volunteers. The Kuder-Richardson method of determining subtest reliability was performed to determine internal consistency (BNT alpha = .98) (Goodglass, Kaplan, & Barresi, 2001). Additionally, BNT test-retest reliability after eight months was reported as .94 in a sample of 51 individuals with intractable epilepsy (Sawrie, Chelune, Naugle, & Luders, 1996). In subsequent studies, the internal consistency (coefficient alpha) for the 60-item form of the BNT has been reported to range between .78 and .96 (Strauss, Sherman, & Spreen, 2006). Regarding validity, Axelrod and colleagues (1994) reported concurrent validity of the BNT with the Visual Naming Test of the Multilingual Aphasia Examination (Benton, Hamsher, & Sivan, 1994).

Wechsler Adult Intelligence Scale. The Wechsler Adult Intelligence Scale (WAIS-R and WAIS-III, Wechsler 1981; 1997) has been one of the most widely used measures in neuropsychological assessment batteries and is considered the "gold standard" in intelligence testing (Franzen, 2000). The WAIS-R full scale IQ (FSIQ) is comprised of verbal subtests (vocabulary, similarities, information, digit span, arithmetic, and comprehension) and performance subtests (picture completion, picture arrangement, block design, digit symbol, and object assembly). According to the technical manual (Wechsler 1981; 1997), split-half reliability of the FSIQ score was calculated with a methodology designed to compute the reliability of a composite group of tests, and was reported as .97. Test-retest reliability for verbal IQ and performance IQ (the two factors which comprise the FSIQ) reportedly ranged from .89-.97. The WAIS-III FSIQ is also comprised of verbal subtests (vocabulary, similarities, information, arithmetic, digit span, and comprehension) and performance subtests (picture completion, digit symbol-coding, matrix reasoning, and picture arrangement). The WAIS-III is correlated with the WAIS-R at .94 (Wechsler, 1997).

The construct validity of the WAIS-R and WAIS-III is so widely accepted that it has often been the standard used to examine the validity of other intelligence tests (Franzen, 2000). It has been somewhat difficult to ascertain the validity of any intelligence test, as the construct of intelligence remains varied in the literature (Strauss et al., 2006). In this case, the theoretical basis for test development broadly assumes both verbal and nonverbal contributions to intelligence, which have been identified as the factors that underlie the FSIQ, a general measure of intelligence. Regarding concurrent validity, the WAIS-III FSIQ score has been highly correlated with the Stanford-Binet IV Global Component score (r =.88; Franzen, 2000) and other measures of intelligence and academic achievement including the WIAT, WIAT-II, and WTAR (r = .36 to .86; Strauss et al., 2006).

CHAPTER 4: Results

The relationship between language lateralization scores was first examined using correlation coefficients. To more closely examine rates of discordance, difference and cut scores were then chosen by researchers and clinicians in the Department of Neurology at the Medical College of Wisconsin, and an operational definition of discordance was developed. The percentages of discordant cases based upon this definition were then calculated. Next, subject variables, IAT factors, fMRI factors, and the IAT and fMRI LIs that were hypothesized to predict discordance were entered into a multiple regression equation, with the absolute value of the IAT/fMRI difference score entered as the dependent variable (i.e., |IAT LI - fMRI LI|). Finally, a small subset of participants who had undergone L-ATL and had IAT, fMRI, and pre- and post-neuropsychological assessment were examined to investigate whether the IAT or fMRI had more accurately predicted their post-operative BNT score. Using this small subset, a regression equation was calculated to predict pre- to post-operative BNT change. This equation was then used to predict BNT outcome in the discordant cases using both IAT LIs and fMRI LIs, to determine which measure yielded a more accurate change prediction. Additional statistical testing was not performed because the subset of discordant cases who had undergone L-ATL was so small ($n = 11$), but the cases were examined qualitatively.

Relationship between Language Lateralization Scores Measured by the IAT and fMRI

Pearson and Spearman correlation coefficients were calculated to investigate the relationship between IAT LIs and fMRI LIs. Functional magnetic resonance imaging LIs were calculated for a number of regions of interest, including the left and right temporal lobe, left and right frontal lobe, left and right angular gyrus, and left and right lateral region. The fMRI LI that was calculated for each of these regions of interest was correlated with the IAT LI.

Pearson correlation was first used to examine the relationship between IAT LI and fMRI LIs in each ROI. The IAT LI was correlated with fMRI LIs from frontal ($r = .54$, $p < .001$), temporal ($r = .52$, $p < .001$), angular gyrus ($r = .59$, $p < .001$), and lateral ($r = .62$, $p < .001$) ROIs, which suggested a moderate level of agreement between IAT and fMRI LIs. However, since the IAT and fMRI LI scores were not normally distributed, a parametric test may not optimally measure their relationship. Additionally, the distribution of IAT LIs was more skewed (-1.88) than those of the frontal (-1.38), temporal (-1.20), angular gyrus (-1.40), and lateral (-1.51) LIs. Therefore, a non-parametric Spearman correlation was also used to examine the relationship between the IAT LI and fMRI LIs. The IAT LIs were again correlated with frontal (*rho* = .32, $p < .001$), temporal (*rho* = .31, $p < .001$), angular gyrus (*rho* = .40, $p < .001$), and lateral (*rho* = .41, $p < .001$) LIs, although to a lesser degree. This indicates that there is a moderate degree of association between the LI scores.

Rates of Discordance between LIs Measured by the IAT and fMRI

There is currently no standardized definition of discordance. Therefore, a panel of clinicians were enlisted to define discordance including the neurologist who developed the fMRI task that was used in this study (Dr. Jeffrey Binder), an fMRI research assistant (Ed Possing), and three neuropsychologists who have administered the IAT (Drs. Sara Swanson, Tom Hammeke, and David Sabsevitz). This panel met a number of times and chose to operationalize discordance in a conservative manner that would not overestimate discordance by using only cut scores (which results in very close scores on either side of the cut score being classified as discordant) or only difference scores (which does not take into account the methodological differences of the IAT and fMRI). When researchers use cut scores to define discordance, it is possible that scores within a few points of each other may be classified as discordant. For example, if a cut score is set at 30 (i.e. $\geq$ 30 = left language dominance, < 30 = atypical dominance), LIs of 29 and 30 would be identified as discordant. Using difference scores to define discordance is problematic as well, due to the measurement differences of the IAT and fMRI (i.e., deactivation vs. activation methods). That is, the LIs for fMRI and IAT have different distributions (i.e., in our sample the IAT LIs were more negatively skewed than fMRI LIs). Therefore, did not seem appropriate to equate raw LIs with one another. In this study, different cut scores were assigned to categorize each measure based on visual examination of the data, with the intent to produce similar rates of bilateral dominance. Additionally, a difference score was included in the determination of discordance and was set at 50, at the recommendation of the clinician panel.

For the IAT LIs, language dominance was categorized using a cut score of 50; left (LI $\geq$ 50), right (LI $\leq$ -50), and bilateral (LI between -50 and 50). For fMRI LIs, language dominance was categorized using a cut score of 20; left (LI $\geq$ 20), right (LI $\leq$ -20), and bilateral (LI between -20 and 20). Additionally, discordant cases were required to have difference scores (i.e., |IAT LI - fMRI LI|) that were greater than 50. “Discordance” was then defined as follows: the IAT and fMRI LIs must be (1) in different categories as outlined above and (2) have a difference score greater than 50. For example, a case with an IAT LI of 55 and an fMRI LI of 15 would not be defined as discordant because it meets the first criteria (i.e., IAT LI indicates left language dominance and fMRI LI indicates bilateral language dominance), but not the second (i.e., the difference score is 40). Similarly, a case with an IAT LI of 100 and an fMRI LI of 30 would not be defined as discordant because it does not meet the first criteria (i.e., both the IAT and fMRI LIs indicate left language dominance), although it does meet the second criteria (i.e., the difference score is 70). In order to be classified as discordant, a case must be in different categories and have a difference score greater than 50.

Rates of discordance were calculated using the cut scores outlined above (i.e., 50 for IAT; 20 for fMRI) and difference scores of 50. The total rates of LI discordance were 14-17%. We reported data using IAT as the measure of reference (i.e., when IAT indicates left, right, or bilateral language dominance, determine what fMRI indicates) and also using fMRI as the measure of reference (i.e., when fMRI indicates left, right, or bilateral language dominance, determine what IAT indicates). In this way, one can choose a subset of cases for one method (e.g., those identified as left dominant by IAT) and see exactly how those cases were characterized by the other method (i.e., IAT or any fMRI ROI). We first examined the data using the IAT as the measure of reference. As indicated in Table 1, when IAT LIs indicated left dominance, fMRI LIs were discordant at rates of 7-12%, whereas when IAT LIs indicated atypical dominance (right or bilateral dominance), fMRI LIs were discordant at rates of 16-50%.

Table 1. Language Discordance Rates when IAT is Left, Right, and Bilateral by fMRI Region of Interest using an IAT Categorization Cut Score of 50 and an fMRI Categorization Cut Score of 20 – IAT as Reference

	fMRI Discordant with IAT			
	Frontal	Temporal	Angular	Lateral
IAT Left	20/183 (11%)	22/183 (12%)	18/183 (10%)	14/187 (7%)
IAT Bilateral	15/32 (47%)	13/32 (41%)	16/32 (50%)	13/32 (41%)

IAT Right	4/14 (29%)	5/32 (16%)	5/14 (36%)	4/14 (29%)
Total	39/229 (17%)	40/229 (17%)	39/229 (17%)	31/229(14%)

Using fMRI as the measure of reference, when fMRI LIs indicated left dominance IAT LIs were discordant at rates of 6-8%, whereas when fMRI LIs indicated atypical dominance, IAT LIs were discordant at rates of 30-71% (see Table 2).

Table 2. Language Discordance Rates when fMRI is Left, Right, and Bilateral by fMRI Region of Interest using an IAT Categorization Cut Score of 50 and an fMRI Categorization Cut Score of 20 – fMRI as Reference

	IAT Discordant with fMRI
	IAT
Frontal	
Left	13/181 (7%)
Bilateral	17/24 (71%)
Right	9/24 (38%)
Total	39/229 (17%)
Temporal	
Left	13/179 (7%)
Bilateral	19/27 (70%)
Right	8/23 (35%)
Total	40/229 (17%)
Angular	
Left	14/184 (8%)
Bilateral	11/17 (65%)
Right	14/28 (50%)
Total	39/229 (17%)
Lateral	
Left	12/187 (6%)
Bilateral	12/19 (63%)
Right	7/23 (30%)
Total	31/229 (14%)

The actual numbers of left, bilateral, and right dominant cases, grouped by language lateralization method and language dominance category are displayed in Tables 3 and 4. Table 3 shows the breakdown of cases categorized as left dominant, bilateral, and right dominant when the IAT is used as the measure of reference. For example, in Table 3, we observed that there were 183 cases characterized as left dominant by IAT and of these cases, 162 were also categorized as left dominant by the frontal ROI fMRI, while 14 were categorized as bilateral and 7 were categorized as right dominant.

Table 3. Number of Left, Bilateral, and Right Dominant Cases Based on an IAT Categorization Cut Score of 50 and an fMRI Categorization Cut Score of 20 (N=229) – IAT as Reference

	fMRI			
	Frontal	Temporal	Angular	Lateral
IAT				
Left	162L (89%)	159L (87%)	165L (90%)	168L (92%)
(n = 183)	14B (8%)	19B (10%)	8B (4%)	10B (5%)
	7R (4%)	5R (3%)	10R (5%)	5R (3%)
Bilateral	19L (59%)	17L (53%)	17L (53%)	18L (56%)
(n = 32)	6B (19%)	6B (19%)	6B (19%)	6B (19%)
	7R (22%)	9R (28%)	9R (28%)	8R (25%)
Right	0L (0%)	3L (21%)	2L (14%)	1L (7%)
(n = 14)	4B (29%)	2B (14%)	3B (21%)	3B (21%)
	10R (71%)	9R (64%)	9R (64%)	10R (71%)

L = left language dominance; B = bilateral language dominance; R = right language dominance

From the reverse perspective, Table 4 shows the number of cases categorized as left dominant, bilateral and right dominant when fMRI is used as the measure of reference. For example, when the frontal fMRI ROI indicated left dominance, the IAT indicated 162 cases with left dominance, 19 cases with bilateral dominance, and zero cases with right dominance.

Table 4. Number of Left, Bilateral, and Right Dominant Cases Based on an IAT Categorization Cut Score of 50 and an fMRI Categorization Cut Score of 20 (N=229) – fMRI as Reference

	IAT		
	Left	Bilateral	Right
fMRI			
Frontal			
Left (n = 181)	162 (90%)	19 (10%)	0 (0%)
Bilateral (n = 24)	14 (58%)	6 (25%)	4 (17%)
Right (n = 24)	7 (29%)	7 (29%)	10 (42%)
Temporal			
Left (n = 179)	159 (89%)	17 (9%)	3 (2%)
Bilateral (n = 27)	19 (70%)	6 (22%)	2 (7%)
Right (n = 23)	5 (22%)	9 (39%)	9 (39%)
Angular			
Left (n = 184)	165 (90%)	17 (9%)	2 (1%)
Bilateral (n = 17)	8 (47%)	6 (35%)	3 (17%)
Right (n = 28)	10 (36%)	9 (32%)	9 (32%)
Lateral			
Left (n = 187)	168 (90%)	18 (10%)	1 (1%)
Bilateral (n = 19)	10 (53%)	6 (32%)	3 (16%)
Right (n = 23)	5 (22%)	8 (35%)	10 (43%)

Overall, although this provides a number of different ways to look at the discordance data, a consistent finding emerges. This data indicates that, across ROIs, when IAT indicated left dominant language, fMRI LIs were highly concordant. However, discordance was greater when IAT LIs indicated atypical language dominance. Similarly, when fMRI LIs indicated left language dominance, IAT LIs showed high agreement, although less so when fMRI LIs indicated atypical language dominance. Taken together, this suggests that discordance is low when fMRI or IAT LIs are high (i.e., indicating left dominance). Moreover, although discordance was greater when both the IAT and fMRI LIs indicated atypical language dominance, the highest percentage of discordance was observed when fMRI LIs indicated atypical dominance.

Upon closer examination of the discordant LI group, the actual number of cases that were identified as atypical language dominant by both IAT and fMRI was quite small: 3/31 (lateral), 6/39 (angular gyrus), 3/40 (temporal), and 5/39 (frontal). In most discordant cases, language dominance was classified as atypical by one method and left by the other. In the lateral LI discordant group, fMRI identified 19 atypical and12 left dominant cases, whereas the IAT identified 15 atypical and 16 left dominant cases. In the angular gyrus LI discordant group, fMRI identified 25 atypical and 14 left dominant cases, whereas the IAT identified 20 atypical and 19 left dominant cases. In the temporal LI discordant group, fMRI identified 27 atypical and 13 left dominant cases, whereas the IAT identified 17 atypical and 23 left dominant cases. In the frontal LI discordant group, fMRI identified 26 atypical cases and 13 left dominant cases, whereas the IAT identified 18 atypical and 21 left dominant cases. Overall, this indicates that the discordant cases were classified as left and atypical language dominant by the IAT at approximately an equal rate, while fMRI classified approximately twice as many cases as atypical language dominant compared to left language dominant.

Factors that Predict Discordance

Hierarchical multiple regression analyses were performed to examine the factors that predicted IAT/fMRI discordance. A number of subject, IAT, and fMRI variables, and the LIs themselves were entered as predictor variables. The criterion variables were the absolute LI difference scores (i.e., |IAT LI - fMRI LI|) for each ROI. Subject factors that were hypothesized to predict discordance included handedness, age at onset of recurrent seizures, anomalous vasculature, presence of MTS or hippocampal atrophy on MRI, and IQ. These factors were chosen because it was thought that they may be associated with language reorganization and/or performance on the IAT and fMRI. Factors related to the IAT that were hypothesized to be predictive of discordance included posterior cerebral artery filling, crossflow ratings, obtundation, and duration of drug effect (number of trials completed prior to return of motor functioning in the contralateral arm). These factors were chosen because they were thought to contribute to the variance of the IAT. The fMRI factors that were examined included behavioral performance on fMRI tasks (percent correct on semantic decision and tone discrimination tasks), signal to noise ratio, motion artifacts (head movement), flags (the number of "bad" image volumes), and residual (error). These variables were chosen because they were thought to contribute to the variance of the fMRI. After examining the discordance rates reported in the previous section, we also were interested in determining whether the IAT or fMRI LIs themselves would be predictive of discordance and added the IAT and fMRI LIs as predictor variables to the multiple regression.

Relationship between Predictor Variables and LI Difference Scores

Hierarchical multiple regression analyses were performed to examine the relationship between the predictor variables and the absolute value of the LI difference scores for each ROI. It has been suggested that a skew of $\pm$ 2 is acceptable for statistical analyses in which the sample size is greater than or equal to 50 (von Hippel, 2010). Therefore, non-normal distributions with a skew of $\pm$ 2 (i.e., RMS mean skew = 4, flags skew = 3.2, and residual skew = 2.8) were transformed using a logarithmic transformation prior to the regression analyses. Variables were entered in the following blocks: 1) subject variables, 2) IAT variables, 3) fMRI variables, and 4) IAT and fMRI LIs. The p-value cut-off was initially set at 0.5 and then corrected for multiple comparisons using a Bonferroni correction (.05/80 total comparisons). The p-value cut-off for statistical significance was subsequently set at .0006. Results indicated that neither subject variables, IAT variables, nor fMRI variables statistically significantly predicted LI difference scores. However, when the IAT and fMRI LIs were entered together as an additional block, a statistically significant finding emerged (see Table 5). The LI block was predictive of difference scores across lateral, angular, temporal, and frontal ROIs (R^2 *change* = .196 lateral; .343 angular gyrus; .214 temporal; .179 frontal, p <.0001). This indicated that the LIs accounted for 18-34% of the variance in LI difference scores. In all ROIs, the fMRI LI was statistically related to difference scores (*beta* = -.518 lateral; -.678 angular gyrus; -.491 temporal; -.504 frontal; p < .0001). That is, lower fMRI LIs predicted greater difference scores, and the IAT LI did not add any predictive value. Additionally, one variable approached statistical significance. The percentage of correct responses on the semantic decision task was predictive of difference scores in the lateral ROI (p = .008). That is, a lower percentage of correct responses was predictive of greater difference scores. While this finding only approached statistical significance, it is useful to consider from a clinical standpoint whether poorer behavioral performance on fMRI tasks may be predictive of discordance.

Table 5. Multiple Regression Results by ROI

	Beta	Significance
Lateral ROI		
Subject Variables		
Handedness	.052	p = .438
Age at onset	.001	p = .991
MTS	-.032	p = .640
Hippocampal sclerosis	-.080	p = .262
Anomalous vasculature	-.073	p = .295
FSIQ	.159	p = .041
R^2 Change	**.032**	**p = .383**

IAT Variables		
IAT total possible left	-.064	*p* = .365
IAT total possible right	.050	*p* = .505
Crossflow left to right	.115	*p* = .108
Crossflow right to left	-.104	*p* = .127
Obtundation	.077	*p* = .261
PCA filling	-.008	*p* = .910
R^2 Change	**.035**	***p* = .344**
fMRI Variables		
Percent correct semantic task	-.201	*p* = .008**
Percent correct tones task	.140	*p* = .067
RMS mean	.071	*p* = .181
Flags	.053	*p* = .601
Residual	-.014	*p* = .470
Signal to noise ratio	.099	*p* = .918
R^2 Change	**.046**	***p* = .206**
LIs		
IAT LI	.066	*p* = .467
Lateral LI	-.518	*p* = .000*
R^2 Change	**.196**	***p*= .000***
Adjusted R^2	**.232**	***p* = .000***
Overall ANOVA	***F* = 3.969**	***p* = .000***
Angular ROI		
Subject Variables		
Handedness	.053	*p* = .378
Age at onset	-.034	*p* = .583
MTS	-.058	*p* = .342
Hippocampal sclerosis	-.073	*p* = .257
Anomalous vasculature	-.119	*p* = .058
FSIQ	.142	*p* = .043
R^2 Change	**.034**	***p* = .349**
IAT Variables		
IAT total possible left	-.095	*p* = .137
IAT total possible right	.069	*p* = .307
Crossflow left to right	.110	*p* = .086
Crossflow right to left	-.088	*p* = .148
Obtundation	.015	*p* = .806
PCA filling	.030	*p* = .623
R^2 Change	**.028**	***p* = .482**
fMRI Variables		
Percent correct semantic task	-.156	*p* = .021
Percent correct tones task	.136	*p* = .047
RMS mean	.028	*p* = .593
Flags	.033	*p* = .817
Residual	.083	*p* = .618
Signal to noise ratio	.036	*p* = .503

R^2 Change	**.036**	***p* = .305**
LIs		
IAT LI	.133	*p* = .080
Angular LI	-.678	*p* = .000*
R^2 Change	**.343**	***p* = .000***
Adjusted R^2 Change	**.379**	***p* = .000***
Overall ANOVA	***F* = 7.011**	***p* = .000***
Temporal ROI		
Subject Variables		
Handedness	-.030	*p* = .658
Age at onset	-.003	*p* = .971
MTS	-.035	*p* = .618
Hippocampal sclerosis	-.060	*p* = .410
Anomalous vasculature	.075	*p* = .289
FSIQ	.060	*p* = .452
R^2 Change	**.019**	***p* = .729**
IAT Variables		
IAT total possible left	-.006	*p* = .931
IAT total possible right	.077	*p* = .317
Crossflow left to right	.131	*p* = .075
Crossflow right to left	-.019	*p* = .794
Obtundation	.028	*p* = .685
PCA filling	-.121	*p* = .085
R^2 Change	**.036**	***p* = .557**
fMRI Variables		
Percent correct semantic task	-.004	*p* = .958
Percent correct tones task	.046	*p* = .561
RMS mean	-.029	*p* = .586
Flags	.072	*p* = .834
Residual	.031	*p* = .337
Signal to noise ratio	.041	*p* = .827
R^2 Change	**.011**	***p* = .806**
LIs		
IAT LI	-.069	*p* = .403
Temporal LI	-.491	*p* = .000*
R^2 Change	**.214**	***p* = .000***
Adjusted R^2 Change	**.199**	***p* = .000***
Overall ANOVA	***F* = 3.444**	***p* = .000***
Frontal ROI		
Subject Variables		
Handedness	.074	*p* = .285
Age at onset	.037	*p* = .598
MTS	-.018	*p* = .794
Hippocampal sclerosis	-.095	*p* = .196
Anomalous vasculature	- .025	*p* = .720

FSIQ	.117	*p* = .143
R^2 Change	**.036**	***p* = .305**
IAT Variables		
IAT total possible left	-.028	*p* = .696
IAT total possible right	-.018	*p* = .810
Crossflow left to right	.026	*p* = .723
Crossflow right to left	.006	*p* = .933
Obtundation	.038	*p* = .588
PCA filling	-.015	*p* = .832
R^2 Change	**.026**	***p* = .423**
fMRI Variables		
Percent correct semantic task	-.191	*p* = .013
Percent correct tones task	.008	*p* = .914
RMS mean	.108	*p* = .533
Flags	-.001	*p* = .441
Residual	-.027	*p* = .985
Signal to noise ratio	.047	*p* = .846
R^2 Change	**.035**	***p* = .377**
LIs		
IAT LI	.111	*p* = .207
Frontal LI	-.504	*p* = .000*
R^2 Change	**.179**	***p* = .000***
Adjusted R^2 Change	**.195**	***p* = .000***
Overall ANOVA	***F* = 3.390**	***p* = .000***

*significant at the $p < .0006$ level
**significant at the $p = .0008$ level
MTS, mesial temporal sclerosis; FSIQ, full scale intelligence quotient; LI, laterality index; PCA, posterior carotid artery

Language Outcome

To investigate post-operative language outcome, we updated a linear regression model (Sabsevitz et al., 2003) in which fMRI LIs and IAT LIs were used to predict change on the BNT from pre to post-operative evaluation. This regression equation was calculated with Dr. David Sabsevitz's assistance. From our original sample (N = 229), we examined the subset of patients who had L-ATL, IAT, fMRI, and pre- and post-operative neuropsychological assessment. This yielded a subset of 69 participants. Of these, we removed the 11 cases that had discordant lateral fMRI LIs and IAT LIs to avoid possible contamination (i.e. using the regression equations with individuals who had also been included in the sample used to develop the regression equations).

We first performed Pearson correlations to determine which ROI would be most closely related to BNT change. We chose to use the lateral fMRI LI because it was most strongly correlated with BNT change compared to the other ROIs (lateral LI, $r = -.362$, angular LI, $r = -.332$; temporal LI, $r = -.307$; frontal LI, $r = -.322$, $p < .0001$). We then calculated two regression equations, one including the IAT LI, pre-operative BNT score, and post-operative BNT change score (i.e., pre-operative BNT score minus post-operative BNT score) and the other including fMRI LI, pre-operative BNT score, and post-operative BNT change score. Although BNT pre-operative score was not statistically significantly correlated with BNT change at the .05 level ($p = .076$ in the IAT regression equation; $p = .082$ in the fMRI regression equation), we replicated the previous regression equation calculation (Sabsevitz et al., 2003) and included pre-operative BNT and LIs as predictors of BNT change. We also decided to include the pre-operative BNT score because it has clinical significance. The contribution of the pre-operative BNT score has clinical significance because pre-operative language functioning has been shown to be predictive of post-operative language functioning (Chelune, et al., 1991; Ivnik et al., 1988; Sabsevitz et al., 2003). The fMRI regression equation was: BNT change = [8.510 + (-.250 x preBNT) + (-6.947 x lateral LI)]. The IAT regression equation was: BNT change = [10.108 + (-.258 x preBNT) + (-.070 x IAT LI)]. The difference between the predicted and observed change score was then examined for fMRI LI and IAT LI in each discordant case.

Of the 11 discordant cases who underwent left ATL, language outcome was more accurately predicted (i.e., closer to the actual BNT change score) by each method in approximately half the cases. In Table 6, pre-operative BNT score, IAT LI, fMRI LI, expected BNT change based on the IAT regression equation, expected BNT change based on the fMRI regression equation, and the actual observed post-operative BNT score are reported. Although by a small margin in some cases, the IAT expected BNT change prediction was more accurate relative to the fMRI expected BNT change prediction in the first five cases, and the fMRI expected BNT change was more accurate relative to the IAT BNT change prediction in the remaining six cases.

Table 6. Expected and Observed Post-operative BNT scores for L-ATL Patients using IAT and Lateral fMRI Language Laterality Indices

		Language Laterality Index		Expected BNT Change		Observed Change
Patient	Pre-op BNT	IAT	fMRI	IAT	fMRI	Post BNT (change)
2385*	49	-98	21.54	4.326	-5.236	49 (0)
551*	44	-29	63.15	0.786	-6.877	44 (0)
639*	54	-16	76.87	-2.704	-10.33	50 (-4)
1737*	51	2	70.65	-3.19	-9.148	47 (-4)
765*	51	75	-56.54	-8.3	-0.312	25 (-26)
597	54	16	92.14	-4.944	-11.39	32 (-22)
706	49	50	-24.21	-6.034	-2.058	53 (+4)
574	49	67	14.21	-7.224	-4.727	51 (+2)
1539	53	67	-24.06	-8.256	-6.411	49 (-4)
633	59	87	12.90	-11.20	-7.136	60 (+1)
638	53	90	-00.93	-9.866	-4.675	53 (0)

*BNT expected change was predicted with greater accuracy with the IAT relative to fMRI
BNT, Boston Naming Test; IAT, Intracarotid Amobarbital Test; fMRI, Functional Magnetic Resonance Imaging

Qualitative examination of predictors of discordance in the L-ATL cases did not reveal any differences between the groups for whom BNT change was more accurately predicted by IAT vs. fMRI (see Table 7). While statistical tests are not appropriate for a subset this small, we qualitatively examined the sex, age, age at onset of recurrent seizures, handedness, presence of mesial temporal sclerosis and/or atrophy, IAT crossflow, IAT duration of drug effect, obtundation, anomalous vasculature, posterior carotid artery filling, full scale IQ, percentage correct on the fMRI semantic decision and tones tasks, fMRI signal-to-noise ratio, RMS mean, flags, and residuals. There did not appear to be qualitative differences between the group for whom the IAT language outcome prediction was more accurate and the group for whom fMRI was more accurate.

Table 7. Predictors of Discordance for Discordant L-ATL Group

							Crossflow		Drug Effect						% Correct					
Pt ID	Sex	Age	Onset	Hand	MTS	HA	Left	Right	Left	Right	OB	AV	PCA	IQ	SM	T	SNR	RMS	Flags	Res
2385*	F	39	0.5	Left	Yes	Yes	Yes	No	12	21	Yes	No	Yes	85	82.1	89.6	76.5	554.6	0	758.2
551*	M	42	20	Right	No	No	Yes	No	21	15	No	Yes	No	113	91.5	91.5	78.4	15.7	0.5	29.3
639*	F	46	9	Right	No	Yes	No	No	15	18	No	No	No	116	81.0	93.8	82.7	22.2	2	45.3
1737*	M	38	14	Left	Yes	No	Yes	No	15	15	No	No	No	98	71.2	91.7	107.9	20.9	0	73.2
765*	M	29	11	Right	Yes	No	No	No	9	24	No	No	No	82	76.6	90.3	103.6	23.16	6	51.8
579	F	26	23	Right	No	No	No	No	21	33	Yes	No	No	80	90.6	97.7				
706	F	56	10	Left	Yes	No	No	No	21	24	Yes	Yes	No	95	74.6	99.2	30.9	36.7	32	51.2
574	M	32	0.3	Right	No	No	No	No	21	21	No	No	No	97	92.5	96.9	133.2	13.62	0	20.7
1539	M	42	17	Left	Yes	No	Yes	No	21	21	No	No	Yes	95	67.8	98.6	54.9	15.5	5	16.0
633	M	37	7	Right	Yes	No	No	No	21	15	No	No	No	102	90.6	99.2	72.5	15.1	0.5	33.6
638	M	35	10	Right	No	No	No	Yes	21	21	No	No	No	109	73.7	93.8	83.2	34.1	0.5	24.7

*BNT expected change was predicted with greater accuracy with the IAT relative to fMRI

F, female; M, male; Onset, age at onset of recurrent seizures; Hand, handedness; MTS, mesial temporal sclerosis; HA, hippocampal atrophy; OB, obtundation; AV, anomalous vasculature; PCA, posterior carotid artery filling; IQ, full scale intelligence quotient; SM, semantic decision fMRI task; T, tones fMRI task; SNR, signal to noise ratio; RMS, measure of head movement; Res, residual.

CHAPTER 5: Discussion

Presentation of Findings

Clinicians are increasingly using fMRI in addition to, or even in place of the traditional IAT to assess language processes in the presurgical evaluation of epilepsy (Baxendale, 2008). As such, it is critically important to determine the clinical utility of fMRI for the purpose of language lateralization and localization. The present study provided IAT/fMRI LI comparison data for the largest sample to date, examined the contributions of subject and methodological variables to IAT/fMRI LI discordance, and qualitatively examined post-surgical language outcome data for a small subset of patients with discordant language LIs. Study findings, limitations, and implications for practice and future research are discussed.

Discordance Rates

This study yielded IAT/fMRI LI discordance rates that were consistent with findings that have been reported in a number of previous comparison studies in which either a semantic decision or reading/naming task was used (Benke et al., 2006; Carpentier et al., 2001; Gaillard et al, 2004; Gaillard et al., 2002). These rates of discordance are similar to those reported in previous studies, though slightly higher than some compared to rates reported in a number of previous studies (0-12% discordant). The difference between discordant rates between studies is likely related to small sample sizes and the inclusion of few patients with atypical language dominance (Adcock, et al., 2003; Baciu et al., 2001; Bahn et al., 1997; Binder et al., 1996; Benson et al., 1999; Deblare et al., 2004; Desmond et al., 1995; Hertz-Pannier et al., 1997; Liegeois et al, 2002; Sabbah et al., 2003; Spreer et al., 2002; Woerman et al., 2003; Worthington et al., 1997; Yetkin et al., 1998). Moreover, some of the highest reported concordance rates were found in studies that had very few participants. Studies that have reported the highest rates of concordance (e.g., 95-100%) typically had sample sizes of approximately 20 with very few cases identified as having atypical language dominance (Bahn et al., 1997; Desmond et al., 1995; Liegeois et al., 2002; Sabbah et al., 2003). It is possible that individuals with atypical language dominance are more likely to have discordant IAT and fMRI LIs, because individuals with left language dominance theoretically have a more localized network of essential language functions that are primarily lateralized to the left hemisphere with some additional participation from the right hemisphere, relative to those with atypical language dominance, who may have more widespread distribution of essential and non-essential language networks (Binder et al., 1997; Grabowski & Damasio, 2000; Ojemann, 1991; Wise & Price, 2006). It may be the case that our measurement tools are not as accurate in assessing the distributed language network that is more common in individuals with atypical language dominance. For example, the IAT may underestimate the contribution of non-essential language processes in the non-dominant hemisphere. Likewise, fMRI may overestimate the same contribution or omit activation if the ROI is limited to a specific region (e.g., frontal, temporal).

Additionally, the results of our study revealed that the lateral fMRI LI was the most concordant with the IAT, which may be related to the similarity of brain regions that are assessed. That is, the area of activation included in the lateral ROI is most similar to the whole hemisphere assessment that occurs with the IAT. Therefore, it was not surprising that the lateral ROI LI would be most closely related to the IAT LI.

Discordance Predictors

Examination of the variables that accounted for variance in IAT/fMRI LI concordance revealed that the fMRI LIs accounted for the greatest amount of variance in discordance in all ROIs at rates of 18-34% depending on ROI, with lower fMRI LIs predicting greater discordance. Lower fMRI LIs were most predictive of discordance and notably, the IAT LIs did not add any predictive value above that of the fMRI LIs. While this tells us very little about potential subject or methodological factors that are associated with discordance, it does yield important information for clinicians to consider, particularly as fMRI begins to replace the IAT as the first-line assessment for language lateralization. When fMRI LIs are high, it is likely that IAT LIs will be concordant, but this likelihood decreases in the event of a low fMRI LI, which may be related to the fact that fMRI is an activation method, whereas the IAT is a deactivation method. That is, fMRI has the capacity to measure all language activation in the brain at the same time, although it is not possible to distinguish essential from non-essential language processes. However, the IAT deactivates each hemisphere in turn, which makes it impossible to factor non-essential language processes into the LI calculation from the cerebral hemisphere that is anesthetized. This should result in a more negatively skewed distribution of IAT LIs (closer to 100) compared to more normally distributed fMRI LIs (closer to 0). Therefore, if the LI includes the non-essential language activation and still indicates left language dominance, it is likely that the IAT LI, which does not include non-essential language processes, will indicate left dominance as well. The reverse would not necessarily be observed, as an IAT that indicated left language dominance would not include non-essential language processes, which might then be picked up by the fMRI, decreasing the fMRI LI.

Relationship between Atypical Language Dominance and Discordance

It is important to note that although there are a relatively greater number of lower IAT and fMRI LIs in the discordant LI group compared to the concordant LI group, atypical language dominance itself (i.e., defined as right or bilateral language dominance on both IAT and fMRI) is not necessarily associated with discordance. Our data showed that the discordant cases were classified as left and atypical language dominant by the IAT at approximately an equal rate, while fMRI classified approximately twice as many cases as atypical language dominant compared to left language dominant. This finding may be associated with the methodological differences of the IAT and fMRI. As an activation method, fMRI it is more likely to identify bilateral activation (i.e., essential and nonessential language processes), which means that non-essential language activation is included in the LI equation. This non-essential language processing is potentially widespread throughout the dominant and non-dominant hemispheres and therefore, should result in an LI that is closer to 0. Conversely, because the IAT is a deactivation method, bilateral activation is not incorporated into the LI unless it is essential for language processes. For example, consider the case of an individual who has essential language processes lateralized to the left cerebral hemisphere and non-essential language processes lateralized to the right cerebral hemisphere. The essential language processes would be captured by both the IAT and fMRI (e.g., left hemisphere language score = 100). However, the non-essential language processes would not be captured by the IAT (e.g., right hemisphere language score = 0), but they would be captured by fMRI (e.g., right hemisphere activation = 60). In this case, the IAT LI would be 100, while the fMRI LI would be 40 due to the different methodologies (i.e., activation method vs. deactivation method).

It is somewhat difficult to draw conclusions from the finding that there are a greater proportion of lower LIs in the discordant group compared to the concordant group. If either fMRI or IAT was entirely accurate, we could postulate that atypical language dominance is associated with IAT/fMRI discordance, as each method predicted greater atypical language dominance in the discordant group (i.e., ~50% with the IAT, ~65% with fMRI), than would be expected in the epilepsy population (~25%, Springer et al., 1999). However, this is speculative at this point, as we do not yet have an evidence base that has demonstrated the greater accuracy of IAT vs. fMRI with regard to post-surgical language outcome. Therefore, although we found that lower fMRI LIs were associated with discordance, we cannot conclude that atypical language dominance itself is associated with discordance.

Language Outcome

Of the eleven individuals who had discordant IAT/fMRI LIs, post-operative language outcome was more accurately predicted by the IAT in five cases, and fMRI in six cases. Qualitative examination of these cases did not reveal any variables that appeared to be associated with only one group (i.e., IAT more accurate vs. fMRI more accurate), with the possible exception of hippocampal atrophy, which was present in 2/5 IAT more accurate cases and 0/6 fMRI more accurate cases. However, given the limited sample size, and because MTS was more evenly distributed across the two groups, it is difficult to draw conclusions from this finding. Given the similarities of the groups, it is also impossible to draw conclusions regarding the accuracy of IAT vs. fMRI, or to determine which one might be a better measure for certain individuals.

Conclusions

Overall, the results of this study indicated that in a large sample of intractable epilepsy patients, rates of IAT/fMRI LI discordance were fairly low. The IAT/fMRI LIs were most discordant for cases in which the fMRI LIs were lower (i.e. closer to -100). There were no additional subject, IAT, or fMRI variables that were associated with discordance. However, it cannot be concluded that atypical language dominance itself is associated with discordant IAT/fMRI LIs, because our findings indicate that the IAT and fMRI were more predictive in approximately half the cases.

Limitations

Although the initial sample size in this study was relatively large compared to existing IAT/fMRI LI comparison studies, we identified a relatively small number of discordant cases. While a high rate of concordance is encouraging for those who are in favor of replacing the IAT with fMRI, the small sample of discordant cases makes it difficult to ascertain consistent group differences or individual or methodological predictors of discordance. Therefore, it is difficult to determine individuals who might be better suited for one language lateralization method over the other. The prediction of post-surgical language outcome using IAT and fMRI LIs is particularly difficult to explore because there are very few cases that have language outcome data, as this requires people to have undergone IAT and fMRI, have discordant IAT and fMRI LIs, have undergone left temporal resection, and completed post-surgical neuropsychological testing. As such, although outcome data is of critical importance, it is limited by the difficulty obtaining individuals who meet all the requirements listed above.

The results of our study were also limited by the characteristics of the sample. This study sample was comprised mainly of Caucasian adults in the Midwest, which is not representative of all individuals with epilepsy, particularly children and multilingual individuals. Epilepsy patients have a higher rate of atypical language (Springer et al., 1999), but so do neurologically normal children. As neurologically normal children age, language becomes increasingly lateralized (Yuan et al., 2006), which may result in a higher incidence of atypical language in children on fMRI and subsequently, greater discordance with IAT. Additionally, the language assessment measures that we used were validated with individuals for whom English is their first language. Therefore, the results of the current study cannot be extended to individuals for whom English is not their first language.

Finally, a limitation of this study is that little standardization exists with regard to IAT and fMRI methodology, LI calculation, and definitions of lateralization and discordance. Additionally, there have been a plethora of different ways suggested and used to compare the IAT and fMRI, and different methods for calculating language lateralization, with little consensus, including categorization methods and difference methods (Adcock, et al., 2003; Baciu et al., 2001; Bahn et al., 1997; Binder et al., 1996; Benson et al., 1999; Deblare et al., 2004; Desmond et al., 1995; Hertz-Pannier et al., 1997; Liegeois et al, 2002; Sabbah et al., 2003; Spreer et al., 2002; Woerman et al., 2003; Worthington et al., 1997; Yetkin et al., 1998). We used clinical judgment to operationally define discordance, which may have under – or over – estimated actual discordance between the IAT and fMRI. In the present study, it was difficult to determine the best way to compare an activation method (fMRI) to a deactivation method (IAT), and although we attempted to account for the unique differences inherent in each method (e.g., examination of parametric and non-parametric correlations, examination of data distributions, exploration of various cut scores and difference scores) by combining categorization and difference cut-scores, there may be a better way to calculate LIs and/or compare the IAT and fMRI LIs.

Implications for Practice and Research

The findings in the present study indicate that there is a high rate of concordance between IAT and fMRI LIs, particularly when fMRI LIs indicate left hemisphere language dominance. The present study demonstrated the highest rate of concordance between the IAT and the fMRI lateral ROI LI, which was also found to be the most predictive of post-operative naming outcome. As epilepsy centers begin to replace the IAT with fMRI, clinicians can have a relatively high degree of confidence in the accuracy of left dominant fMRI LIs and may not feel the need to proceed with the IAT in every case. However, when fMRI LIs indicate atypical language dominance, further language assessment may continue to be warranted. Although we observed greater discordance with the IAT when fMRI indicated atypical language dominance, we were unable to identify any subject or methodological variables that were consistently associated with discordance. Unfortunately, the present study does not provide evidence of the relative accuracy of one method over the other, as post-operative language outcome data indicated that IAT and fMRI each predict outcome in certain cases, suggesting some error variance with each mapping method.

As fMRI begins to replace the IAT for the presurgical assessment of language lateralization in epilepsy, unanswered questions remain regarding the accuracy of fMRI, particularly for individuals who have atypical LIs on fMRI. As neuroimaging becomes more widely used for language lateralization, larger sample sizes may be available with which to further explore discordant groups. However, the current variations in fMRI protocols, definitions of language lateralization and discordance, and lack of outcome data make it difficult to draw conclusions about the reliability and validity of using fMRI when different tasks and methods are used to identify language networks and predict language outcome. Multicenter studies that use a standardized fMRI protocol, IAT procedure, and pre- and post- language neuropsychological assessment may generate the needed sample size to further explore and refine language lateralization and localization methods. Most importantly, it will be necessary to investigate language outcome following surgery, and to improve the predictive value of fMRI in conjunction with other variables (e.g., age at seizure onset, pre-operative naming score) with regard to post-surgical language outcome. Finally, future studies are needed that examine whether using fMRI to guide surgical resection boundaries improves cognitive outcome.

Conclusions

Functional magnetic resonance imaging is a potential alternative to the IAT for the lateralization of language functioning in epilepsy surgery candidates and is currently being used in a number of Comprehensive Epilepsy Centers. We sought to better understand the factors that affect the concurrent and predictive validity of fMRI. We compared the IAT and fMRI using a tightly controlled language/control task protocol with a large sample of epilepsy patients whose language dominance ranged across the continuum.

Overall, the results of this study indicated that in a large sample of intractable epilepsy patients, rates of IAT/fMRI LI discordance were fairly low. The IAT/fMRI LIs were most discordant for cases in which the fMRI LIs were lower. There were no additional subject, IAT, or fMRI variables that were associated with discordance. However, it cannot be concluded that atypical language dominance itself is associated with discordant IAT/fMRI LIs because our findings indicate that the IAT and fMRI were more predictive in approximately half the cases. Moreover, we were unable to predict the accuracy of one method over another, as post-operative language outcome data indicated that IAT and fMRI each predict outcome in certain cases, suggesting some error variance with each mapping method.

REFERENCES

Abad, R.S., Vilaplana, F.X.S., Fernandez, J.M.S. (2007). Genetic causes of epilepsy. *The Neurologist, 13*, 47-51.

Abou-Khalil, B. (2007). An update on determination of language dominance in screening for epilepsy surgery: The Wada test and newer noninvasive alternatives. *Epilepsia, 48*, 442-455.

Adcock, J.E., Wise, R.G., Oxbury, J.M., Oxbury, S.M., & Matthews, P.M. (2003). Quantitative fMRI assessment of the differences in lateralization language-related brain activation in patients with temporal lobe epilepsy. *Neuroimage, 18*, 423-438.

Ahern, G.L., Herring, A.M., Tackenberg, J.N., Schwartz, G.E., Seeger, J.F., Labiner, D.M., et al. (1994). Affective self-report during the intracarotid sodium amobarbital test. *Journal of Clinical and Experimental Neuropsychology, 16*, 372-376.

Aldenkamp, A.P. (1997). Effect of seizures and epileptiform discharges on cognitive function. *Epilepsia, 38(Suppl. 1),* S52-S55.

Al-Kaylani, M., Konrad, P., Lazenby, B., Blumenkopf, B., & Abou-Khalil, B. (2007).Seizure freedom off antiepileptic drugs after temporal lobe epilepsy surgery. *Seizure, 16*, 95-98.

Anderson, D.P., Harvey, A.S., Saling, M.M., Anderson, V., Kean, M., Abbott, D.F., et al. (2006). fMRI lateralization of expressive language in children with cerebral lesions. *Epilepsia, 47*, 998-1008.

Andrade, D.M., Zumsteg, D., Sutula, T.P., & Wennberg, R.A. (2006). Clinical aspects of temporal/limbic epilepsy and their relationships to intractability. *Advances in Neurology, 97*, 39-44.

Annegers, J.F., Rocca, W.A., & Hauser, W.A. (1996). Causes of Epilepsy: Contributions of the Rochester epidemiology project. *Mayo Clinic Proceedings, 71,* 570-575.

Axelrod, B.N., Ricker, J.H., & Cherry, S.A. (1994). Concurrent validity of the MAE visual naming test. *Archives of Clinical Neuropsychology, 9*, 317-321.

Baciu, M., Juphard, A., Cousin, E., & Le Bas, J.F. (2005). Evaluating fMRI methods for assessing hemispheric language dominance in healthy subjects. *European Journal of Radiology, 55*, 209-218.

Baciu, M., Kahane, P., Minotti, L., Charnallet, A., David, D., Le Bas, J., et al. (2001). Functional MRI assessment of the hemispheric predominance for language in epileptic patients using a simple rhyme detection task. *Epileptic Disorders, 3,* 117-124.

Bahn, M.M., Lin, W., Silbergeld, D.L., Miller, J.W., Kuppusamy, K., Cook, R.J., et al. (1997). Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *American Journal of Radiology, 169,* 575-579.

Bartha, L., Benke, T., Bauer, G., & Trinka, E. (2005). Interictal language functions in temporal lobe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 76,* 808-814.

Bates, E., Reilly, J., Wulfeck, B., Dronkers, N., Opie, M., Fenson, J., et al. (2001). Differential effects of unilateral lesions on language production in children and adults. *Brain and Language, 79,* 223-265.

Batzel, L.W. Fraser, R.T. (1993). Resection surgery for epilepsy: Outcome and quality of life. *Neurosurgery Clinics of North America, 4,* 345-351.

Baxendale, S., Thompson, P.J., & Duncan, J.S. (2008). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: An international survey. *Epilepsia, 49,* 715-719.

Begley, C.E., Famulari, M., & Annegers, J.F. (2000). The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia, 41,* 342-351.

Bell, B.D., Davies, K.G., Haltiner, A.M., & Walters, G.L. (2000). Intracarotid amobarbital procedure and prediction of postoperative memory in patients with left temporal lobe epilepsy and hippocampal sclerosis. *Epilepsia, 41,* 992-997.

Bell, B.D., Davies, K.G., Hermann, B.P., & Walters, G. (2000). Confrontation naming after anterior temporal lobectomy is related to age of acquisition of the object names. *Neuropsychologia, 38,* 83-92.

Bell, G.S. & Sander, J.W. (2001). The epidemiology of epilepsy: The size of the problem. *Seizure, 10,* 306-316.

Benbadis, S.R. (2001). Epileptic seizures and syndromes. *Neurologic Clinics, 19,* 251-270.

Benke, T., Koylu, B., Visani, P., Karner, E., Brenneis, C., Bartha, L., et al. (2006). Language lateralization in temporal lobe epilepsy: A comparison between fMRI and the Wada test. *Epilepsia, 47,* 1308-1319.

Benson, R.R., FitzGerald, D.B., LeSueur, L.L., Kennedy, D.N., Kwong, K.K., Buchbinder, B.R., et al. (1999). Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology, 52*, 798-809.

Benton, A.L., Hamsher, K., & Sivan, A.B. (1994). *Multilingual Aphasia Examination* (3rd ed.). Iowa City: AJA.

Berkovic, S.F., Newton, M.R., Chiron, C., & Dulac, O. (1993). Single photon emission tomography. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.233-244.

Berg, A.T. (2006). Defining intractable epilepsy. *Advances in Neurology, 97*, 5-10.

Berg, A.T., Testa, F.M., Levy, S.R., & Shinnar, S. (1996). The epidemiology of epilepsy: Past, present, and future. *Neurologic Clinics, 14*, 383-398.

Berl, M.M., Balsamo, L.M., Xu, B., Moore, E.N., Weinstein, S.L., Conry, J.A., et al. (2005). Seizure focus affects regional language networks assessed by fMRI. *Neurology, 65*, 1604-1611.

Binder, J.R., Frost, J.A., Hammeke, T.A., Cox, R.W., Rao, S.M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *The Journal of Neuroscience, 17*, 353-362.

Binder, J.R. & Raghavan, M. (2006). Epilepsy. *Functional MRI; Applications in Clinical Neurology and Psychiatry*, 81-113.

Binder, J.R., Rao, S.M., Hammeke, T.A., Frost, J.A., Bandettini, P.A., Jesmanowicz, A. et al. (1995). Lateralized human brain language systems demonstrated by task subtraction functional magnetic resonance imaging. *Archives of Neurology, 52*, 593-601.

Binder, J.R., Sabsevitz, D.S., Swanson, S.J., Hammeke, T.A., Raghavan, M., & Mueller, W.M. (2008). Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. *Epilepsia, 49,* 1377-1394.

Binder, J.R., Swanson, S.J., Hammeke, T.A., Morris, G.L., Mueller, W.M., Fischer, M., et al. (1996). Determination of language dominance using functional MRI: A comparison with the Wada test. *Neurology, 46*, 978-984.

Binder, J.R., Swanson, S.J., Hammeke, T.A., & Sabsevitz, D.S. (2008). A comparison of five fMRI protocols for mapping speech comprehension systems. *Epilepsia, 49,* 1980-1997.

Binder, J.R., Westbury, C.F., McKiernan, K.A., Possing, E.T., & Medler, D.A. (2005). *Journal of Cognitive Neuroscience, 17*, 905-917.

Boatman, D., Alidoost, M., Bergey, G., Gordon, B., Crone, N., Hart, J., et al. (2000). Right hemisphere language dominance in a right-handed patient with late-onset seizures. *Epilepsy and Behavior, 1*, 281-286.

Bonilha, L., Yasuda, C.L., Rorden, C., Li, L.M., Tedeschi, H., de Oliverira, E., et al.(2007) Does resection of the medial temporal lobe improve the outcome of temporal lobe epilepsy surgery? *Epilepsia, 48*, 571-578.

Bouwer, M.S., Jones-Gotman, M., & Gotman, J. (1993). Duration of sodium amytal effect: Behavioral and EEG measures. *Epilepsia, 34*, 61-68.

Bradzil, M., Zakopcan, J., Kuba, R., Fanfrdlova, Z., & Rektor, I. (2003). Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. *Epilepsy and Behavior, 4*, 414-419.

Branch, C.B., Milner, B., & Rasmussen, T. (1964). Intracarotid sodium amytal for the lateralization of cerebral speech dominance: Observations on 123 patients. *Journal of Neurosurgery, 21*, 399-405.

Brennan, N.M.P., Whalen, S., de Morales Branco, D., O'Shea, J.P., Norton, I.H., & Holby, A.J. (2007). *Neuroimage, 37*, S100-S108.

Briellmann, R.S., Labate, A., Harvey, A.S., Saling, M.M., Sveller, C., Lillywhite, L., et al. (2006). Is language lateralization in temporal lobe epilepsy patients related to the nature of the epileptogenic lesion? *Epilepsia, 47*, 916-920.

Broca, P. (1861). Remarques su le siege de la faculte de la parole articulee, suives d'une observation d'aphemie (perte de parole). *Bulletin de la Societe d'Anotome (Paris) 36*, 330-357.

Buchtel, H.A., Passaro, E.A., Selwa, L.M., Deveikis, J., Gomez-Hassan, D. (2002). Sodium methohexital (brevital) as an anesthetic in the Wada test. *Epilepsia, 43*, 1056-1061.

Carpentier, A., Pugh, K.R., Westerveld, M., Studholme, C., Skrinjar, O., Thompson, J.L., et al. (2001). Functional MRI of language processing: Dependence on input modality and temporal lobe epilepsy. *Epilepsia, 42*, 1241-1254.

Chawla, S., Aneja, S., Kashyap, R., & Mallika, V. (2002). Etiology and clinical predictors of intractable epilepsy. *Pediatric Neurology, 27*, 186-191.

Chelune, G.J., Naugle, R.I., Hermann, B.P., Barr, W.B., Trenerry, M.R., Loring, D.W., et al. (1998). Does pre-surgical IQ predict seizure outcome after temporal lobectomy? Evidence from the Bozeman Epilepsy Consortium. *Epilepsia, 39*, 314-318.

Chelune, G.J., Naugle, R.I., Luders, H., & Awad, I.A. (1991). Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. *Neurology, 41*, 399-404.

Chelune, H., Schramm, J., Kral, T., Helmstaedter, C., Ostertun, B., Fimmers, R., et al. (2002). Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *Journal of Neurosurgery, 97*, 1131-1141.

Chlebus, P., Mikl, M., Brazdil, M., Pazourkova, M., Drupa, P., & Rektor, I. (2007). fMRI evaluation of hemispheric language dominance using various methods of laterality index calculation. *Experimental Brain Research, 179*, 365-374.

Commission on Classification and Terminology of the International League Against Epilepsy (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, *22*, 489-501.

Commission on Classification and Terminology of the International League Against Epilepsy (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia, 30*, 389-399.

Culham, J.C. (2006). Functional neuroimaging: Experimental design and analysis. In R. Cabeza and A. Kingstone (Eds). *Handbook of Functional Neuroimaging of Cognition.* 2nd ed. Cambridge: MIT Press, pp.53-82.

Cunningham, J.M., Morris, G.L., Drea, L.A., & Kroll, J.L. (2008). Unexpected right hemisphere language representation identified by the intracarotid amobarbital procedure in the right-handed epilepsy surgery candidates. *Epilepsy and Behavior, 13*, 139-143.

Davies, K.G., Bell, B.D., Bush, A., Hermann, B.P., Dohan Jr., F.C., & Jaap, A.S. (1998). Naming decline after left anterior temporal lobectomy correlates with pathological status of resected hippocampus. *Epilepsia, 39*, 407-419.

Deblare, K., Boon, P.A., Vandemaele, P., Tieleman, A., Vonck, K., Vingerhoets, G., et al. (2004). MRI language dominance assessment in epilepsy patients at 1.0 T: ROI analysis and comparison with intracarotid amytal testing. *Neuroradiology*, *46*, 413-420.

della Rocchetta, A.I., Gadian, D.G., Connelly, A., Polkey, C.E., Jackson, G.D., Watkins, K.E., et al. (1995). Verbal memory impairment after right temporal lobe surgery: Role of contralateral damage as revealed by ^{1}H magnetic resonance spectroscopy and T_2 relaxometry. *Neurology, 45*, 797-802.

Desmond, J.E., Sum, J.M., Wagner, A.D., Demb, J.B., Shear, P.K., Glover, G.H., et al. (1995). Functional MRI measurement of language lateralization in Wada-tested patients. *Brain, 118*, 1411-1419.

Detre, J. (2004). fMRI: Applications is epilepsy. *Epilepsia, 45*, 26-31.

Dinner, D.S. (1991). Intracarotid amobarbital test to define language lateralization. In H Luders (Ed) *Epilepsy Surgery*. New York: Raven Press, 503-506.

Dlugos, D.J. (2001). The early identification of candidates for epilepsy surgery. *Archives of Neurology, 58*, 1543-1546.

Dodrill, C.B., Batzel, L.W., & Fraser, R. (1991). Psychosocial changes after surgery for epilepsy. In H.L. (Ed) *Epilepsy Surgery*. New York: Raven Press, pp 661-667.

Dodrill, C.B., Wilkus, R.J., & Ojemann, L.M. (1992). Use of psychological and neuropsychological variables in selection of patients for epilepsy surgery. In W.H. Theodore (Ed) *Surgical Treatment of Epilepsy*. New York: Raven Press, pp. 71-75.

Draeger, B., Jansen, A., Bruchmann, S., Forster, A.F., Pleger, B., Zwitserlood, P., et al. (2004). How does the brain accommodate to increased task difficulty in word finding? A functional MRI study. *Neuroimage, 23*, 1152-1160.

Dreifuss, F.E. & Henriksen, O. (1992). Classification of epileptic seizures and the epilepsies. Acta Neurologica Scandinavia, 140, 8-17.

Duchowny, M. (2007). Language localization, the developing brain, and childhood epilepsy: Back to the future. *Journal of the International Neuropsychological Society, 13*, 501-504.

Engel, J. (2006). ILAE classification of epilepsy syndromes. *Epilepsy Research, 70*, 5-10.

Engel, J. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology. *Epilepsia, 42*, 796-803.

Engel Jr., J. (1987). Outcome with respect to epileptic seizures. In J. Engel (Ed). *Surgical Treatment of the Epilepsies*. New York: Raven Press, pp. 553-571.

Engel Jr., J., & Shewmon, D.A. (1993). Overview. Who should be considered a surgical candidate? In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.23-34.

Epilepsy Foundation of America. Epilepsy and Seizure Statistics. http://www.epilepsyfoundation.org/about/statistics.cfm Retrieved 7/18/08.

Epstein, C.M., Woodard, J.L., Stringer, A.Y., Bakay, R.A.E., Henry, T.R., Pennell, P.B., et al. (2000). Repetitive transcranial magnetic stimulation does not replicate the Wada test. *Neurology, 55*, 1025-1027.

Farrell, K., Wirrell, E., & Whiting, S. (2006). The definition and prediction of intractable epilepsy in children. *Advances in Neurology, 97*, 435-442.

Fedio, P. & Weinber, L.K. (1971). Dysnomia and impairment of verbal memory following intracarotid injection of sodium amytal. *Brain Research, 31*, 159-168.

Fernandez, G., Specht, K., Weis, S., Tendolkar, I., Reuber, M., Fell, J., et al. (2003). Intrasubject reproducibility of pre-surgical language lateralization and mapping using fMRI. *Neurology, 60,* 969-975.

Fisher, R.S., van Emde Boas, W., Blume, W., Elger, C., Gentron, P., et al. (2005). Epileptic seizures and epilepsy. Definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia, 46*, 470-470.

Franzen, M. (2000). *Reliability and Validity in Neuropsychological Assessment*. New York: Springer.

Frost, J., Binder, J.R., Springer, J.A., Hammeke, T.A., Bellgowan, P.S.F., Rao, S.M., et al. (1999). Language processing is strongly left lateralized in both sexes: Evidence from functional fMRI. *Brain, 122,* 199-208.

Gardner, W.J. (1941). Injection of procaine into the brain to locate speech area in left-handed persons. *Archives of Neurology and Psychiatry, 46*, 1035-1038.

Gaillard, W.D., Balsamo, L., Xu, B., Grandin, C.B., Braniecki, S.H., Papero, P.H., et al. (2002). Language dominance in partial epilepsy patients identified with an fMRI reading task. *Neurology, 59*, 256-265.

Gaillard, W.D., Balsamo, L., Xu, B., McKinney, C., Papero, P.H., Weinstein, S., et al. (2004). fMRI language task panel improves determination of language dominance. *Neurology, 63*, 1403-1408.

Gaillard, W.D., Berl, M.M., Moore, E.N., Ritzl, E.K., Rosenberger, L.R., Weinstein, S.L., et al. (2007). Atypical language in lesional and nonlesional complex partial epilepsy. *Neurology, 69*, 1761-1771.

Geschwind, N. (1971). Aphasia. *New England Journal of Medicine, 284,* 654-656.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). The assessment of aphasia and related disorders. Philadelphia: Lippincott Williams & Wilkins.

Gleissner, U., Helmstaedter, C., Schramm, J., & Elger, C.E. (2002). Memory outcome after selective amygdalohippocampectomy: A study in 140 patients with temporal lobe epilepsy. *Epilepsia, 43,* 87-95.

Gleissner, U., Helmstaedter, C., Schramm, J., & Elger, C.E. (2004). Memory outcome after selective amygdalohippocampectomy: One-year follow-up. *Epilepsia, 45*, 960-962.

Glosser, G., Cole, L.C., Deutsch, G.K., Donofrio, N., Bagley, L., Baltuch, G., et al. (1999). Hemispheric asymmetries in arousal affect outcome of the intracarotid amobarbital test. *Neurology, 52,* 1583-1590.

Grabowski, T.J. & Damasio, A.R. (2000). Investigating language with functional neuroimaging. In A.W. Toga and J.C. Mazziotta (Eds) *Brain Mapping: The Systems*. San Diego: Academic Press, 425-462.

Grote, C.L., Wierenga, C., Smith, M.C., Kanner, A.M., Bergen, D.C., Geremia, G., et al. (1999). Wada difference a day makes: Interpretive cautions regarding same-day injections. *Neurology, 52*, 1577-1582.

Haag, A., Knake, S., Hamer, H.M., Boesebeck, F., Freitag, H., Schulz, R., et al. (2008). The Wada test in Austrian Dutch, German, and Swiss epilepsy centers from 2000 to 2005: a review of 1421 procedures. *Epilepsy and Behavior, 13*, 83-89.

Hamberger, M.J. & Drake, E.B. (2006). Cognitive functioning following epilepsy surgery. *Current Neurology and Neuroscience Reports, 6*, 319-326.

Hardy, S.G., Miller, J.W., Holmes, M.D., Born, D.E., Ojemann, G.A., Dodrill, C.B., et al. (2003). Factors predicting outcome of surgery for intractable epilepsy with pathologically verified mesial temporal sclerosis. *Epilepsia, 44*, 565-568.

Hardyck, C., Petrinovic, L.F. (1977). Left-handedness. *Psychological Bulletin, 84*, 385-404.

Harrington, G.S., Buonocore, M.H., & Farias, S.T. (2006). Intrasubject reproducibility of functional MR imaging activation in language tasks. American Journal of *Neuroradiology, 27*, 938-944.

Hauser, W.A., Annegers, J.F., & Rocca, W.A. (1996). Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. *Mayo Clinic Proceedings*, 71, 576-586.

Helmstaedter, C., Kurthen, M., Linke, D.B., & Elger, C.E. (1997). Patterns of language dominance in focal left and right hemisphere epilepsies: relation to MRI findings, EEG, sex, and age at onset of epilepsy. *Brain and Cognition, 33,* 135-150.

Helmstaedter, C., Van Roost, D., Cusmann, H., Urbach, H., Elger, C.E., & Schramm, J. (2004). Collateral brain damage, a potential source of cognitive impairment after selective surgery for control of mesial temporal lobe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*, 323-326.

Henry, T.R., Chugani, H.T., Abou-Khalil, B.W., Theodore, W., & Swartz, B.E. (1993). Positron emission tomography. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.211-232.

Hermann, B., Davies, K., Foley, K., & Bell, B. (1999). Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: A randomized prospective clinical trial. *Epilepsia, 40*, 1070-1076.

Hermann, B.P., Seidenberg, M., Dohan Jr., F.C., Wyler, A.R., Haltiner, A., Bobholz, J., et al. (1995). Reports by patients and their families of memory change after left anterior temporal lobectomy: Relationship to degree of hippocampal sclerosis. *Neurosurgery, 36*, 39-44.

Hertz-Pannier, L., Gaillard, W.D., Mott, S.H., Cuenod, C.A., Bookheimer, S.Y., Weinstein, S., et al. (1997). Noninvasive assessment of language dominance in children and adolescents with functional MRI: A preliminary study. *Neurology, 48*, 1003-1011.

Holmes, M.D., Dodrill, C.B., Ojemann, G.A., Wilensky, A.J., & Ojemann, L.M. (1997). Outcome following surgery in patients with bitemporal interictal epileptiform patterns. *Neurology, 48*, 1037-1040.

Hermann, B.P., Wyler, A.R., Somes, G., & Clement, L. (1994). Dysnomia after left anterior temporal lobectomy without functional mapping: Frequency and correlates. Neurosurgery, 35, 52-57.

Hong, S.B., Kim, K., Seo, D.W., Kim, S.E., Na, D.G., & Byun, H.S. (2000). Contralateral EEG slowing and amobarbital distribution in Wada test: An intracarotid SPECT study. *Epilepsia, 41*, 207-212.

Hund-Georgiadis, M., Lex, U., & Yves von Cramon, D. (2001). Language dominance assessment by means of fMRI: Contributions from task design, performance, and stimulus modality. *Journal of Magnetic Resonance Imaging, 13*, 668-675.

Ivnik, R.J., Sharbrough, F.W., & Laws, E.R. (1988). Anterior temporal lobectomy for the control of partial complex seizures: Information for counseling patients. *Mayo Clinic Process, 63*, 783-793.

Jallon, P. (2002). Epilepsy and epileptic disorder, and epidemiological marker? Contribution of descriptive epidemiology. *Epileptic Disorders, 4*, 1-13.

Jansen, A., Menke, R., Sommer, J., Forster, A.F., Bruchmann, S., Himpleman, J., et al. (2006). The assessment of hemispheric lateralization in functional MRI – Robustness and reproducibility. *Neuroimage, 33*, 204-217.

Janszky, J., Jokeit, H., Heinemann, D., Schulz, R., Woermann, F.G., & Ebner, A. (2003). Epileptic activity influences the speech organization in medial temporal lobe epilepsy. *Brain*, *126*, 2043-2051.

Janszky, J., Mertens, M., Janszky, I., Ebner, A., & Woermann, F.G. (2006). Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: An fMRI study. *Epilepsia*, *47*, 921-927.

Jeffery, P.J., Monsein, L.H., Szabo, Z., Hart, J., Fisher, R.S., Lesser, R.P., et al. (1991). Mapping the distribution of amobarbital sodium in the intracarotid Wada test by use of Tc-99m HMPAO with SPECT. *Radiology, 178*, 847-850.

Jeha, L.E., Majm, I., Bingaman, W., Dinner, D., Widdess-Walsh, P., & Luders, H. (2007). Surgical outcome and prognostic factors of frontal lobe epilepsy. *Brain, 130*, 574-584.

Jokeit, H. & Ebner, A. (2002). Effects of chronic epilepsy on intellectual functions. *Progress in Brain Research*, *135,* 455-463.

Jones-Gotman, M. (2008). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: An international survey – Commentary on Baxendale et al. *Epilepsia, 49*, 725.

Jones-Gotman, M., Bouwer, M.S., & Gotman, J. (1994). EEG slow waves and memory performance during the intracarotid amobarbital test. *Epilepsia, 35,* 61-69.

Jones-Gotman, M., Smith, M.L., & Zatorre, R.J. (1993). Neuropsychological testing for localizing and lateralizing the epileptogenic region. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2^{nd} ed. New York: Raven Press, pp.245-262.

Kadis, D.S., Iida, KI. Kerr, E.N., Logan, W.J., McAndrews, M.P., Ochi, A., et al. (2007). Intrahemispheric reorganization of language in children with medically intractable epilepsy of the left hemisphere. *Journal of the International Neuropsychological Society, 13,* 505-516.

Kansaku, K., Yamaura, A., & Kitazawa, S. (2000). Sex differences in lateralization revealed in the posterior language areas. *Cerebral Cortex, 10,* 866-872.

Kaplan, E.F., Goodglass, H., & Weintraub, S. (1983). Boston Naming Test. Philadelphia: Lea and Febiger.

Kho, K.H., Leijten, F.S.S., Rutten, G., Vermeulen, J., van Rijen, P., & Ramsey, N.F. (2005). Discrepant findings for Wada test and functional magnetic resonance imaging with regard to language function: use of electrocortical stimulation mapping to confirm results. *Journal of Neurosurgery, 102,* 169-173.

Kim, J.H., Joo, E.Y., Han, S.J., Cho, J., Lee, J., Seo, D.W., et al. (2007). Can pentobarbital replace amobarbital in the Wada test? *Epilepsy and Behavior, 11*, 378-383.

King, D.W., Olivier, A., Spencer, S.S., & Wyllie, E. (1993). Postscript: Exclusional criteria. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2^{nd} ed. New York: Raven Press, pp.119-122.

Kloppel, S. & Buchel, C. (2005). Alternatives to the Wada test: a critical view of functional magnetic resonance imaging in preoperative use. *Current Opinion in Neurology, 18*, 418-423.

Knake, S., Haag, A., Pilgramm, G., Dittmer, C., Reis, J., Abmann, H., et al. (2006). Language dominance in mesial temporal lobe epilepsy: A functional transcranial Doppler sonography study of brain plasticity. *Epilepsy and Behavior, 9*, 345-348.

Knecht, S., Deppe, M., Draeger, B., Bobe, L., Lohmann, H., Ringelstein, E.B., et al. (2000). Language lateralization in healthy right-handers. *Brain, 123*, 74-81.

Kutas, M., Federmeier, K.D., Staab, J., & Kluender, R. (2007). Language. In J.T. Cacioppo, L.G. Tassinary, & G.G. Berntson (Eds). *Handbook of Psychophysiology*. 3^{rd} ed. Cambridge: Cambridge University Press, pp. 555-580.

Kuzniecky, R.I., Cascino, G.D., Palmini, A., Jack Jr., C.R., Berkovic, S.F., Jackson, G.D., et al. (1993). Structural neuroimaging. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2^{nd} ed. New York: Raven Press, pp.197-210.

Kuzniecky, R. & Devinsky, O. (2007). Surgery insight: surgical management of epilepsy. Nature Clinical Practice *Neurology, 3*, 673-681.

Lancman, M.E., Benbadis, S., Geller, E., & Morris, H.H. (1998). Sensitivity and specificity of asymmetric recall on Wada test to predict outcome after temporal lobectomy. *Neurology, 50*, 455-458.

Lee, C.C., Jack, Jr., C.R., Riederer, S.J. (1996). Use of functional magnetic resonance imaging. *Neurosurgery Clinics of North America, 7*, 665-683.

Lee, D., Swanson, S.J., Sabsevitz, D.S., Hammeke, T.A., Winstanley, F.S., Possing, E.T., & et al. (2008). Functional MRI and Wada studies in patients with interhemispheric dissociation of language functions. *Epilepsy & Behavior, 13,* 350-356.

Lehericy, S., Cohen, L., Bazin, B., Samson, S., Giacomini, E., Rougete, R., et al. (2000). Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology, 54, 1625-1633.

Lichtheim, L. (1885). On aphasia. *Brain, 7,* 433-484.

Liebenthal, E., Binder, J.R., Spitzer, S.M., Possing, E.T., & Medler, D.A. (2005). Neural substrates of phonemic processing. *Cerebral Cortex*, *15*, 1621-1631.

Liegeois, F., Connelly, A., Cross, J.H., Boyd, S.G., Gadian, D.G., Vargha-Khadem, et al. (2004). Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain, 127*, 1229-1236.

Liegeois, F., Connelly, A., Salmond, C.H., Gadian, D.G., Vargha-Khadem, F., & Baldeweg, T. (2002). A direct comparison for lateralization of language activation using fMRI: Comparison with invasive assessments in children with epilepsy. *Neuroimage, 17*, 1861-1867.

Liotti, M., Gay, C.T., & Fox, P.T. (1994). Functional imaging and language: Evidence from positron emission tomography. *Journal of Clinical Neuropsychology, 11*, 175-190.

Loddenkemper, T. (2008). Complications with the Wada test. *Epilepsy and Behavior, 13,* 551-553.

Loddenkemper, T., Moddel, G., Schuele, S.U., Wyllie, E., & Morris, I. (2007). Seizures during intracarotid methohexital and amobarbital testing. *Epilepsy and Behavior, 10*, 49-54.

Lohmann, H., Deppe, M., Jansen, A., Schwindt, & Knect, S. (2004). Task repetition can affect function magnetic resonance imaging-based measures of language lateralization and lead to pseudoincreases in bilaterality. *Journal of Cerebral Blood Flow & Metabolism, 24*, 179-187.

Loring, D.W. (2008). Should we “stick” with the Wada?: Probing practicable preferences. *Epilepsia*, *49*, 722-724

Loring, D.W., Meador, K.J., & Lee, G.P. (1992). Amobarbital dose effects on Wada memory testing. *Epilepsy, 5*, 171-174.

Loring, D.W., Meador, K.J., Lee, G.P., & King, D.W. (1992). *Amobarbital effects and lateralized brain function: The Wada test*. New York: Springer-Verlag.

Loring, D.W., Meador, K.J, Lee, G.P., Murro, A.M., Smith, J.R., Flanigin, H.F., et al. (1990). Cerebral language lateralization: Evidence from intracarotid amobarbital testing. *Neuropsychologia, 28*, 831-838.

Luders, J.O., Engel Jr., J., & Munari, C. (1993). General principles. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.137-154.

Luria, A.R. (1966). *Higher Cortical Functions in Man*. New York: Basic Books.

Malmgren, K., Bilting, M., Hagberg, I., Hedstrom, A., Silfvenius, H., & Starmark, J.E. (1992). A compound score for estimating the influence of inattention and somnolence during the intracarotid amobarbital test. *Epilepsy Research, 12,* 253-259.

Mateer, C.A., & Dodrill, C.B. (1983). Neuropsychological and linguistic correlates of atypical language lateralization: Evidence from sodium amytal studies. *Human Neurobiology, 2*, 135-142.

Max, J.E. (2004). Effect of side of lesion on neuropsychological performance in childhood stroke. *Journal of the International Neuropsychological Society, 10*, 698-708.

McKiernan, K.A., D'Angelo, B.R., Kaufman, J.N., & Binder, J.R. (2006). Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage, 29,* 1185-1191.

McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., & Binder, J.R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of cognitive Neuroscience, 15,* 394-408.

Ojemann, G.A. (1979). Individual variability in cortical localization of language. *Journal of Neurosurgery, 50,* 164-169.

Ojemann, G.A. (1991). Cortical organization of language. *The Journal of Neuroscience, 11*, 2281-2287.

Ottman, R. (1997). Genetic epidemiology of epilepsy. *Epidemiologic Reviews, 19*, 120-128.

Pataraia, E., Simos, P.G., Castillo, E.M., Billingsley-Marshall, R.L., McGregor, A.L., Breier, J.I., et al. (2004). Reorganization of language-specific cortex in patients with lesions or mesial temporal epilepsy. *Neurology, 63,* 1825-1832.

Pelletier, I., Sauerwein, H.C., Lepore, F., Saint-Amour, D. & Lassonde, M. (2007). Non-invasive alternatives to the Wada test in the pre-surgical evaluation of language and memory functions in epilepsy patients. *Epileptic Disorders, 9*, 111-126.

Perria, L., Rosadini, G., Rossi, G.F. (1961). Determination of side of cerebral dominance with amobarbital. *Archives of Neurology*, *4,* 69-77.

Perrine, K., Devinsky, O., Luciano, D.J., Choi, I.S. & Nelson, P.K. (1995). Correlates of the arterial-filling patterns in the intracarotid amobarbital procedure. *Archives of Neurology, 52,* 712-716.

Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, R.T., Skudlarski, P., Fulbright, R.K., et al. (1996). Cerebral organization of component processes in reading. *Brain, 119*, 1221-1238.

Pujol, J., Deus, J., Losilla, J.M., & Capdevilla, A. (1999). Cerebral lateralization of language in normal left- handed people studied by functional MRI. *Neurology, 52*, 1038-1043.

Quesney, L.F., Risinger, M.W., & Shewmon, D.A. (1993). Extracranial EEG evaluation. In J. Engel Jr. (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.173-196.

Radhakrishnan, K., So, E.L., Silbert, P.L., Jack Jr., C.R., Cascino, G.D., Sharbrough, F.W., et al. (1998). Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: A multivariate study. *Neurology, 51*, 465-471.

Raichle, M. (2006). Functional neuroimaging: A historical and physiological perspective. In R. Cabeza and A. Kingstone (Eds). *Handbook of Functional Neuroimaging of Cognition.* 2nd ed. Cambridge: MIT Press, pp.3-20.

Ramsey, N.F., Sommer, I.E.C., Rutten, G.J., & Kahn, R.S. (2001). Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. *Neuroimage, 13*, 719-733.

Rasmussen, T. & Milner, B. (1977). The role of early left brain injury, handedness, determining lateralization of cerebral speech functions. *Annals of the New York Academy of Science, 299*, 355-369.

Rausch, R., Silfvenius, Wieser, H., Dodrill, C.B., Meador, K.J., & Jones-Gottman, M. (1993). Intraarterial amobarbital procedures. In J. Engel (Ed) *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.341-357.

Rausch, R. & Walsh, G.O. (1984). Right-hemisphere language dominance in right-handed epileptic patients. *Archives of Neurology, 41*, 1077-1081.

Rey, M., Dellatolas, G., Bancaud, J., & Talairach, J. (1988). Hemispheric lateralization of motor and speech functions after early brain lesion: Study of 73 epileptic patients with intracarotid amytal test. *Neuropsychologia, 26*, 167-172.

Rosadini, G. & Rossi, G.F. (1967). On the suggested cerebral dominance for consciousness. *Brain, 90*, 101-112.

Ruff, I.M., Swanson, S.J., Hammeke, T.A., Sabsevitz, D., Mueller, W.M., & Morris, G.L. (2007). Predictors of naming decline after dominant temporal lobectomy: Age at onset of epilepsy and age of word acquisition. *Epilepsy and Behavior, 10,* 272-277.

Rutten, G.J.M., Ramsey, N.F., van Rijen, P.C., & van Veelen, C.W.M. (2002). Reproducibility of fMRI-determined language lateralization in individual subjects. *Brain and Language, 80*, 421-437.

Sabbah, P., Chassoux, F., Leveque, C., Landre, E., Baudoin-Chial, S., Devaux, B., et al. (2003). Functional MR imaging in assessment of language dominance in epileptic patients. *Neuroimage*, *18*, 460-467.

Sabsevitz, D.S., Swanson, S.J., Hammeke, T.A., Spanaki, M.V., Possing, E.T., Morris, G.L., et al. (2003). Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology, 60*, 1788-1792.

Sabsevitz, D.S., Swanson, S.J., Morris, G.L., Mueller, W.M., & Seidenberg, M. (2001). Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. *Epilepsia*, *42*, 1408-1415.

Sander, J.W. (2003). The epidemiology of epilepsy revisited. *Current Opinion in Neurology, 16*, 165-170.

Sander, J.W. & Shorvon, S.D. (1996). Epidemiology of the epilepsies. J*ournal of Neurology, Neurosurgery, and Psychiatry, 61*, 433-443.

Sander, J.W. & Shorvon, S.D. (1987). Incidence and prevalence studies in epilepsy and their methodological problems: a review. *Journal of Neurology, Neurosurgery, and Psychiatry, 50*, 829-839.

Sass, K.J., Westerveld, M., Buchanan, C.P., Spencer, S.S., Kim, J.H., Spencer, D.D. (1994). Degree of hippocampal neuron loss determines severity of verbal memory decrease after left anteromesiotemporal lobectomy. *Epilepsia, 35*, 1179-1186.

Sawrie, S.M., Chelune, G.J., Naugle, R.I., & Luders, H.O. (1996). Empirical methods for assessing meaningful change following epilepsy surgery. *Journal of the International Neuropsychological Association, 2*, 556-564.

Seghier, M.L., (2008). Laterality index in functional MRI: Methodological issues. *Magnetic Resonance Imaging*, *26*, 594-601.

Seghier, M.L., Lazeyras, F., Pegna, A.J., Annoni, J., Zimine, I., Mayer, E., et al. (2004). Variability of fMRI activation during a phonological and semantic language task in healthy subjects. *Human Brain Mapping, 23*, 140-155.

Seidenberg, M., Hermann, B., Wyler, A., Davies, K., Dohan, F.C., & Leveroni, C. (1998). Neuropsychological outcome following anterior temporal lobectomy in patients with and without the syndrome of mesial temporal epilepsy. *Neuropsychology, 12,* 303-316.

Serafetinides, E.A., Hoare, R.D., & Driver, M.V. (1965). Intracarotid sodium amylobarbitone and cerebral dominance for speech and consciousness. *Brain, 88*, 107-130.

Snyder, P.J., & Harris, L.J. (1997). The intracarotid amobarbital procedure: An historical perspective. *Brain and Cognition, 33*, 18-32.

Snyder, P.J., Novelly, R.A., & Harris, L.J. (1990). Mixed speech dominance in the intracarotid sodium amytal procedure: Validity and criteria issues. *Journal of Clinical and Experimental Neuropsychology, 12*, 629-643.

Song, A.W., Huettel, S.A., & McCarthy, G. (2006). Functional neuroimaging: Basic principles of functional MRI. In R. Cabeza and A. Kingstone (Eds). *Handbook of Functional Neuroimaging of Cognition.* 2nd ed. Cambridge: MIT Press, pp.22-52.

Sperling, M.R., O'Connor, M.J., Saykin, A.J., & Plummer, C. (1996). Temporal lobectomy for refractory epilepsy. *Journal of the American Medical Association, 276*, 470-475.

Spreen, O. & Strauss, E. (1998). *A compendium of neuropsychological test: Administration, Norms, and Commentary. (2nd ed.*) Oxford: Oxford University Press.

Spreer, J., Altenmuller, D.M., Arnold, S., Schulze-Bonhage, A., Steinhoff, B.J., & Schumacher, M. (2001). Unsuspected atypical hemispheric dominance for language as determined by fMRI. *Epilepsia, 42*, 957-959.

Springer, J.A., Binder, J.R., Hammeke, T.A., Swanson, S.J., Frost, J.A., Bellgowan, P.S.F., et al. (1999). Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. *Brain, 122*, 2033-2045.

Starreveld, E. & Guberman, A. (2006). The spectrum of intractable epilepsy: A proposed scale. *Advances in Neurology, 97*, 493-496.

Steven, D.A. & Wiebe, S. (2006). Evaluating surgery effectiveness. *Advances in Neurology, 97*, 557-562.

Strauss, E., Loring, D., Chelune, G., Hunter, M., Hermann, B., Perrine, K., et al. (1995). Predicting cognitive impairment in epilepsy: Findings from the Bozeman Epilepsy Consortium. *Journal of Clinical and Experimental Neuropsychology, 17*, 909-917.

Strauss, E., Sherman, E., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (3rd ed.).* Oxford: University Press.

Strauss, E. & Wada, J. (1983). Lateral preferences and cerebral speech dominance. *Cortex*, *19*, 165-177.

Subirana, A. (1964). The relationship between handedness and language function. *International Journal of Neurology, 4*, 215-234.

Suchy, Y., Sands, K., & Chelune, G.J. (2003). Verbal and nonverbal fluency performance before and after seizure surgery. *Journal of Clinical and Experimental Neuropsychology*, *25*, 190-200.

Sveller, C., Hons, B.N., Briellmann, R.S., Saling, M.M., Lillywhite, L., Abbott, D.F., et al. (2006). Relationship between language lateralization and handedness in left-hemispheric partial epilepsy. *Neurology, 67*, 1814-1817.

Swanson, S.J., Sabsevitz, D.S., Hammeke, T.A., & Binder, J.R. (2007). Functional magnetic resonance imaging of language in epilepsy. *Neuropsychology Review, 17*, 491-504.

Szaflarski, J.P., Binder, J.R., Possing, E.T., McKiernan, K.A., Ward, B.D., & Hammeke, T.A. (2002). Language lateralization in left-handed and ambidextrous people: fMRI data. *Neurology, 59*, 238-244.

Szaflarski, J.P., Holland, S.K., Jacola, L.M., Lindsell, C., Privitera, M.D., & Szaflarski, M. (2008). Comprehensive pre-surgical functional MRI language evaluation in adult patients with epilepsy. *Epilepsy & Behavior, 12*, 74-83.

Taylor, D.C. (1993). Epilepsy as a chronic sickness: Remediating its impact. In J. Engel (Ed). *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, pp.11-22.

Tellez-Zenteno, J.F., Dhar, R., & Wiebe, S. (2005). Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain*, *128*, 1188-1198.

Thivard, L., Hombrouck, J., Tezenas du Montcel, S., Delmaire, C., Cohen, L., Samson, S., et al. (2005). Productive and perceptive language reorganization in temporal lobe epilepsy. *Neuroimage*, *24*, 841-851.

Trenerry, M.R., Jack Jr., C.R., Ivnik, R.J., Sharbrough, F.W., Cascino, G.D., Hirschorn, K.A., et al. (1993). MRI hippocampal volumes and memory function before and after temporal lobectomy. *Neurology, 43*, 1800-1805.

Trenerry, M.R., & Loring, D.W. (1995). Intracarotid amobarbital procedure: The Wada test. *Neuroimaging Clinics of North America*, *5*, 721-728.

Trenerry, M.R., Westerveld, M., & Meador, K. (1995). MRI hippocampal volume and neuropsychology in epilepsy surgery. *Magnetic Resonance Imaging*, *13*, 1125-1132.

van der Kalen, B.F.W., Morris, G.L., Yetkin, F.Z., van Erning, L.J.T.O., Thijssen, H.O.M., & Haughton, V.M. (1998). Hemispheric language dominance studied with functional MR: Preliminary study in healthy volunteers and patients with epilepsy. *American Journal of Neuroradiology*, *19*, 73-77.

Vingerhoets, G., Deblare, K., Backes, W.H., Achten, E., Boon, P., Boon, P.J., et al. (2004) Lessons for neuropsychology from functional MRI in patients with epilepsy. *Epilepsy & Behavior, 5,* S81-S89.

von Hippel, P. (2010). Skewness. In M. Lovric. (Ed). *International Encyclopedia of Statistical Science*. New York: Springer.

Wada, J. & Rasmussen, T. (1960). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. *Journal of Neurosurgery, 17*, 266-282.

Weber, B., Wellmer, J., Reuber, M., Mormann, F., Weis, S., Urbah, H., et al. (2006). Left hippocampal pathology is associated with atypical language lateralization in patients with focal epilepsy. *Brain*, *129*, 346-351.

Weber, B., Wellmer, J., Schur, S., Dinkelacker, V., Ruhlmann, J., Mormann, F., et al. (2006). Pre-surgical language fMRI in patients with drug-resistant epilepsy: Effects of task performance. *Epilepsia, 47*, 880-886.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale-Revised*. New York: Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-Third Edition.* New York: Psychological Corporation.

Wellmer, J., Weber, B., Weis, S., Klaver, P., Urbach, H., Reul, J., et al. (2008). Strongly lateralized activation in language fMRI of atypical dominant patients – Implications for pre-surgical work-up. *Epilepsy Research, 80*, 67-76.

Wernicke, C. (1874). The aphasic symptom complex: a psychological study on a neurological basis. Kohn and Weigert, Breslau. Reprinted in R.S. Cohen & M.W. Wartofsky (Eds) *Boston Studies in the Philosophy of Science, 4* Reidel, Boston.

Wiebe, S. (2000). Epidemiology of temporal lobe epilepsy. *Canadian Journal of Neurological Science*, *27 (suppl 1)*, S6-S10.

Wiebe, S., Blume, W.T., Girvin, J.P., Eliasziw, M. (2001). A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England Journal of Medicine, 345*, 311-319.

Wilke, M., Lidzba, K., Staudt, M., Bucheanau, K., Grodd, W., & Krageloh-Mann, I. (2006). An fMRI task battery for assessing hemispheric language dominance in children. *Neuroimage, 32*, 400-410.

Wilkinson, I., & Lennox, G. (2005). Essential neurology, 4th ed. Malden: Blackwell Publishing.

Wise, R.J.S., & Price, C.J. (2006). Functional neuroimaging of language. In R. Cabeza and A. Kingstone (Eds). *Handbook of Functional Neuroimaging of Cognition.* 2^{nd} ed. Cambridge: MIT Press, pp.192-227.

Woermann, F.G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., et al. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology, 61*, 699-701.

Woods, R.P., Dodrill, C.B., Ojemann, G.A. (1988). Brain injury, handedness, and speech lateralization in a series of amobarbital studies. *Annals of Neurology, 23*, 510-518.

Worthington, C. Vincent, D.J., Bryant, A.E., Roberts, D.R., Vera, C.L., Ross, D.A., et al. (1997). Comparison of functional magnetic resonance imaging for language localization and intracarotid speech amytal testing in pre-surgical evaluation for intractable epilepsy. *Stereotactic and Functional Neurosurgery, 69*, 197-201.

Wyllie, E., Luders, H., Murphy, D., Morris, H., Dinner, D., Lesser, R., et al. (1990). Intracarotid amobarbital (Wada) test for language dominance: correlation with results of cortical stimulation. *Epilepsia, 31*, 156-161.

Xiong, J., Rao, S., Gao, J., Woldorff, M., & Fox, P.T. (1998). Evaluation of hemispheric dominance using functional MRI: A comparison with positron emission tomography. *Human Brain Mapping, 6*, 42-58.

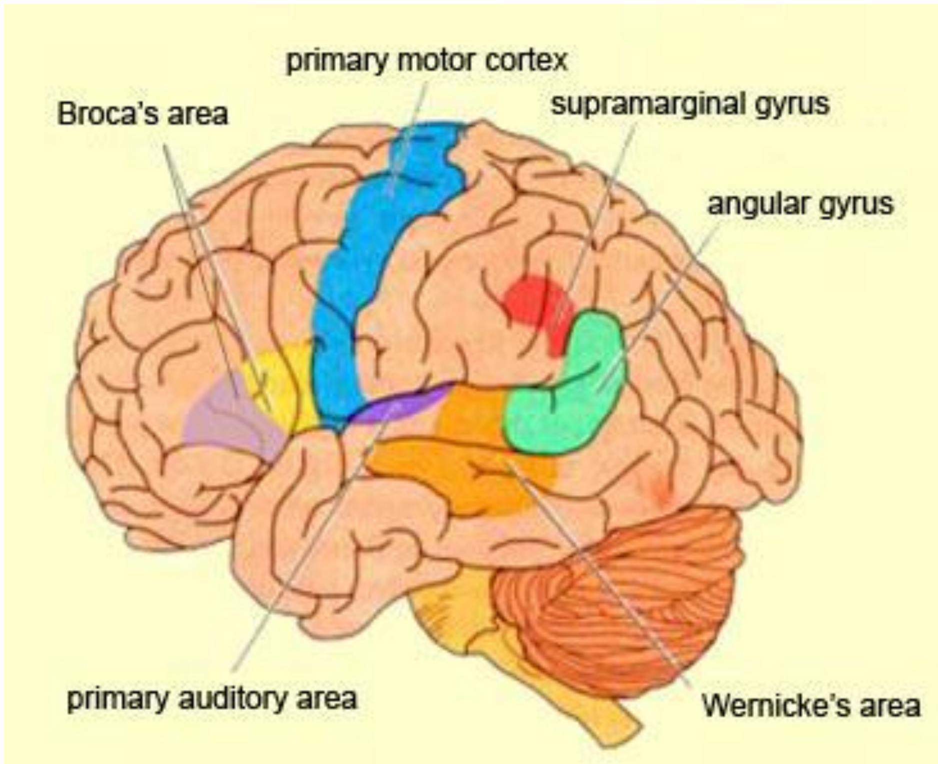
Yeo, R.A., Thoma, R.J., & Gangestad, S.W. (2002). Human handedness: A biological perspective. In S.J. Segalowicz & I. Rapin (Eds.) *Handbook of Neuropsychology*, 2^{nd} ed, Vol. 8, Part 1. Elsevier Science.

Yetkin, F.Z., Swanson, S., Fischer, M., Akansel, G., Morris, G., Mueller, W., et al. (1998). Functional MR of frontal lobe activation: Comparison with Wada language results. *American Journal of Neuroradiology, 19*, 1095-1098.

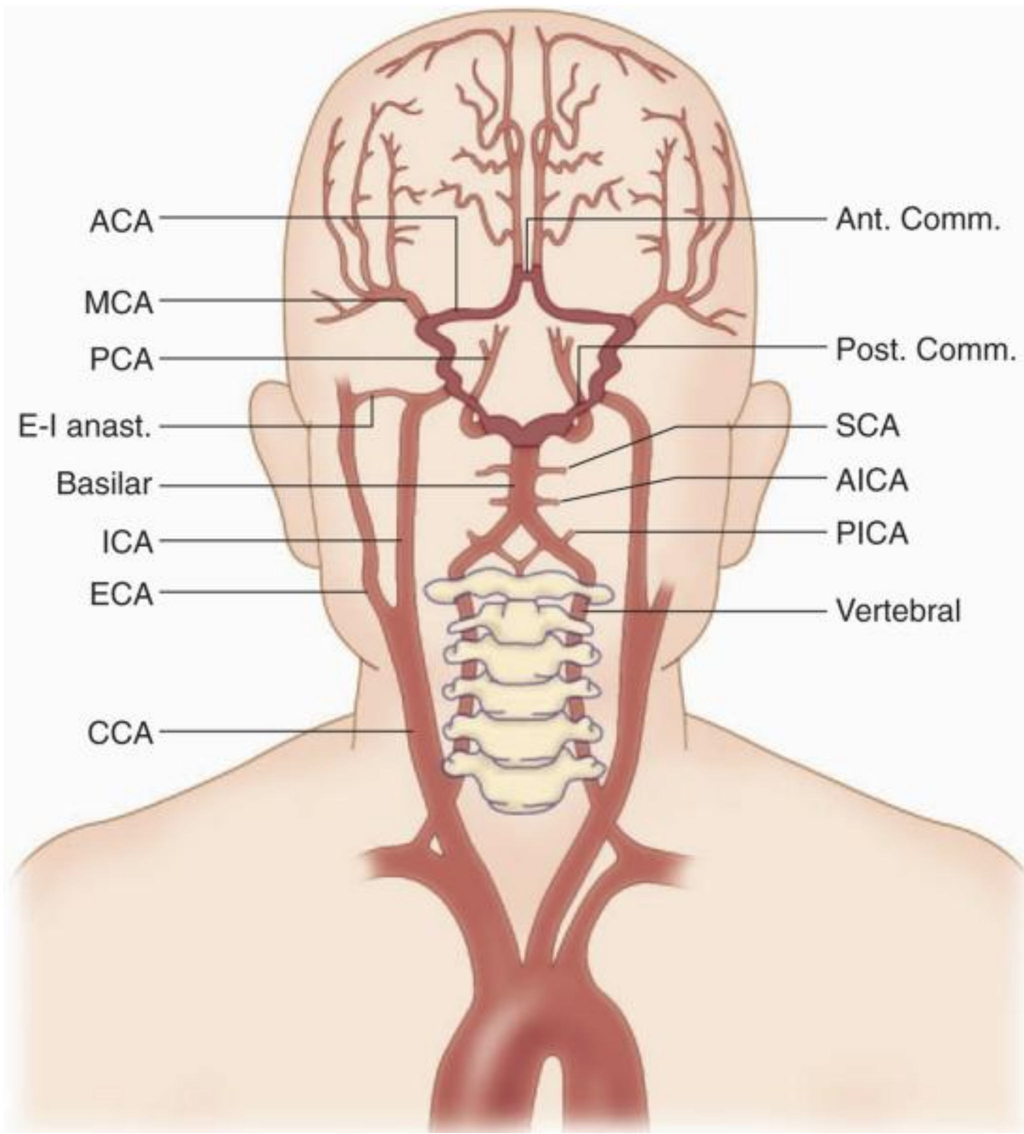
Yuan, W., Szaflarski, J.P., Schmithorst, V.J., Schapiro, M., Byars, A.W., Strawsburg, R.H., et al. (2006). fMRI shows atypical language lateralization in pediatric epilepsy patients. *Epilepsia, 47*, 593-600.

Zatorre, R.J. (1989). Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. *Neuropsychologia, 27*, 1207-1219.

Appendix A: Brain Regions Involved in Language Processing



Appendix B: Typical Cerebral Vasculature



ACA = anterior cerebral artery; AICA = anterior inferior cerebellar artery; Ant. Comm. = anterior communicating artery; **CCA = common carotid artery**; ECA = external carotid artery; E-I anast. = extracranial-intracranial anastomosis; ICA = internal carotid artery; **MCA = middle cerebral artery**; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; Post. Comm. = posterior communicating artery; SCA = superior cerebellar artery. *(Modified from Lord R: Surgery of Occlusive Cerebrovascular Disease. St Louis, Mosby, 1986.)*

Appendix C: Example IAT Language Protocol

The Medical College of Georgia IAT Protocol

The protocol that is used by the Medical College of Wisconsin is modeled after the empirically supported protocol that was developed at the Medical College of Georgia. This protocol has been described in detail elsewhere (Loring et al., 1992), and the aspects that apply to language assessment are described below.

Language protocol. All epilepsy patients who are candidates for any type of resective surgery undergo the IAT. Baseline testing is performed 1-2 hours prior to the procedure, including presentation of line drawings (e.g., coffee cup and shoe). Just prior to the procedure, an angiography is done. Immediately following the angiography, the IAT is performed with the patient in a supine position. Left and right IATs are performed on the same day with a minimum of 30 minutes between the two injections. Prior to testing, patients hold both hands straight up and begin counting repeatedly from 1-20. Then, a single bolus injection of 100mg amobarbital sodium (5% solution) is administered via catheter over a 4 second interval following a transfemoral approach into the internal carotid artery.

Immediately following a demonstration of hemiplegia (i.e., the dropping of the hand contralateral to injection) and evaluation of eye gaze deviation, the patient is requested to execute a simple command (e.g., “touch your nose”). Multiple language tasks are administered. The patient is presented with a modified Token Test in which colored shapes are presented on a vertical card. If the patient cannot execute a single stage command (e.g., “point to the red circle”), the assessment is paused until some return of language function occurs. Return of some language function can be demonstrated by the patient's execution of a simple midline command (e.g., "stick out your tongue"), and response to simple questions with recognizable, though not necessarily correct utterances. Next, two objects are presented to the patient, and he/she is asked to name them. Paraphasic errors are noted. Repetition of a simple nursery rhyme is obtained, followed immediately by reading a simple sentence. Additional naming ability is assessed during verbal memory tasks, such as naming pictures that have been previously seen.

Language rating. Language rating is based upon performance of 4 linguistic tasks; counting disruption, comprehension, naming, and repetition). The expressive language score is based upon disruption of counting ability (0=normal, slowed, or brief pause ≤20 seconds; 1=counting perseveration with normal sequencing; 2=sequencing errors; 3=single number or word perseveration; 4=arrest > 20 seconds). Comprehension from the modified Token Task is rated on a 3-point scale: 1. "point to the red circle after the green square," 2. "point to the red circle and then point to the green square," 3. "point to the red triangle." A score of 0 is awarded for completion of the complex 2-stage command with inverted syntax, a score of 1 reflects successful simple 2-stage command, 2 is scored for the 1-stage commands, and 3 if the patient cannot perform any commands. Confrontation naming for the 2 objects is scored as pass or fail for each stimulus. Nursery rhyme repetition is graded on a 0-3 rating scale. In all 4 categories, a score of 0 reflects normal function.

A conservative language classification system is used. For language impairment to be inferred, impairments (scores >0) had to be observed in two categories, with one of the scores greater than 1. Language impairment could also be inferred if at least ¾ of the language categories are only mildly impaired.