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# Multi-Modality Assessment Of Language Function

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**MULTI-MODALITY ASSESSMENT OF LANGUAGE FUNCTION**

by

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## DEDICATION

*I dedicate this work*

*...to my friends, who relieve stress and boost the ego.*

*...to my brothers, Jonathon, Cory, and Garrett, who always believe in me and have always been there to ensure that I knew I had someone looking up to me.*

*...to my parents, Diana and Fred, who have always strived for the best for me and brag about me embarrassingly.*

*...to my grandpa John, a fellow traveler and someone who always urged me to come to my own conclusions.*

*...to my grandma Rosemary, most of all, who always thought I was the greatest person who ever lived and literally had no doubt that I would be capable of saving the world.*

*I've tried to do some good things in life to make you proud.*

*This is one of them.*

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*I hope that all of you know that you are my friends.*
*Thank you to all of my family and friends for keeping me sane and encouraging me.*
*Without you, I am nothing.*

**よろしくお願いします**
*Yoroshiku Onagaishimasu*

## PREFACE

Most of the studies presented in this thesis were undertaken for the purpose of studying normal language structure and function. All of the subjects are epilepsy surgery patients because the primary methodology employed herein is invasive and largely only available for ethical use in such a patient population. The only exception to this is the final study presented, which aims to study the effect of spontaneous epileptiform activity upon language-relate cortical activity.

As described in the thesis, the relevant electrocorticographic signals representing intracortical processing are those in a frequency range between 50 and 150 Hz. Traditionally, electrographic signals from the cortex in excess of 30 Hz are referred to as 'gamma'. However, evidence exists to suggest that, although all signals greater than 30 Hz are positively correlated with intracortical processing, signals greater than 50 Hz are separable from those between 30 and 50 Hz. The underlying functional mechanisms differentiating these frequency bands are not well understood. As such, there is no standard naming convention for frequency bands greater than 50Hz; sometimes referred to as 'gamma', 'high gamma', 'supra-gamma', 'chi', and others. To ensure broader acceptance and understanding, we have chosen to use the term 'gamma-activity' while stating in each study what frequency range we are referring to. We urge investigators in the field to further investigate the underlying mechanisms that may differentiate the 'high frequency' band and come to agreement on rational naming conventions based on scientific principles.

Many of the studies presented as part of this thesis were published before completion of the thesis. These are identified at the beginning of the respective chapter

or subsection. The overall works are largely unchanged from their individually published forms. To ensure that this thesis complements the literature rather than copy it, two tasks were completed: 1.) some updating of the works was undertaken and writing published in the literature as 'supplementary' was incorporated into the main work presented here. 2) The patient numbering scheme was extended across studies rather than within the studies. The studies themselves are not necessarily presented in the order that they were conducted. Within each study, patients are ordered chronologically. If a study involves a patient presented earlier in the document as part of another study, the patient number will reflect this. As such, the reader can recognize which patients contribute to more than one study.

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## GENERAL INTRODUCTION

Language is a uniquely human skill (Andreason and Black, 2006; McNelly et al., 2009). Our basic understanding of cortical language organization rests upon the Wernicke-Lichtheim model formulated by 1885 (Graves, 1997). Lichtheim brilliantly converted Wernicke's ideas of language organization into diagrammatic form to enable ease of understanding. These elegant interpretations of data gathered at that time made way for the prediction of disorders that could be linked directly to identifiable cortical locales. Despite the power of such a model in enabling the application of scientific knowledge, it remains inadequate when describing how our brain processes language. For example, the exact localization of different language functions have high inter-individual localization variability (Berger et al., 1989; Duchowny et al., 1996; Hamberger et al., 2007; Ojemann et al., 1989; Ojemann et al., 2003). Evidence suggests the topography of language function to be so highly variable that precise localization cannot be reliably inferred from anatomical landmarks (Hamberger, 2007; Ojemann et al., 1989). Even within well established language-related regions, such as Broca's area for expressive language and Wernicke's region for language comprehension, various different underlying functions can be detected with modern techniques such as functional magnetic resonance imaging (fMRI) (Embick et al., 2000) and diffusion-weighted MRI (DW-MRI) (Brauer et al., 2011). Such fluidity in this localizationist view of language structure and function highlight the need for further investigation utilizing various modalities with differing strengths and weaknesses to yield a more complete understanding.

Language was originally studied primarily by observing the effects of different lesions upon function (Dronkers et al., 2007; Graves, 1997; Lichtheim, 1885). Such study relies upon the spontaneous occurrence of non-lethal brain lesions in living persons. While valuable, such study possesses no experimental control and detailed post-mortem evaluations of lesion extent are necessary to understand the loss of which brain structures were associated with certain deficits. Indeed, the data that gave rise to the historical and widely known concept of Broca's area suffers from lack of a thorough anatomical evaluation of lesion extent. Broca's two famous cases of expressive language deficit, now known as Broca aphasia, resulted from lesion of the posterior two thirds of the inferior frontal gyrus, which were observed post-mortem. However, these lesions were only observed superficially and the brains were never dissected (Dronkers et al., 2007); hence the terminology 'area' which suggests a two-dimensional structure or surface (Bogen and Bogen, 1976). Investigation with modern imaging of the preserved brains of these two patients has shown that these lesions extended deep into the cerebrum and involved many white matter pathways that interconnect other local and distant cortical regions (Dronkers et al., 2007). Therefore, it is important to consider language-related networks and connectivity patterns, in addition to local cortical functions, in order to understand how different cortical regions communicate and share information.

The cortical processing of language still has many unanswered questions that include both the anatomical networks required and how these networks form during development (Duffau, 2008). This is, in part, due to our inability to study cortical networks in humans in ways similar to our studies of other behaviors in animals.

Electrical brain stimulation has been used since the original studies of language to induce transient lesions in awake surgical patients, providing more control in experimentation. Recently developed technologies have also included both electrophysiological and magnetic resonance imaging (MRI) techniques and allow for the study of language structure and function in live, awake, and healthy subjects. Electrophysiological techniques include electroencephalography (EEG) and magnetoencephalography (MEG) which directly detect cortical signals in real-time. MRI techniques include fMRI which detects the blood-oxygen-level-dependent (BOLD) signal representing cortical processing-dependent changes in blood flow and oxygenation (Logothetis, 2003). With these modalities, new models of language organization have emerged that begin to build further upon the original models developed by Wernicke, Lichtheim (Lichtheim, 1885), Broca (Dronkers et al., 2007), and Geschwind (Geschwind, 1970). Such new models are beginning to incorporate not only cortical regions outside of Broca's area and Wernicke's region, but also identifying finer details within these traditional language areas (Amunts and Zilles, 2012; Bernal and Altman, 2010; Friederici, 2012; Hickok, 2012). It will be critical to examine these non-traditional language regions in order to expand our understanding of how language arises from cortical processes.

In addition to basic knowledge of human language, an improved understanding of activity and connectivity of areas associated with language function has clinical relevance; i.e. guiding important decisions during neurosurgical procedures to minimize language deficits (Brown et al., 2008). Surgical procedures for medically refractory focal epilepsy and tumors often require such cortical mapping, either intra- or extra-

operatively, to ensure that function is preserved following surgery. Electrical brain stimulation serves as the clinical gold-standard. More recently, however, the intracranial counterpart to EEG, known as electrocorticography (ECoG), has emerged as an additional, developing functional mapping modality. ECoG possesses all of the benefits of EEG including the direct measurement of cortical activity and excellent temporal resolution but with the additional benefit of enhanced signal-to-noise ratio otherwise unachievable (Crone et al., 2006a; Jerbi et al., 2009), allowing for the measurement of very high frequency cortical activities beyond the traditional gamma range (Crone et al., 2011). Functional mapping with task-related ECoG has the potential to become a powerful clinical as well as scientific tool to delineate physiological function, including language, such that we might learn not only 'where' language functions are located, but also 'when'. The identification of 'when' a subset of cortical activities occurs during task performance is critical (Asano et al., 2013). If we can garner information about 'when' a cortical process occurs, then we can have a clue as to exactly 'what' sub-process is taking place; for example, we will expect that audition precedes comprehension which precedes expressive processes which may in turn precede sensorimotor activation.

Generally, fMRI has become the dominant tool in the study of language and other cortical functions (Price, 2010). However, the data generated from the BOLD signal is indirect, at best, and all interpretations will require correlation and confirmation with modalities yielding more direct measurements of cortical activity (Brown et al., 2012b; Logothetis, 2003). Modalities such as positron emission tomography (PET), using either 2-deoxy-2-($^{18}$F)fluoro-D-glucose (FDG) or $D_2$-$^{15}$O radiotracers, and near-infrared spectroscopy (NIRS) also detect processes related to the BOLD effect (Portnow et al.,

2013; Sakatani et al., 2007), remaining indirect measures of cortical activity. NIRS possesses enhanced temporal resolution but is highly limited in signal-to-noise ratio; being very useful in newborns and infants but highly limited in detection capabilities in older children and adults (Ghosh et al., 2012). PET represents a widely used but older technology measuring metabolic processes that has largely been replaced by fMRI due to its rather complete lack of temporal resolution and requirement for a radioactive tracer (Price, 2012). Beyond fMRI, MRI technologies have spun off diffusion-weighted (DW-MRI) techniques that allow for the detection of major white matter pathways. Tractography based upon DW-MRI data enables the visualization of such white matter structures and is capable of yielding information regarding long-range cortico-cortical communication that may augment the findings of functional modalities. EEG and MEG can be used in healthy subjects to yield direct measurements of brain activity. However, due to the distance of electrodes from the cortex, these non-invasive electrophysiological modalities are highly limited in signal-to-noise ratio, limiting analyses to lower frequency activities; electromagnetic signal strength declines with the square of the distance. EEG and MEG also suffer from a phenomenon known as the 'inverse problem', greatly limiting spatial resolution; the inverse problem represents the mathematical process of estimating signal sources measured at a distance (Grech et al., 2008). The availability of extra-operative task-related ECoG data in awake surgical patients may provide high yield and unique data of both abnormal and normal brain physiology and function (Lachaux et al., 2012). Functional as well as structural data from less direct modalities may be contrasted by invasive electrophysiology to enhance the formulation and refinement of new theories of 'how' language manifests from brain.

This dissertation presents a series of studies that employ task-related ECoG alongside other modalities to enhance the literature regarding cortical language structure and function. The aims are both clinical and scientific. Clinically, language-related ECoG has the potential to augment standard clinical methodologies, especially in young children where the clinical gold-standard electrical brain stimulation has been suggested to fail in the mapping of cortical language functions (Schevon et al., 2007). Additionally, the detection of language-related signals in epileptic patients enables measurement of the effects of epilpeptiform activity upon ongoing language function, which may explain and expand clinical observations as well as help to guide clinical decision making. Scientifically, language-related ECoG may serve as a validating modality for indirect, non-invasive measures such as fMRI and the BOLD effect. By employing task-related ECoG using multiple tasks and constricting structural modalities such as DW-MRI, we may find that the underlying structure and function of language processes can be 'dissected' and evaluated in a manner that begins to resemble true experimentation. We approached these problems with the expectation that we'd likely walk away with further questions about language and beyond, as is the case in all of science. Potentially, the contributions that we can make utilizing task-related ECoG, will help to guide our next steps in the field that will lead us to new scientific understanding and useful clinical applications capable of enhancing the treatment of patients with epilepsy.

## CHAPTER 1: Techniques in the Cortical Language Mapping for Epilepsy Surgery

About 1% of the general population has epilepsy. One-fifth of pediatric epilepsy is medically intractable, frequently resulting in cognitive declines known as epileptic encephalopathy (Zupanc, 2009). Subsets of such patients, e.g. those with well defined seizure foci, benefit from surgical resection aiming to alleviate seizures while minimizing postoperative deficits. Subdural electrode implantation enables extra-operative electrical brain stimulation as well as electrocorticography (ECoG) to identify cortex of vital function as well as the epileptogenic focus itself, respectively (Asano et al., 2013; Berger et al., 1989; Fukuda et al., 2010a; Jayakar et al., 1994; Khajavi et al., 1999; Ojemann et al., 2003; Schevon et al., 2007). Language is one of several functions that are targeted for post-operative preservation but it is one with high inter-individual localization variability (Berger et al., 1989; Duchowny et al., 1996; Hamberger et al., 2007; Ojemann et al., 1989; Ojemann et al., 2003), highlighting the need for such extra-operative language mapping. Electrical brain stimulation is the clinical gold-standard technique for this purpose. However, electrical brain stimulation mapping of language function possesses poor sensitivity in young children; particularly those younger than 10.2 years of age (Schevon et al., 2007).

Language-related activation patterns observed on fMRI differ across ages (Brauer et al., 2008; Gaillard et al., 2003; Schapiro et al., 2004; Szaflarski et al., 2006; Wood et al., 2004). Regarding focal epilepsy, language localization can be further altered by lesions (Rosenberger et al., 2009; Wellmer et al., 2009; Wilke et al., 2011) and interictal epileptiform discharges may directly affect cognitive functions (Shewmon and Erwin, 1989). Despite enhanced language variability in epileptic patients, those undergoing

grid implantation are unique study subjects. In such patients, it is possible to study cortical activity directly by measuring task-related changes in electrocorticographic signals (Brown et al., 2008; Crone et al., 2011; Miller et al., 2008) at a combined temporal and spatial resolution that is unmatched by most non-invasive modalities available (Lachaux et al., 2012).

*Electrical Brain Stimulation*

Electrical brain stimulation (also known as neurostimulation) has a history of use spanning over a century in the study of cortical functions (Penfield and Welch, 1949), including language (Hamberger, 2007). Penfield introduced this technique to clinical use in 1961 for mapping motor functions while the patient was still under general anesthesia (Garrett et al., 2012). The concept is simple: deliver a non-destructive dose of electrical current to a small region of cortex and observe the functional effect, or lack thereof. In regards to language mapping, the patient must be engaged in a task during stimulation such that any disruption in task performance can be observed; i.e. a transient lesion of a structure essential for language function will be associated with some language-related impairment. Traditionally, the task-of-choice for such language mapping is a naming task (Hamberger, 2007; Ojemann et al., 2003). It is thought that the cortical functions involved in naming are central to language function since it has been observed that all forms of *aphasia* are associated with some degree of *dysnomia*, or functional deficit in naming (Hamberger et al., 2007). All stimulation results mentioned in this dissertation were obtained extraoperatively while utilizing subdural electrode grids and strips that had been previously implanted as part of surgical management; details of our method of

electrical current delivery are described in Chapter 2. By cortical stimulation, language function can often be subdivided into auditory, language comprehension, expressive language, and sensorimotor function of the face, mouth, and intraoral structures. Auditory function is identified as either a perceived sound, usually a 'buzz', or a distortion in a speaker's voice. Language comprehension is identified by a lack of comprehension during stimulation that is not associated with any auditory phenomena. Expressive language function is identified when the patient can comprehend the auditory stimulus but is unable to deliver the appropriate naming response during stimulation; sometimes the patient's correct response will come immediately following removal of stimulation. Finally, language-related sensorimotor function of the face and mouth is identified by a patient-reported sensation related to or a motor movement induced by stimulation.

*Task-Related Electrocorticography*

Electrocorticography (ECoG) is the intra-cranial counterpart to electroencephalography (EEG). Rather than the scalp, ECoG electrodes are in direct contact with cortex. Because electromagnetic interference generated by cranial musculature is minimized and electrodes lie far closer to the source, the signal-to-noise ratio of ECoG is 20 to 100 times improved over EEG and magnetoencephalography (MEG); enabling analysis of signals beyond 200 Hz (Ball et al., 2009; Brown et al., 2008; Fukuda et al., 2008; Gaona et al., 2011). Source localization estimation is unnecessary and temporal resolution is on the order of milli-seconds.

Techniques such as EEG, MEG, and ECoG detect a range of frequencies known as local-field potentials (LFPs) (Logothetis, 2003). Traditionally, signals are classified based on the dominant frequency: delta (0.5 - 3.5 Hz), theta (4 - 7 Hz), alpha (8 -12 Hz), beta (13 - 30 Hz), and gamma (> 30 Hz). Different components of cortical function are attributed to these frequency bands. Delta waves are the low-frequency, high-amplitude 'slow waves' that are associated with deep sleep and cortical dysfunction (Engel and Fries, 2010). The theta band has been associated with working memory functions (Engel and Fries, 2010; Raghavachari et al., 2001) and interest has especially been inspired in the role of theta-range phase in modulating gamma activity (Scheffzuk et al., 2011). Regarding cortical processing, and this dissertation, the most relevant frequency bands are alpha, beta, and gamma. Alpha and beta are often grouped together as they are both associated with task-related decreases in amplitude (Miller et al., 2008). Many EEG and MEG studies rely upon such alpha/beta demodulations (i.e. attenuation) in the study of task related cortical function. ECoG data has shown that task-related alpha and beta modulations can be slow and lingering rather that tightly corresponding to the onset and offset of cortical processing (Crone et al., 2011; Fukuda et al., 2010a). The gamma range, however, is most closely associated with cortical processing in both space and time (Crone et al., 2011). Task related gamma activities are high frequency, low-amplitude signals that are often difficult to detect on EEG and MEG but regularly measured on ECoG. Gamma activity has been shown to predict focused attention (Cardin et al., 2009), is observed to occur over a broad range of processes (Engel and Fries, 2010), and fails to occur in disease (Cardin et al., 2009). Some evidence exists that suggest that a 'low' gamma and a 'high' gamma range may exist (Kim et al., 2013;

Matsuzaki et al., 2012). These can be dissociated in some unique situations (Ray and Maunsell, 2011). This distinction is poorly understood but the low-frequency cutoff for broadband 'high' gamma activity appears to be approximately 50 Hz (Miller et al., 2008; Ray and Maunsell, 2011). In this document, we utilize the frequency range from 50 - 150 Hz for most of the studies, unless otherwise specified, and we refer to this as task-related gamma.

Analysis of task-related spectral changes on scalp EEG was originally introduced by Pfurtscheller and Aranibar in 1977 (Pfurtscheller and Aranibar, 1977). In short, amplitude augmentation in gamma activity (>30Hz) represents functional activation (Crone et al., 2006a; Pfurtscheller and Aranibar, 1977; Pfurtscheller et al., 1994). It has been demonstrated that sites of gamma-augmentation often exhibit relevant symptoms upon stimulation (Asano et al., 2009b; Fukuda et al., 2008; Koga et al., 2011; Nagasawa et al., 2010a); employing overt auditory (Brown et al., 2008; Nagasawa et al., 2010a) and visual (Lachaux et al., 2005; Sinai et al., 2005; Tallon-Baudry et al., 2005) tasks. Spatial concordance between ECoG and stimulation (Cervenka et al., 2013; Crone et al., 1998a; Crone et al., 1998b; Fukuda et al., 2008; Koga et al., 2011; Kojima et al., 2012; Kojima et al., 2013b; Nagasawa et al., 2010a; Thampratankul et al., 2010) provides scientific validation to the approach.

*Electrocorticography-Centered Study of Language*

This dissertation presents a series of studies that collectively aim to enhance the understanding of language structure and function with a special emphasis on data garnered with analysis of language-related electrocorticographic signals. The series

begins with an initial evaluation of the primary naming task used to elicit language-related cortical processing. The clinical gold-standard of electrical brain stimulation is utilized as an alternative contrast modality for validation. This is followed by ECoG-focused studies that employ the primary language task alongside contrast and control tasks designed to functionally dissect the underlying mechanism of language-related cortical processing. A magnetic resonance imaging (MRI) technique, diffusion weighted MRI (DW-MRI), capable of identifying major white matter tracts is utilized in the study presented in the fourth chapter to combine a structurally-focused modality with language-related ECoG findings to shed light on the topic of language-related connectivity. Finally, the benefit of language-related ECoG is turned toward the disease that afflicts all of the subjects generating the data such that the effect of epileptiform activity upon ongoing language processing is explored. Taking a multi-modal approach to the use of language-related ECoG signals should provide a unique contribution to the language literature as well as yield evidence that may benefit the patients from whom this data is collected.

Clearly, one inherent limitation in ECoG studies is that all subjects are undergoing a surgical procedure for the treatment of a neurological disorder, typically epilepsy or brain tumor. Thus, patients in ECoG studies are often assumed to represent an ‘abnormal’ population. Few would argue that intracranial studies of epileptic patients by Penfield et al. largely contributed to our current knowledge of the functional organization of motor, sensory and language systems. Disputing all previous intracranial studies may result in denial of the basis of our current knowledge. The presence of focal epilepsy does not infer that the rest of the brain is entirely abnormal. For the rightfully skeptical

mind, methods do exist by which the degree of departure from normality can be estimated. For example, Processing Speed Index (PSI) values <90, approximately, may indicate a >1 standard deviation departure from normal electrographic indicators of auditory information processing in patients with intractable epilepsy (Korostenskaja et al., 2010). Age at onset of epilepsy, whether prior to or after age 14, is another measure shown to be important in predicting brain dysfunction (Kaaden and Helmstaedter, 2009). We provide PSI and age at onset of epilepsy data, when available. Information such as verbal comprehension index (VCI), verbal intelligence quotient (VIQ), sodium amobarbital procedure (Wada test) results, as well as qualitative educational information, when available, are provided in the following studies. In our studies of normal language function (i.e. excluding the final chapter) our patient selection methods impose an exclusion criterion when the VCI or VIQ was known to be less than 70, indicative of severe cognitive impairment in the realm of verbal functions. Additionally, it has been shown that patients with epilepsy have a BOLD effect in response to auditory language tasks similar to that observed in normal subjects, especially when atypical language lateralization is not present (Carpentier et al., 2001). Like normal subjects, epileptic patients show increased BOLD response in superior temporal regions to forward speech compared to reverse speech (Gaillard et al., 2004). Thus, although all subjects involved in ECoG data collection possess a neurological disease, it is possible to garner information generalizable to the broader, healthy population. Consensus in the Neuroscience community concludes that intracranial studies, including ECoG recording, will continue to serve as essential brain mapping techniques (Lachaux et al., 2012) bridging the gap between non-invasive neuroimaging and neurophysiology studies.

# CHAPTER 2: Clinical Utility of Naming-Related Gamma Activity on ECoG in Language Mapping in Epilepsy Surgery

*This chapter is modified from the original publication in the scientific journal NeuroImage - (Brown et al., 2008)*

## *Introduction*

Cortical areas essential for language are highly variable in location between individuals with focal epilepsy (Duchowny et al., 1996; Ojemann et al., 1989). Thus, functional cortical mapping for language is often performed in patients with intractable neocortical epilepsy to assess the risk of language deficit following resection of the presumed epileptogenic zone. Electrical brain stimulation via implanted subdural electrodes has been demonstrated to be a powerful technique for language mapping in a large number of patients and remains today's “gold standard” for such clinical use. However, a recent study found stimulation inadequate for language mapping in children under 10 years of age (Schevon et al., 2007), and alternative language mapping techniques would be desirable in these cases.

Quantitative measurement of high-frequency gamma oscillations (80 to 100 Hz) on extraoperative electrocorticography (ECoG) during a picture naming task has been proposed as an alternative language mapping technique. Utilizing picture naming tasks, spatial concordance was observed between the language areas determined by such ECoG analysis and electrical brain stimulation in presurgical evaluation for patients ranging in age from mid-adolescence well into adulthood (Crone et al., 2001b; Sinai et al., 2005). However, the literature does not reveal such language mapping by ECoG analysis performed on patients younger than mid-adolescence. In the present study, we

determined “where” and “when” an auditory communication task increased gamma activity (50 to 150 Hz) on subdural electrodes implanted on the left hemisphere in children with intractable focal epilepsy. We also determined the spatial relationship between the presumed language areas suggested by increased gamma activity and those suggested by stimulation as well as the brain's anatomical structures.

## *Methods*

### *Subjects*

The present study included four native English speaking children who were diagnosed to have intractable focal epilepsy with the presumed epileptogenic zone in the left hemisphere (3 girls aged 7, 9 and 10 years; 1 boy aged 15 years). All patients underwent a two-stage epilepsy surgery between January and May of 2007. All four children underwent preoperative scalp video-electroencephalography (video-EEG), preoperative magnetic resonance imaging (MRI), 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography (FDG-PET), preoperative neuropsychological examination, extraoperative intracranial electrocorticography (ECoG), and extraoperative functional cortical mapping for language using stimulation. Recording of gamma activity was employed on ECoG, while each patient was evaluated for baseline language performance. The study was approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

Clinical data are summarized in Table 1. Patient 1 had previously undergone unsuccessful tumor resection of the superior portion of the left pre-central gyrus at

another institution. Patient 2 possessed a solitary tumor in the left superior frontal region. Patient 3 had multiple cortical tubers involving both hemispheres. MRI was normal in patient 4 but FDG-PET scan showed widespread cortical regions with glucose hypometabolism in the left hemisphere.

**Table 1**
**Summary of Clinical Information**

| Patient | Gender | Age (years) | Antiepileptic Medications | Seizure Seimiology | Interictal Spikes on scalp EEG | Ictal onset scalp EEG | Electrode Placement | Seizure onset zones on ECoG | ECoG contacts | Histology |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 16 | CBZ, LEV | Focal Sz w/ sGTC | Diffuse, BiFrontal | N/A | Lt FPT | Lt F | 94 | Tumor |
| 2 | F | 10 | LEV | Focal Sz w/ sGTC | N/A | Lt F | Lt FPT | Lt F | 74 | Tumor |
| 3 | F | 9 | VGB, PHT | Focal Sz | Lt F, Lt T and Rt F | Lt F and Lt T | Lt FPT | Lt F | 117 | Cortical Tubers |
| 4 | F | 7 | OXC, ZNS | Focal Sz w/ sGTC | Lt TPOC | Lt TPO | Lt POTF | Lt T; Lt F | 128 | Gliosis |

F: female. M: male. Lt: left. Rt: right. CBZ: carbamazepine. LEV: levetiracetam. VGB: vigabatrin. PHT: phenytoin. OXC: oxcarbazepine. ZNS: zonisamide. VCI: verbal comprehension index. N/A: not applicable. VIQ: verbal IQ. Sz: seizure. sGTC: secondarily generalized tonic clonic seizures. F: frontal. T: temoral. O: occipital. P: parietal. C: central.

Patient 3 underwent preoperative intracarotid sodium amobarbital procedure (also known as Wada test) as part of her neuropsychological evaluation; left-hemispheric language dominance was proven. Language dominance was assumed to be left-hemispheric in patients 1and 2 due to right-handedness (Knecht et al., 2000a). The assumption of left-hemispheric language dominance in patient 2 was also supported by a prolonged post-ictal aphasia that characterized her seizures. Due to left-handedness and widespread glucose hypometabolism involving the left hemisphere, patient 4 had less certain lateralization of language dominance prior to resective surgery.

*Subdural electrode placement*

For extraoperative video-ECoG recording, platinum grid electrodes (10 mm inter-contact distance; 4 mm diameter; Adtech, Racine, WI, USA) were surgically implanted on the presumed epileptogenic hemisphere. In all patients, electrodes also covered the lower pre- and post-central gyri, posterior inferior frontal region, and lateral temporal

region. Additionally, electrode strips were placed in the inter-hemispheric space to record the ECoG of medial frontal, parietal or occipital regions. One or more additional strips were also placed under the medial temporal region. The total number of electrode contacts ranged from 74 to 128 (Table 1).

*Coregistration of subdural electrodes on individual three-dimensional MRI*

MRI including a T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image was obtained preoperatively. Planar X-ray images (lateral and anteroposterior) were acquired with the subdural electrodes in place for electrode localization on the brain surface; three metallic fiducial markers were placed at anatomically well-defined locations on the patient's head for coregistration of the X-ray image with the MRI. A three-dimensional surface image was created with the location of electrodes as directly defined on the brain surface, as previously described (Muzik et al., 2007; von Stockhausen et al., 1997).

*Extraoperative video-ECoG recording*

Extraoperative video-ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA), which has an input impedance of 200 MΩ, a common mode rejection ratio greater than 110 dB, an A/D conversion of 16 bits, a sampling frequency at 1000 Hz, and the amplifier band pass at 0.08 to 300 Hz. ECoG signals were re-montaged to an average reference, to obtain reference-free topographic maps of spectral measures. Channels contaminated with large interictal epileptiform discharges

or artifacts were excluded from the average reference. Antiepileptic medications were discontinued or reduced during ECoG monitoring until a sufficient number of habitual seizures were captured, and seizure onset zones were visually identified.

*Language mapping using time-frequency analysis of ECoG*

*Auditory Language Task*

All tests necessary for language mapping by measurement of auditory-language-related gamma activity were performed while each patient was awake and comfortably seated on the bed. The patient received a series of 60 custom-made question-and-answer trials, and the patient's baseline performance was evaluated. Provided questions ranged from 1 to 2 s in duration. All questions were read aloud by a neuropsychologist (R.R.) and designed to elicit 1 or 2 word answers with nouns; i.e. Q: “What flies in the sky?” This audible session was recorded using a Digital Voice Recorder (WS-300M, Olympus America Inc, Hauppauge, NY, USA) concurrently with ECoG recording, and the amplified audio waveform was integrated into the Digital ECoG Recording System. Subsequently, the onset of the auditory question as well as the onset of the patient's vocalization of the answer was marked for each question-and-answer session (Fig. 1). Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA) was used to visually and audibly aid in the manual determination of the onset of the patient's vocalization (Fig. 1).

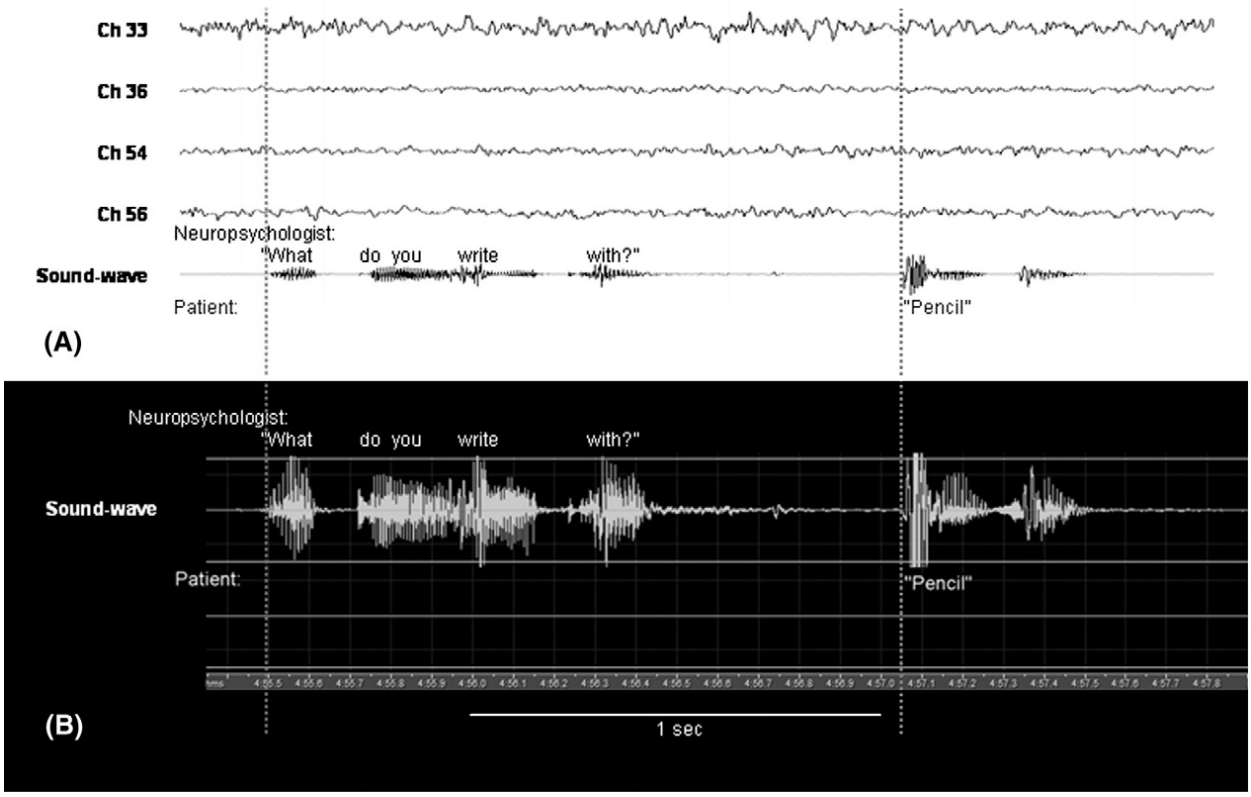


**Figure 1**: **Simultaneous ECoG and Audio Recording.** Simultaneous recording of ECoG and vocal sound waves in patient 1. (A) An example of an ECoG trace suitable for quantitative analysis is shown with band-pass filter cut-offs of 53 and 300 Hz, respectively. Vocal sound waves were simultaneously recorded with ECoG. The time-lock trigger was placed at the onset of the patient's vocalization. (B) Audio sound wave on Cool Edit Pro Software is shown, and this was used to visually and audibly aid in the manual determination of the onset of the patient's vocalization.

*Analysis of gamma activity relative to "the onset of patient's vocalization"*

Data analysis was performed using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany). Language task-related amplitude modulations were evaluated using the trigger point set at the onset of the patient's vocalization. Especially, alteration of gamma (at 50 Hz or above) amplitude (unit: μV) time-locked to the patient's vocalization was assessed; this analytic method was designed to evaluate sequential brain activation associated with comprehension, word retrieval and vocalization (Fig. 2).

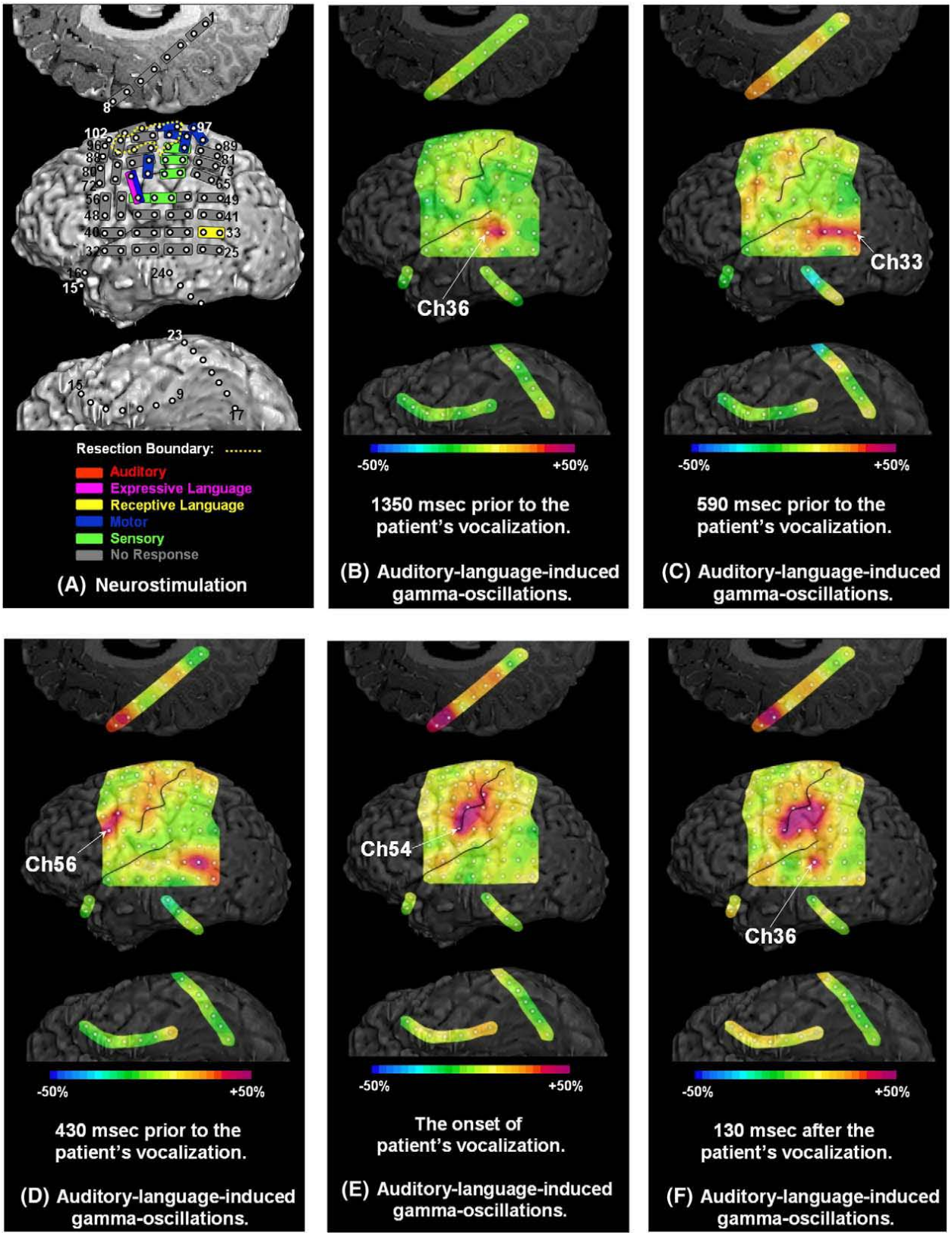


**Figure 2**: **Animation of Language Function on ECoG.** Summary animation time-points showing gamma activity during the auditory naming task. Continued on next page.

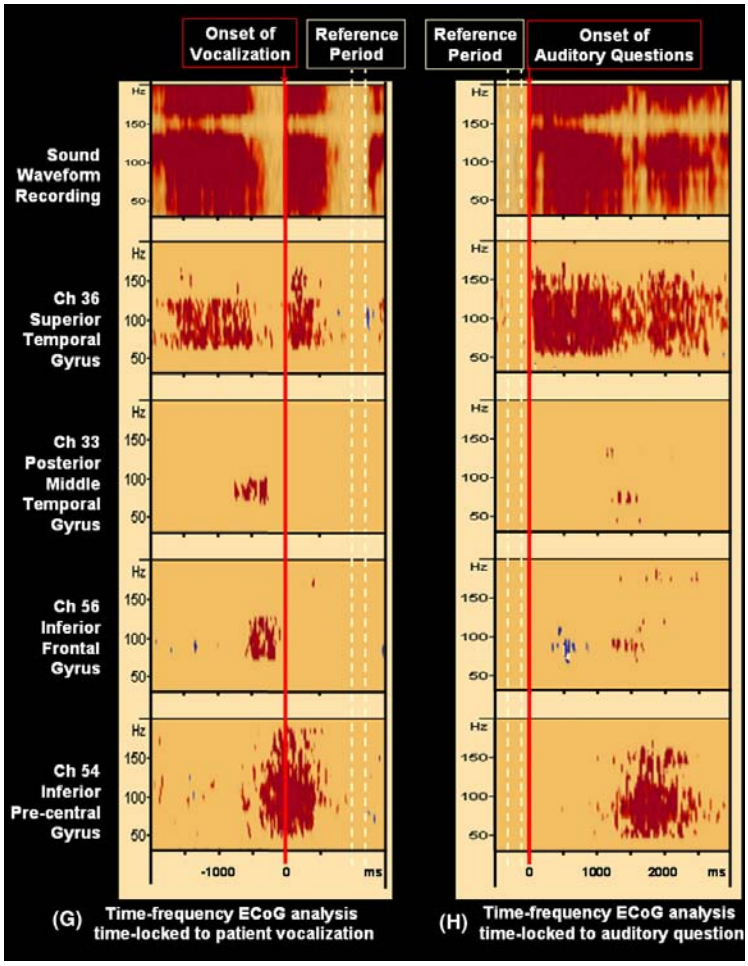


**Figure 2**: Language mapping patient 1. (A) Neurostimulation: Stimulation of electrode pair: Ch 33-34 (yellow box) induced language comprehension deficit; Ch 54-70 (pink–blue box) resulted in pure speech arrest at 6 mA and speech arrest associated with facial movement at 9 mA; Ch 53-54, 52-53, 67-68 (green boxes) resulted in tingling of the mouth and tongue; Ch 75-76, 83-84 (green boxes) resulted in sensory responses involving the right upper extremity; Ch 69-77 (blue box) induced facial movement; and Ch 83-91, 91-92, 90-97, 98-99 (blue boxes) induced motor responses involving the right upper extremity. Surgical resection resulted in no postoperative language deficits. (B–G) ECoG time–frequency analysis time-locked to patient's vocalization: activity proceeded sequentially from left superior temporal gyrus (B), to left middle temporal gyrus (C), to left inferior and superior frontal gyrus (D), to left superior frontal gyrus as well as pre- and post-central gyri at the onset of patient's vocalization (E), and back to left superior temporal gyrus (F). Response-onset-locked (G) and stimulus-onset-locked (H) plots to complement animation slides; full animation with Brown et al., 2008.

The inclusion criteria defining ECoG epochs suitable for this time–frequency analysis included: i) patient's vocalization of the answer must be not longer than 1000 ms in duration; ii) the variability of delay between offset of the question and onset of the patient's vocalization must be within 1000 ms across trials; iii) a period of silence (as a reference period) lasting 200 ms must be available between 1000 and 1400 ms after onset of the patient's vocalization; iv) another period of silence lasting 200 ms must be present immediately prior to the above-defined reference period of 200 ms, in order to minimize the potential effect of lingering self-vocalization-induced amplitude modulation on each reference period; and v) the patient only vocalized a correct answer. The

exclusion criteria included: i) ECoG trace was affected by movement artifacts; ii) ECoG trace was affected by electrographic seizures; and iii) ECoG trace from the left superior temporal gyrus was affected by runs of interictal epileptiform discharges. All ECoG epochs (starting 2000 ms prior to and ending 1400 ms after the trigger) which satisfied all of the inclusion and exclusion criteria were utilized for the time–frequency ECoG analysis described below.

Each suitable ECoG trial was transformed into the time–frequency domain using complex demodulation technique as featured in the BESA software (Fan et al., 2007; Hoechstetter et al., 2004). In that technique, the time–frequency transform was obtained by multiplication of the time–domain signal with a complex exponential, followed by a low-pass finite impulse response (FIR) filter of Gaussian shape. Details on the complex demodulation technique for time-frequency transformation are described elsewhere (Hoechstetter et al., 2004; Papp and Ktonas, 1977). This is equivalent to a wavelet transformation with constant wavelet width across frequencies. As a result of this transformation, the signal was assigned a specific amplitude and phase as a function of frequency and time (relative to the onset of the patient's vocalization). In this study, only the amplitude averaged across all trials, was used for further analysis. Time–frequency transformation was performed for frequencies between 30 and 200-Hz and latencies between −2000 ms and +1400 ms relative to the onset of the patient's vocalization, in steps of 5 Hz and 10 ms. This corresponded to a time–frequency resolution of ±7.1 Hz and ±15.8 ms (50% power drop of the FIR filter).

At each time–frequency bin, we analyzed the percentage change in amplitude (averaged across trials) relative to the mean amplitude in a reference period, defined as

the resting state following patient's vocalization. This parameter is commonly termed “event-related synchronization and desynchronization” (Pfurtscheller, 1977) , whereas a less suggestive terminology is “temporal spectral evolution” (TSE) (Salmelin and Hari, 1994).

To test for statistical significance for each obtained TSE value, two-step statistics was performed using the BESA software: First, statistics based on bootstrapping approach (Davidson and Hinkley, 1999) was applied to obtain an uncorrected p-value at each time-frequency bin. In a second step, correction for multiple testing was performed (each electrode was analyzed at 11,935 time–frequency bins, with TSE values at neighboring bins being partially dependent). A modification of the correction developed by Simes (1986) was used as suggested for time–frequency analysis by Auranen (2002): p-values of one frequency bin and channel were sorted in ascending order ($p_i$, $i$=1, …, N). The maximum index $m$ in the sorted array for which $p_i<\alpha\times i/N$ was determined. All uncorrected $p$-values with $i<m$ were accepted as significant. The corrected significance level $\alpha$ was set to 0.05. This approach is less conservative than the classic Bonferroni correction and is specifically suited for partially dependent multiple testing (Auranen, 2002; Simes, 1986). In all figures, blue indicated a significant decrease of amplitude and red indicated a significant increase in the corresponding time–frequency bin relative to the baseline as obtained by this procedure.

An additional correction for testing in multiple electrodes (the number of subdural electrodes ranged from 74 to 128 across subjects) was employed; TSE values in a given electrode were declared to be statistically significant only if a minimum of 8 voxels in the gamma range were arranged in a continuous array spanning (i) at least 20 Hz in

width and (ii) at least 20 ms in duration. Such correction provides a very small probability of type I error in the determination of cortical activation or deactivation. Task-related changes in gamma activity on intracranial ECoG studies commonly involved wide frequency bands ranging at least 20 Hz in width (Crone et al., 2011; Wu et al., 2011). Several human ECoG studies analyzed event-related gamma activity of 20 Hz width (Crone et al., 1998a; Flinker et al., 2010). An epoch with duration of 20 ms can contain only a single cycle of 50 Hz gamma. We recognize that our definition of significance may potentially underestimate gamma-modulations with a restricted frequency band (less than 20 Hz in width) or those with a short duration (less than 20 ms). Yet, discovery of very short-lasting gamma-augmentation confined to 15 Hz or less in width was not the purpose of this study.

*Analysis of gamma activity relative to "the onset of the auditory question"*

Language task-related amplitude modulations were also evaluated using the trigger point set at the onset of the auditory question, and this analytic method was designed to evaluate brain activation associated with the initiation of the auditory question. Limitation of this analytic method includes a potential temporal overlap between the sounds presented by the neuropsychologist and the sounds produced by the patient. Since the duration of questions was not uniform, the onset of patient's vocalization in a session with short question may begin before the offset of auditory question in another session with a relatively longer question (Fig. 2).

The inclusion criteria defining ECoG epochs suitable for this time–frequency analysis included: i) at least 300 ms of silence occurred before the onset of auditory question;

and ii) the patient was observed to have heard the question—indicated by any relevant response. The same exclusion criteria described above were applied. All 3300 ms ECoG epochs (starting 300 ms prior to and ending 3000 ms after the onset of auditory question) which satisfied all of the inclusion and the exclusion criteria were utilized for the time–frequency ECoG analysis. A reference period of 200 ms was set within the period of silence at 300 to 100 ms prior to the auditory question. Alteration of ECoG amplitude was determined using the statistical approach as described above.

*Language mapping using electrical brain stimulation*

Language mapping by stimulation was performed during extraoperative ECoG recording, using a method similar to those described previously (Haseeb et al., 2007; Sinai et al., 2005). Questions that could not be answered quickly and reliably at the baseline evaluation were eliminated from the protocol used in stimulation mapping. A pulse-train of electrical stimuli was delivered using the Grass S88 constant-current stimulator (Astro-Med, Inc, West Warwick, RI, USA). To minimize stimulation-induced seizure risk, a loading dose of phenytoin was administered intravenously prior to the mapping session (Haseeb et al., 2007). To determine the presence of after-discharges, subdural ECoG and video were recorded continuously during the procedure.

Subdural electrode pairs were stimulated by an electrical pulse-train of 10 s maximum duration using pulses of 300 μs in duration. Initially, stimulus intensity was set to 3 mA and stimulus frequency was set to 50 Hz. Stimulus intensity was increased from 3 to 9 mA in a stepwise manner by 3 mA until a clinical response or after-discharge was observed. During each period of 10 s stimulation, each patient was asked to answer two

brief questions used in the above-mentioned language mapping task. Other tasks such as picture naming, counting and reciting ABC's were also assigned as needed. When the patient failed to answer a question or complete the assigned task during a stimulation period, he/she was asked why he/she failed. Brain regions at which stimulation consistently induced a clinical response were declared eloquent for that function. When after-discharge without an observed clinical response or when neither clinical response nor after-discharge was induced by the maximally intense stimuli, the brain region was declared to have not been proven eloquent. This electrical brain stimulation session required 1 to 2 h of patient time.

*Delineation of ECoG data on three-dimensional MRI*

ECoG data for each electrode channel were exported to the given electrode site on the individual three-dimensional brain surface in two different ways. In order to delineate “when”, “where” and “at what frequency band” significant alteration of ECoG amplitude occurred, time–frequency plot matrices created above were placed onto a three-dimensional MRI at the cortical sites corresponding to their respective subdural electrode positions (Figs. 2 and 3). In order to animate “when”, “where”, and “how many fold” gamma activities were augmented, “gamma amplitude” (defined as the amplitude averaged across 50 to 150 Hz frequency bands and normalized to that of the baseline) was sequentially delineated on the individual three-dimensional MRI (Fig. 2), using a method similar to that previously described (Asano et al., 2005). In short, “gamma amplitude” for each electrode channel at each 10 ms epoch was registered into the SurGe Interpolation Software 1.2 (web site: mujweb.cz/www/SurGe/surgemain.htm),

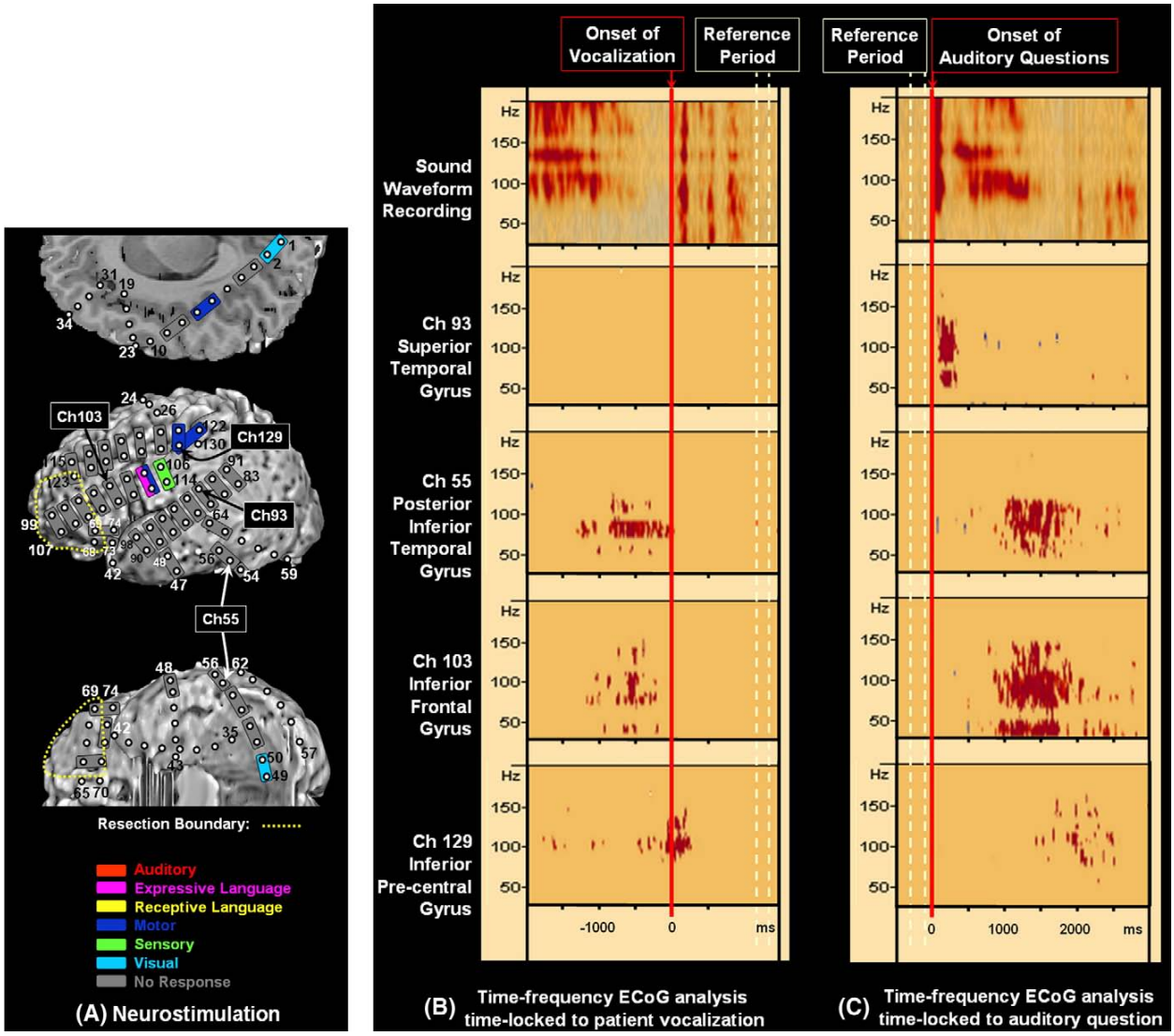


**Figure 3**: **Language Mapping with Stimulation and ECoG - An Intra-Individual Comparison.** Language mapping in patient 3. (A) Neurostimulation: Stimulation of electrode pairs: Ch 1-2 and 49-50 (light-blue boxes) resulted in visual symptoms; Ch 105-113 (pink–blue box) induced speech arrest with throat movement; Ch 106-114 (green box) resulted in tingling of teeth; Ch 121-129 (blue box) resulted in mouth movement; Ch 122-129 (blue box) resulted in thumb movement; Ch 6-7 (blue box) resulted in tonic extension of the bilateral upper extremities. ECoG time–frequency analysis time-locked to patient's vocalization (B) and auditory question (C) for comparison with neurostimulation. Note sites not confirmed by neurostimulation; especially Ch 103.

and interpolated topography maps of “gamma amplitude” at each 10 ms epoch was accurately superimposed to the individual three-dimensional MRI. Finally, all interpolated topography maps were sequentially registered to the Microsoft Windows

Movie Maker 5.1 (Microsoft Corporation, Redmond, WA, USA), and this procedure yielded a movie file showing sequential alteration of gamma activity related to language activity; available as a supplementary video in scientific literature (Brown et al., 2008).

**Table 2**
**Behavioral Data**

| Patient | Gender | Age (years) | Handedness | VCI | VIQ | Wada test | Response time, mean ± SD |
|---|---|---|---|---|---|---|---|
| 1 | M | 16 | Right | 81 | N/A | N/A | 529 ± 134 |
| 2 | F | 10 | Right | 85 | N/A | N/A | 661 ± 156 |
| 3 | F | 9 | Right | 99 | N/A | Left Language Dominance | 669 ± 217 |
| 4 | F | 7 | Left | N/A | 75 | N/A | 942 ± 275 |

F: female. M: male. VCI: Verbal Comprehension Index. VIQ: Verbal Intelligence Quotient. N/A: Not Applicable. SD: Standard Deviation. The presented data include: the mean and standard deviation or response latencies (the interval between the offset of auditory question and the onset of patient's vocalization; unit: ms) derived from the trials included into the ECoG analysis time-locked to patient's vocalization.

## *Results*

### *Gamma activity time-locked to patient's vocalization*

Behavioral data are presented in Table 2. Three (patients 1–3) out of four patients satisfactorily completed the language task. A total of 42, 44, and 40 trials, respectively, were considered suitable and included for time–frequency analysis time-locked to the onset of patient's vocalization. About one-third of the epochs failed to be included, mostly because vocalization of the answer lasted longer than 1 s, the response was much delayed compared to the others, the answer was not correct, and the presumed reference period of silence was affected by some forms of noise. Conversely, the youngest child with attention deficits (patient 4) was highly uncooperative during the question-and-answer session, and only six ECoG epochs were found to be suitable for the analysis. We recognized that patient 4 more readily answered questions relating to sleep and animals, whereas questions concerning airplanes, hospitals, or everyday objects were of little interest and were often not answered. This question-and-answer session required 10 to 20 min of patient time. Data analysis required up to 4 h of

unmanned computing time. Once the statistical data were processed, a quick review revealed regions of important language function.

**Table 3**
**Spatial, temporal, and frequency characteristics of language-related gamma-augmentation**

| Patient | Number of trials included | STG | MTG and ITG | IFG | SFG and Cingulate Gyrus | Medial Temporal Lobe | Pre - and Post-Central Gyri |
|---|---|---|---|---|---|---|---|
| *(A) Spatial, temporal, and frequency characteristics of gamma-augmentation relative to "the onset of patient's vocalization"* | | | | | | | |
| 1 | 42 | 3 sites; 65 to 165 Hz; -1750 to -320 ms and +70 to +520 ms | 2 sites; 70 to 100 Hz; -740 to -280 ms | 2 sites; 75 to 125 Hz; -510 to -160 ms | 3 sites; 55 to 155 Hz; -700 to +500 ms | 1 site; 90 to 110 Hz; -70 to -20 ms | 15 sites; 50 to 185 Hz; -470 to +500 ms |
| 2 | 44 | 2 sites; 75 to 110 Hz; -1580 to -720 ms and -20 to +700 ms | Not covered | 2 sites; 40 to 105 Hz; -570 to -60 ms | 2 sitess; 65 to 100 Hz; -610 to -400 ms | 1 site; 80 to 100 Hz; -510 to -280 ms | 7 sites; 65 to 190 Hz; -550 to +630 ms |
| 3 | 40 | 0 sites | 1 site; 75 to 125 Hz; -1220 to -150 ms | 2 sites; 40 to 140 Hz; -590 to -150 ms | 2 sites; 65 to 115 Hz; -980 to -80 ms | 0 sites | 2 sites; 70 to 145 Hz; -210 to +350 ms |
| 4 | 6 | 0 sites | 0 sites | 0 sites | 0 sites | 0 sites | 0 sites |
| *(B) Spatial, temporal, and frequency characteristics of gamma-augmentation relative to "the onset of auditory question"* | | | | | | | |
| 1 | 51 | 8 sites; 55 to 165 Hz; +30 to +2900 ms | 1 site; 65 to 105 Hz; +1260 to +1770 ms | 0 sites | 3 sites; 60 to 150 Hz; +1050 to +2500 ms | 0 sites | 10 sites; 50 to 170 Hz; +990 to +2480 ms |
| 2 | 38 | 3 sites; 65 to 110 Hz; +90 to +960 ms and +1510 to +2800 ms | Not covered | 0 sites | 1 site; 75 to 130 Hz; +1000 to +1360 ms | 0 sites | 2 sites; 70 to 190 Hz; +1410 to +2500 ms |
| 3 | 56 | 3 sites; 55 to 140 Hz; +70 to +1970 ms | 3 sites; 50 to 120 Hz; +1020 to +1830 ms | 2 sites; 35 to 145 Hz; +910 to +1920 ms | 3 sites; 50 to 150 Hz; +910 to +2020 ms | 1 site; 70 to 110 Hz; +1310 to +1960 ms | 4 sites; 65 to 160 Hz; +1030 to +2900 ms |
| 4 | 28 | 1 site; 75 to 100 Hz; +320 to +1210 ms | 0 sites | 0 sites | 0 sites | 0 sites | 0 sites |

(A) Gamma-augmentation relative to the onset of the patient's vocalization, and (B) Gamma-augmentation relative to "the onset of the auditory question." The presented data include: the number of sites showing significant gamma-augmentation in a continuous array spanning at least 20 Hz in width and at least 20 ms in duration as well as the frequency range and latency of such gamma-augmentation. STG: Superior Temporal Gyrus. MTG: Middle Temporal Gyrus. ITG: Inferior Temporal Gyrus. IFG: Inferior Frontal Gyrus. SFG: Superior Frontal Gyrus.

Spatial and temporal patterns of amplitude modulations are described in Figs. 2 and 3 and Table 3 in detail; a substantial inter-subject variability in the spatial distribution of language-induced gamma-augmentation was noted. In short, cortical activation mostly presented as augmented gamma activity at 50 to 150 Hz and sequentially involved: i) the posterior superior temporal gyrus when listening to the question, ii) the posterior inferior-and-middle temporal gyri, the inferior frontal gyrus, the medial superior frontal region and the medial temporal lobe structure in the time interval between question completion and the patient's vocalization, iii) the pre- and post-central gyri immediately

preceding and during the patient's vocalization and iv) the posterior superior temporal gyrus following the patient's vocalization. No significant cortical activation was noted in patient 4, probably due to lack of a sufficient number of trials included into the analysis.

*Gamma activity time-locked to auditory questions*

Time–frequency ECoG analysis time-locked to the onset of auditory question was satisfactorily performed for all four patients, and a total of 51, 38, 56, and 28 trials, respectively, were considered to be suitable and included for the analysis. The remaining trials were excluded from the analysis due to the same reasons described above. Although patient 4 frequently failed to provide correct answers, this child appeared to listen to many questions.

Spatial and temporal patterns of amplitude modulations are described in Figs. 2 and 3 and Table 3 in detail. In short, cortical activation involved the posterior superior temporal gyrus when listening to the question in all patients. Further cortical activation was not noted in patient 4 since she failed to provide correct answers in most trials. In the remaining three patients, subsequent cortical activation involved the brain regions as described in Table 3.

*Relationship between language areas suggested by ECoG and stimulation*

The spatial relationship between the eloquent cortices suggested by ECoG amplitude analyses and stimulation is described in Figs. 2 and 3 in detail. In short, the language-related cortices suggested by stimulation showed evidence of cortical

activation on the above-mentioned ECoG analyses. The size of language-related cortices suggested by ECoG analyses was larger than that of stimulation.

Among six electrode pairs of which stimulation revealed underlying language functions (1 pair: auditory response; 1 pair: receptive-language response; and 4 pairs: expressive-language response), five pairs included at least an electrode showing language event-related cortical activation on ECoG analyses. The remaining pair was located between two electrodes both showing cortical activation.

Among 11 electrode pairs of which stimulation revealed underlying mouth–throat sensory–motor functions, nine pairs included at least an electrode showing cortical activation on the above-mentioned ECoG analysis. Neither electrode pair of which stimulation resulted in teeth tingling showed cortical activation on ECoG analyses. An electrode pair, of which stimulation resulted in lip movement, was not satisfactorily assessed by the ECoG analysis time-locked to patient's vocalization, since patient 4 failed to cooperate to the language tasks as described above.

The spatial relationship between the presumed language areas and the extent of cortical resection is shown in Figs. 2 and 3. None of the children developed apparent language deficits postoperatively. Following resective surgery, patients 1–3 have been seizure-free, while patient 4 experienced two complex partial seizures (the mean follow-up: 6 months). As expected preoperatively, patient 1 developed a slight worsening of hemiparesis in the right-sided upper extremity and patient 4 developed a right-sided hemianopsia.

## *Discussion*

In the present study of children with uncontrolled focal epilepsy, measurement of event-related gamma activity delineated not only “where” but also “how” the brain cortices participated in language activity with high temporal and spatial resolution. *In vivo* animation of task-related gamma activity on an individual three-dimensional MRI surface image is a novel technique which increases our understanding of the cortical pathways and activation patterns related to auditory language activity. Localization of the presumed language-related cortices suggested by the ECoG amplitude analyses was concordant with the generally accepted functional brain map derived from a number of previous studies using other diagnostic modalities. The size of language-related cortices suggested by the ECoG amplitude analyses was generally larger than that by stimulation in the present study.

### *Successive cortical activations involving the left temporal neocortices*

The ECoG amplitude analyses in the present study revealed successive cortical activations involving two distinct temporal neocortical areas. Cortical activation initially involved the superior temporal gyrus and such cortical activation was present during auditory questions. Cortical activation subsequently involved the posterior part of middle or inferior temporal gyri. The observed pattern of cortical activation is consistent with the results in previous human studies. An intraoperative stimulation study in 12 adults with brain tumors showed that stimulation of the posterior inferior temporal region temporally elicited semantic paraphasia (Mandonnet et al., 2007). An auditory evoked potential study of healthy adults using object discrimination tasks revealed that an initial cortical

potential involved the posterior part of the left superior temporal gyrus 70 ms after stimulus onset and subsequently involved the lateral aspect of the inferior temporal gyrus 200 to 250 ms after stimulus onset (Murray et al., 2006). A study of adults with focal epilepsy using extraoperative ECoG recording demonstrated that gamma-augmentation (80 to 100 Hz) was induced by auditory tones in the left superior temporal gyrus (Crone et al., 2001a). Another study of adults with focal epilepsy using intraoperative ECoG recording also showed that auditory tones were associated with gamma-augmentation in the left superior temporal gyrus and that the frequency band of maximum response could appear anywhere from 70 to 160 Hz (often around 100 Hz) (Edwards et al., 2005). A functional MRI study in healthy adults showed that auditory semantic words stimuli induced increased blood oxygen level-dependent (BOLD) signals in the left posterior superior temporal gyrus 4 s after auditory stimuli and subsequently in the posterior part of the middle and inferior temporal gyri 10 to 12 s after the auditory stimuli (Humphries et al., 2007). Thus, we speculate that initial cortical activation in the superior temporal gyrus seen in the present study represented the auditory processing, whereas the secondary activation in the posterior middle and inferior temporal gyri represented the processing of semantic comprehension. Based on the task given in the present study, however, we are not able to determine whether the initial cortical activation in the superior temporal gyrus was specifically responsible for acoustic perception, linguistic function or both of those. Further studies using a contrasting task may address this issue.

*Successive cortical activations in the left supra-sylvian neocortices*

The ECoG amplitude analyses in the present study revealed successive cortical activations involving three supra-sylvian neocortices. Cortical activation involved the inferior frontal gyrus and the medial superior frontal gyrus; such frontal activation occurred prior to activation in the pre- and post-central gyri and subsided with the onset of vocalization. Immediately prior to and during vocalization, cortical activation involved the pre- and post-central gyri. The observed pattern of such successive cortical activations is consistent with observations from previous studies described below.

It has been shown that adults with focal lesions in the left inferior frontal gyrus often exhibit impaired semantically appropriate word generation (Thompson-Schill et al., 1998). A study of healthy adults showed that repetitive transcranial magnetic stimulation of the left inferior frontal gyrus temporarily blocked both capacities of speaking aloud and internally (Aziz-Zadeh et al., 2005). Studies in adults with focal epilepsy showed that electrical stimulation of the inferior frontal gyrus induced speech arrest as well as evoked potentials in the orofacial representational area of primary motor cortex (Greenlee et al., 2004; Matsumoto et al., 2004). Studies using functional MRI suggested that syntactic and semantic processing tasks induced increased BOLD signals in the inferior frontal gyrus (Embick et al., 2000; Roskies et al., 2001). Thus, we speculate that cortical activation in the inferior frontal gyrus seen in the present study represented the processing of semantically appropriate word generation.

It has been suggested that the medial superior frontal cortices (including the supplementary motor area, the pre-supplementary motor area, and the cingulate gyrus) play a role in voluntary control over the initiation and suppression of vocal utterance,

whereas the pre- and post-central gyri carry out voluntary control over the acoustic structure of vocalizations (Jürgens, 2002). A study in monkeys showed that stimulation of the cingulate cortex resulted in vocalization (Jurgens and Pratt, 1979). A study of adults with focal epilepsy showed that stimulation of the pre-supplementary motor area induced various forms of clinical responses including vocalization, speech arrest and slowing of speech (Fried et al., 1991). It has also been reported that cerebral infarction or surgical resection involving the left medial superior frontal gyrus resulted in temporary mutism, defined as a state where a patient is conscious but unable to talk (Crutchfield et al., 1994; Masdeu et al., 1978). A study of adults with focal epilepsy showed that movement-related potentials were noted in the medial superior frontal gyrus 300 ms prior to voluntary orofacial movements (Ikeda et al., 1992). Functional MRI studies in healthy adults showed that overt verbal fluency tasks induced increased BOLD signals not only in the left inferior frontal gyrus but also in the medial superior frontal gyrus (Abrahams et al., 2003). Thus, we speculate that cortical activation in the medial superior frontal gyrus seen in the present study represented the preparation of fluent vocalization, and that activation in the pre- and post-central gyri represented the active process of voluntary control over the acoustic structure of vocalizations.

*Relationship between language areas suggested by ECoG and stimulation*

In the present study, the size of language areas suggested by gamma-augmentation was larger than that by stimulation, and this observation is in contrast to the observation in a previous study (Sinai et al., 2005) that the size of language areas suggested by stimulation was larger than that by analysis of gamma activity. This discrepancy in the

results of two studies may be partly attributed to differences in the study population. The present study included only children with focal epilepsy, whereas the study by Sinai et al. (2005) included adults and mid-adolescents. Previous studies of young patients with focal epilepsy demonstrated a positive correlation between the age of patients and the number of sites where stimulation produced naming errors in language mapping (Ojemann et al., 2003; Schevon et al., 2007). Difference in methodologies between the present study and the study by Sinai et al. (2005) also includes the approach to determine significant gamma-augmentation in each electrode site. Our ECoG analysis included a frequency range from 30 to 200 Hz; significant activations across this spectrum were determined using corrected p-values spanning at least 20 Hz frequency bands and 20 ms in duration. On the other hand, the study by Sinai et al. (2005) evaluated sequential changes of ECoG powers at an 80 to 100 Hz band using 100 ms epochs. Finally, it should be also noted that auditory-naming tasks were given in the present study, whereas picture naming tasks were given in the study by Sinai et al. (2005). Evidence suggests auditory tasks to perform better than visual tasks in mapping language functions by naming (Cervenka et al., 2013).

*Methodological limitations in the present study*

Few investigators have reported language mapping using ECoG amplitude modulations in children with uncontrolled focal epilepsy. Potential methodological limitations of such analysis should be discussed. First, data collection for the purpose of functional cortical mapping for language by ECoG required the performance of many simple language tasks to enable statistical analysis. Ideal patient performance involves

maintaining a consistent answer delay following the provided questions as well as a period of silence after each answer. This requires a certain level of verbal intelligence and motivation to cooperate that may be hard to find in very young children; i.e. patient 4 of the present study, a 7-year-old girl, prevented ECoG analysis time-locked to patient vocalization by exhibiting uncooperative behavior.

Significant cortical activation (or deactivation) was determined using corrected p-values. This indicates that cortical activation (or deactivation) could fail to reach significance due to insufficient number of suitable trials. Thus, a number of question-and-answer sessions enjoyable by young children should be prepared to minimize the risk of such a type II error in statistical tests. It should be also noted that cortical activation (or deactivation) could fail to reach significance if temporal variability across events of interest is large. In order to minimize such a temporal variability of events, we analyzed the ECoG data using two distinct time-lock triggers initially set at the onset of patient's vocalization and subsequently set at the onset of auditory questions (Fig. 2).

In the ECoG analysis time-locked to patient's vocalization, a silent period of 200 ms between an answer and the next question was utilized as a reference period; each 200 ms reference period had twenty time-frequency sampling points for each frequency band. We recognize that usage of a longer reference period would have further increased the statistical power to determine significant cortical activation as well as deactivation. Yet, presence of various types of external sounds (such as coughing and next auditory questions) prevented a reference period from expanding longer than 200 ms in the present study. We recognize that the selection of reference period could have influenced the results in the present study, particularly if there was a lingering brain

activation following the offset of the patient's vocalization (Trautner et al., 2006). In the ECoG analysis time-locked to auditory question, on the other hand, we cannot rule out the possibility that expectancy or readiness-related brain activation may have been present during the reference period of 200 ms.

It should be noted that focal alpha- and beta-attenuation (also known as alpha- and beta-desynchronization) have been previously reported as evidence of focal cortical activation (Crone et al., 1998b; Hirata et al., 2004; Miller et al., 2007a; Pfurtscheller, 1977). ECoG oscillations slower than 30 Hz were not evaluated in the present study, and language-induced alpha- and beta-attenuation could be the subject of future studies.

One of the major limitations of extraoperative ECoG recordings is sampling error. ECoG analysis was limited to the brain region where subdural electrodes were placed. In the present study, subdural electrodes were placed only in the presumed epileptogenic hemisphere; we were not able to evaluate cortical activation in the other hemisphere. Patient 4 had very little language-related gamma activity in the left superior temporal gyrus and no apparent language deficits following the surgical resection involving the left temporal–occipital–parietal region as well as a part of the middle inferior frontal gyri; we assume patient 4 had right-sided language dominance. Yet, we were not able to prove language task-related cortical activation in the right hemisphere, since subdural electrode placement on the right hemisphere was not indicated in this patient.

Antiepileptic drugs may affect the findings of cortical mapping using stimulation as well as measurement of gamma activity on ECoG. In the present study, phenytoin was

loaded intravenously prior to mapping, to minimize stimulation-induced seizure risk. A previous study of healthy volunteers demonstrated phenytoin to elevate motor thresholds to transcranial magnetic stimulation without effect on motor-evoked potential amplitudes, silent period duration, or intracortical excitability (Chen et al., 1997).

*Synthesis*

This first, preliminary study in the mapping of language function utilizing an auditory naming task with ECoG recording serves as a necessary step in the validation of language-related ECoG crucial to the remainder of the studies presented in this dissertation. Since this study, teams within and outside of our laboratory have provided further evidence that analysis of gamma modulations during an auditory naming task is an effective and robust methodology for language mapping. Modifications to our methodology include expanded questions, increased reference period duration from 200 to 400 ms, increased temporal distance between the reference period and question onset from 100 to 200 ms, and recorded playback rather than live delivery for greater stimulus control. Our team has published two such studies since (Kojima et al., 2012; Kojima et al., 2013b). One of which is the largest study of language-related ECoG findings to date; including data from 77 patients (Kojima et al., 2013b). We found bilateral involvement of superior temporal gyri as well as the Rolandic regions. Left dominant involvement was observed in middle temporal, medial temporal, medial frontal, inferior frontal (including Broca's area), and dorsolateral-premotor regions of the frontal lobe. We were able to detect an age-related increase in activity of dorsolateral-premotor and inferior frontal regions across patients performing our auditory naming

task with ECoG. Most importantly, independent from the results of electrical brain stimulation, we demonstrated that language mapping utilizing our auditory naming task during ECoG recording was capable of predicting post-operative deficit; i.e., the number of active sites, defined by analysis of ECoG signals, detected in the superior temporal, inferior frontal, dorsolateral-premotor, and inferior Rolandic regions of the left hemisphere predicted the incidence of postoperative language deficit requiring speech therapy (Kojima et al., 2013b). Indeed, we have been able to report on a case of an 8 year old male in whom resection of cortical tissue defined by ECoG mapping, but not by electrical brain stimulation, to be involved in language function led to a post-operative language deficit (Kojima et al., 2012). A team outside of our laboratory published a similar study using a task similar to ours, which they refer to as 'auditory descriptive naming', has demonstrated similar results (Cervenka et al., 2013). Across 16 patients, they detected four patients developing post-operative language deficits following the resection of sites defined as involved in language function by ECoG analysis, but not detected by electrical brain stimulation (Cervenka et al., 2013). Their team as well as ours has demonstrated auditory naming tasks to be more effective for language mapping using ECoG compared to visual naming tasks (Cervenka et al., 2013; Kojima et al., 2013a); explaining the negative results of investigators who had previously attempted language mapping utilizing ECoG to little success (Sinai et al., 2005). In all, data garnered on the use of language mapping utilizing ECoG with an auditory descriptive naming task, following our original study, present validating evidence that such a modality can provide both clinical and scientific data that may aid in the treatment of surgical patients as well as improving our understanding of the brain itself.

# CHAPTER 3: Dissecting Frontal and Temporal Language Functions on ECoG

## Section 3.1: Determining Language-Specific Temporal Lobe Auditory Functions

### Subsection 3.1A: Failed Validation of the Reverse Speech Control Task

*This section is modified from the original publication in the scientific journal NeuroImage - (Brown et al., 2012b)*

*Introduction*

Uniquely developed in humans (McNelly et al., 2009), understanding the cortical processes of language requires the direct study of human participants. Researchers have employed a broadening array of non-invasive modalities to study the complex structure and function of auditory language; including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), near-infrared spectroscopy (NIRS), and magnetoencephalography (MEG). Functional study generally relies upon performance of a well designed task to elicit cortical activity. Often, a control task is necessary to contrast with the primary task in order to isolate particular realms of function. However, validation of a particular task's design and hypothetical effect is not simple, partly due to a lack of appropriate animal models of human language. Intuition about language is frequently the only guide in developing new tasks for non-invasive language study. Here, we use task-related electrocorticography (ECoG) as an external validating modality of the results obtained from non-invasive neuroimaging.

Intracranial ECoG, recorded in patients with focal epilepsy and/or brain tumor prior to surgical resection of diseased tissue, is a unique functional brain mapping tool. Based on the same principles as scalp EEG, the measure of interest in task-related

ECoG mapping is the degree of augmentation of high frequency activity, compared to a baseline reference (Pfurtscheller and Lopes da Silva, 1999). The signals detected and routinely analyzed by ECoG methods fall within a class of electrophysiological activities known as local field potentials (LFP), which have been shown to correlate well with the blood-oxygen-level-dependent (BOLD) signal detected by fMRI (Logothetis, 2003). Indeed, task-related augmentation of broadband gamma-range signals in excess of 50 Hz has not only been shown to accurately localize cortical function (Crone et al., 2011; Jerbi et al., 2009; Miller et al., 2008) but has also been repeatedly shown to best predict the BOLD response, accounting for over 20% of BOLD signal variability (Conner et al., 2011; Hermes et al., 2011). Low frequency alpha/beta activities are very minor predictors of the BOLD response (Hermes et al., 2011) that may describe electrocortical phenomena that are independent of that revealed by high frequency gamma components (Cardin et al., 2009; Conner et al., 2011; Engel and Fries, 2010). We utilize an auditory naming task to elicit high frequency gamma (50 to 150 Hz) activity in cerebral regions mediating language (Brown et al., 2008; Koga et al., 2011; Wu et al., 2011). Task-related ECoG may be useful in externally validating the language findings of non-invasive methods.

We are interested in contrasting our auditory naming task with a control task in order to segregate cortical gamma activity specific to auditory language from those attributable to a more broad involvement in auditory perception. The literature from functional studies points to a commonly used reverse speech control task (Gherri and Eimer, 2011; Moore-Parks et al., 2010; Perani et al., 1996; Redcay and Courchesne, 2008; Redcay et al., 2008; Sato et al., 2011). Generally, a reverse speech control task

is a replica of the primary forward speech task that has been reversed in time. Such a control task is said to share auditory elements of the primary task (e.g. spectral details, intensity) but largely lack the intelligibility of language (e.g. syntax, semantics).

Previous fMRI studies report that forward speech induces stronger BOLD responses in bilateral superior temporal regions compared to reverse speech (Moore-Parks et al., 2010; Redcay and Courchesne, 2008; Redcay et al., 2008). This phenomenon has been observed across a wide age range, including children. These findings suggest that reverse speech may consistently control for non-language auditory activity that might otherwise confound temporal lobe activity related to the primary language task.

The aim of the present study is to externally validate the results of non-invasive language mapping modalities using task-related ECoG. Here, we test the hypothesis that forward speech will elicit larger augmentation of gamma-activity compared to reverse speech in bilateral superior temporal regions. Analysis of the effects upon low frequency activity is included as a secondary measure.

## *Methods*

### *Study Patients*

Patients were selected by using the following inclusion criteria: (i) a history of intractable focal epilepsy scheduled for extraoperative subdural ECoG recording as part of presurgical evaluation at Children's Hospital of Michigan or Harper University Hospital, Detroit, between December 2010 and July 2011, (ii) age of 8 years or older, and (iii) measurement of ECoG amplitude augmentations driven by a language task described in the 'Auditory naming task' section below. Exclusion criteria consisted of: (i)

presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and sylvian fissure, (ii) history of hearing impairment, (iii) right language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left-handedness when Wada test results are not available (Knecht et al., 2000a), (iv) multiple seizure foci involving both hemispheres, (v) Verbal Comprehension Index (VCI) or Verbal Intelligence Quotient (VIQ) less than 70, (vi) inability to complete the language task described in the 'Auditory naming task' section below due to lack of adequate vocabulary or cooperation, and (vii) history of previous neurological surgery. We studied a consecutive series of eight patients satisfying all criteria (age range: 12–44 years; four females; Table 4). This study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from all patients or their legal parent or guardian. Subdural platinum grid electrode (10 mm inter-contact distance; 4 mm diameter; Adtech, Racine, WI, USA) placement was as described previously by our team (Wu et al., 2011). Extraoperative video–ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc., Foothill Ranch, CA, USA) at a sampling frequency of 1000 Hz as previously described (Wu et al., 2011). Total electrode contact number ranged from 100 to 120 (Table 4).

*Coregistration of electrodes on individual three-dimensional MRI*

MRI, including a volumetric-T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image of the entire head, was obtained

preoperatively using a previously described protocol (Nagasawa et al., 2010a). Planar X-ray images (lateral and antero-posterior) were acquired with subdural electrodes in place for localization on the brain surface; three metallic fiducial markers at anatomically well-defined locations aided coregistration with MRI. A three-dimensional MRI brain surface image was created with electrode sites delineated (Alkonyi et al., 2009a; Muzik et al., 2007; von Stockhausen et al., 1997). Accuracy was confirmed by intraoperative digital photographs showing *in situ* electrode locations (Asano et al., 2005; Nagasawa et al., 2010a; Wu et al., 2011).

**Table 4**
**Summary of Clinical Information**

| Pt | Gdr | Age at surgery (years) | Dom. Hand | Age at epilepsy onset | Antiepileptic medications | PSI† | VCI† | VIQ† | Schooling | Wada test† | Sz type | ECoG electrode coverage | Seizure onset zone | ECoG contacts (total) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | M | 17 | Rt | 0 | TPM, OXC | 56 | 71 | N/A | *Below ave., normal 11th grade* | Lt | Focal sz | Rt FPTO | Rt PTO | 108 | Atrophy and gliosis |
| 6 | F | 15 | Rt | 13 | LEV | N/A | N/A | N/A | Above ave., normal 10th grade | N/A | Focal sz w/ sGTC | Lt FPTO | Lt Anterior T | 100 | Low grade tumor and gliosis |
| 7 | M | 44 | Both | 26 | LEV, OXC | N/A | N/A | N/A | Incomplete graduate school | Lt | Focal sz w/ sGTC | Rt FPTO | Rt PO | 108 | Atrophy and gliosis |
| 8 | F | 37 | Rt | 19 | LAM, LAC | N/A | N/A | 72 | Completed high school | Lt | Focal sz w/ sGTC | Lt FPTO | Lt Mesial T | 112 | Mild gliosis |
| 9 | F | 14 | Rt | 13 | LEV, OXC, LAC | 100 | 124 | N/A | Above ave., normal 9th grade | N/A | Focal sz w/ sGTC | Lt FPTO | Lt Lateral P | 120 | Low grade tumor |
| 10 | M | 20 | Rt | 14 | LAC, CBZ | N/A | N/A | 82 | College student | Lt | Focal sz w/ sGTC | Lt FPTO | Lt Mesial T | 100 | Mild gliosis |
| 11 | F | 14 | Rt | 7 | LAM | 100 | 79 | N/A | Normal 8th grade | N/A | Focal sz w/ sGTC | Rt FPTO | Rt Mesial T | 104 | Neuronal loss and gliosis |
| 12 | M | 12 | Rt | 3 | VAL, OXC, LAC | 80 | 83 | N/A | Normal 6th grade | Lt | Focal sz | Lt FPTO | Lt anterior and inferior T | 116 | Mild gliosis |

Pt: patient. Gdr: gender. Ave: average. LEV: levetiracetam. LAM: lamotrigine. LAC: lacosamide. CBZ: carbamazepine. OXC: oxcarbazepine. TPM: topiramate. VAL: valproate. Rt: right. Lt: left. Sz: seizure. sGTC: secondarily generalized tonic-clonic sz. F: frontal. T: temporal. O: occipital. P: parietal. † PSI: processing speed index. VCI: verbal comprehension index. VIQ: verbal intelligence quotient. Neuropsychological testing was performed based on clinical necessity. Wada testing (i.e. intracarotid sodium amobarbital procedure) results are provided to indentify the language-dominant hemisphere. Due to use of an auditory language task, we include the measures VIQ and VCI, when available. We have also included PSI, when available, which has been suggested to correlate with the degree of dysfunction of cortical auditory information processing in patients with intractable epilepsy (Korostenskaja et al, 2010).

*Auditory Naming Task*

Language mapping by measurement of auditory naming-related gamma activity was performed using an auditory naming task similar to that previously reported (Brown et al., 2008); see Chapter 2. None of the patients had a seizure within two hours prior to or during task performance. While awake and comfortably seated on a bed in a room with unwanted noises minimized, patients received 85 question-and-answer trials. Question stimuli ranged from 1- to 2.5-s in duration. All questions were delivered via playback of an audio recording of the author's (E.C.B.) voice using Presentation version 9.81 software (Neurobehavioral Systems Inc., Albany, CA, USA) and were designed to elicit 1 or 2 word answers with nouns; e.g. “What flies in the sky?” In this study, we also delivered reverse speech trials during the task. To generate these reverse speech trials, a random set of 30 stimulus questions was selected. The audio recordings of these forward speech trials were duplicated and then reversed in time with Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA). See Table 5 for details on presentation order for individual patients. The audible session was recorded and integrated with ECoG as previously described (Brown et al., 2008; Wu et al., 2011). Subsequently, the onset and offset of auditory stimuli as well as the onset of the patient's vocalization of the response were marked for each trial. Cool Edit Pro was used to visually and audibly aid in the manual determination of these time-points. The response time was defined as the period between offset of stimulus presentation and onset of the respective overt response. Patients were instructed to answer “I don't know” when they did not know the answer to or did not understand a stimulus.

*Evaluation of ECoG amplitude changes*

Each ECoG trace was transformed into the time-frequency domain, and we determined 'when' and 'where' gamma activity was augmented. The time-frequency analysis used in the present study was previously validated (Brown et al., 2008; Hoechstetter et al., 2004; Nagasawa et al., 2010a; Wu et al., 2011). In short, the primary measures of interest were the percent change in amplitude of gamma activity relative to that during the reference period (i.e.: the resting baseline) as well as statistical significance of task-related augmentation of gamma activity. The details of analytic methods are described below. The secondary measures include evaluation of low frequency alpha- and beta-oscillations.

**Table 5**
**Stimulus Order and Behavioral Results**

| Patient | Stimulus order | Response time: forward mean (95% CI) | Response time: reverse mean (95% CI) | Correct responses %forward (%reverse) |
|---|---|---|---|---|
| 5 | 30 forward and 30 reverse stimuli pseudorandomly presented with 55 other forward stimuli | 1339 (996-1681) ms | 909 (771-1047) ms | 97% (97%) |
| 6 | Same as patient 5 | 1573 (1177-1969) ms | 1257 (1136-1378) ms | 100% (100%) |
| 7 | Same as patient 5 | 1831 (1402-2259) ms[a] | 984 (863-1105) ms[a] | 100% (97%) |
| 8 | Same as patient 5 | 1878 (1268-2489) ms | 1104 (937-1271) ms | 90% (97%) |
| 9 | Same as patient 5 | 1253 (1131-1375) ms[a] | 1057 (1014-1100) ms[a] | 100% (100%) |
| 10 | 30 forward and 30 reverse stimuli pseudorandomly presented independent of other stimuli | 1000 (870-1130) ms | 832 (721-942) ms | 100% (100%) |
| 11 | Similar to pt 10 except different stimulus list | 2760 (1537-3982) ms | 1833 (640-3026) ms | 90% (100%) |
| 12 | Similar to pt 11 except different stimulus order | 2104 (1608-2600) ms | 1430 (1056-1803) ms | 90% (93%) |
| Grand average | N/A | 1707 (1509-1905) ms[a] | 1173 (1029-1336) ms[a] | 95.9% (98%) |

All response times averaged from stimulus onset analysis trials. pt = patient
[a] t-Test indicates difference between forward and reverse speech trials; α = 0.05.

*Analysis of ECoG amplitude changes relative to stimulus onset*

A maximum of 60 trials were considered for analysis: 30 reverse speech trials and the 30 corresponding forward speech trials. Reverse and forward speech trial sets were analyzed separately. The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) a period of silence serving as a reference period of 400 ms duration was available between 600 and 200 ms prior to the onset of stimulus

presentation. The exclusion criteria included: (i) ECoG trace was affected by movement artifacts, (ii) ECoG trace was affected by electrographic seizures, (iii) the corresponding forward or reverse speech trial was excluded due to failure to satisfy criteria, and (iv) ECoG trace from the superior temporal gyrus was affected by runs of interictal epileptiform discharges lasting 3 s or longer.

Time-frequency analysis was performed using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany). Each suitable ECoG trial was transformed into the time-frequency domain using a previously described complex demodulation technique (Hoechstetter et al., 2004; Papp and Ktonas, 1977; Wu et al., 2011). A given ECoG channel was assigned amplitude values as a function of frequency and time. For evaluation of high frequency gamma activity, time-frequency transformation was performed for frequencies between 10 and 200 Hz and latencies between −600 ms and +4000 ms relative to the onset of stimulus presentation, in steps of 5 Hz and 10 ms as described in Chapter 2 (Brown et al., 2008). Low frequency components considering the frequency range from 8 to 24 Hz were analyzed in steps of 2 Hz by 25 ms between 4 and 30 Hz, similar to our previous studies (Fukuda et al., 2010a). The low frequency range contains alpha- and beta-band frequencies that have previously been shown to explain portions of the BOLD-fMRI signal (Conner et al., 2011; Hermes et al., 2011).

At each time-frequency bin, we analyzed the percent change in amplitude (averaged across trials) relative to the grand mean amplitude of the reference period for each frequency epoch. Results are referred to as “event-related synchronization and

desynchronization" (Pfurtscheller and Lopes da Silva, 1999) or "temporal spectral evolution" (TSE) (Salmelin and Hari, 1994).

To test for statistical significance in obtained TSE values, a two step statistical analysis was performed using BESA software (Brown et al., 2008; Nagasawa et al., 2010a; Wu et al., 2011). Initially, a studentized bootstrap statistic (Davidson and Hinkley, 1999) was applied to obtain an uncorrected p-value independently for each time-frequency bin. In a second step, correction for multiple testing was performed, accounting for the partial correlation between neighboring TSE values. The following modified Bonferroni correction was used (Auranen, 2002; Simes, 1986): p-values derived for a particular channel were sorted in ascending order ($p_i$, i=1,…, N, where N is the number of bins) and the maximum index, m, for which $p_i<\alpha*i/N$ was determined. The corrected significance level, α, was set to 0.05. All TSE values corresponding to indices i<m were considered statistically significant. This is less conservative than classical Bonferroni correction but well suited for multiple correlated items (Simes, 1986).

As described previously (Asano et al., 2009b; Brown et al., 2008; Fukuda et al., 2010b; Nagasawa et al., 2010a; Nagasawa et al., 2010b; Wu et al., 2011), an additional manual correction was employed. TSE values in a given electrode were declared significant only if, after the modified Bonferroni correction, a minimum of eight time-frequency bins contained within the gamma range from 50 to 150 Hz were arranged in a continuous array spanning (i) at least 20 Hz in width and (ii) at least 20 ms in duration. All electrodes identified herein have exhibited statistically significant augmentation by this method for either the forward speech trials or the reverse speech trials. In all charts of the present study, a positive deflection indicates augmentation.

*Analysis of ECoG amplitude changes relative to stimulus offset*

We maintained a pre-stimulus reference period that was jittered based upon stimulus duration. For each patient, we determined the longest stimulus duration, referred to here as $t_{stim}$ in milli-seconds. The inclusion criteria defining trials suitable for this time-frequency analysis included: (i) patient provides a correct response and (ii) a period of silence serving as a reference period lasting 400 ms immediately preceding the time point $-t_{stim}$ − 200 ms, with stimulus-offset defined as 0 ms. Time-frequency transformation was performed for latencies between $-t_{stim}$ − 200 ms and $-t_{stim}$ + 5000 ms relative to the offset of stimulus presentation. The exclusion criteria, waveform evaluation, and statistics were as described in the 'Analysis of ECoG amplitude changes relative to stimulus onset' section.

*Analysis of ECoG amplitude changes relative to response onset*

We maintained a pre-stimulus reference period that was jittered based upon the combined stimulus and response-time duration. For each patient, we determined the longest stimulus+response time, referred to here as $t_{resp}$ in milli-seconds. The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) patient provided a correct response, (ii) the response-time variability must be within 1000 ms across trials (Brown et al., 2008), and (iii) a period of silence serving as a reference period of 400 ms immediately preceding the time point $-t_{resp}$ − 200 ms, with response-onset defined as 0 ms. Time-frequency transformation was performed for latencies between $-t_{resp}$ − 200 ms and $-t_{resp}$ + 5000 ms relative to the onset of the patient's response. The exclusion criteria, waveform evaluation, and statistics were as

described in the 'Analysis of ECoG amplitude changes relative to stimulus onset' section.

*Categorization of electrode sites with significant gamma-augmentation*

The anatomical localization of language functions can be highly variable, even in patients selected for left hemispheric language dominance (Berger et al., 1989; Duchowny et al., 1996; Hamberger et al., 2007; Ojemann et al., 1989; Ojemann et al., 2003). Therefore, we have chosen to leverage the excellent temporal resolution of ECoG measures. We categorized electrode sites based solely on the temporal characteristics of gamma-augmentations. A given electrode is defined as an ‘Auditory’ site if (i) significant gamma-augmentation begins within 300 ms following stimulus onset (Flinker et al., 2010) and (ii) ends prior to 300 ms following stimulus offset during either forward or reverse speech trial sets. Thus, Auditory sites are those that are temporally ‘locked’ to the stimuli; a stimulus refers to the entire auditory question. All other electrodes with significant gamma-augmentation were treated as ‘Non-Auditory’ sites. These Non-Auditory sites were further subcategorized based upon the temporal domain in which peak gamma-augmentation occurred. That is, ‘Late Stimulus’ sites exhibited peak augmentation during the stimulus, ‘Pre-Response’ sites exhibited peak augmentation after stimulus-offset but prior to response-onset, and ‘Post-Response’ sites exhibited peak augmentation following response-onset.

*Comparing forward to reverse speech*

We compared forward and reverse speech stimulus sets with identical durations and overall auditory characteristics (e.g. same voice and volume) but differing only by relative reversal in time. Statistics were generated using IBM SPSS Statistics version 19 software (SPSS Inc., Chicago, IL, USA). For behavioral and latency measures, a t-test was performed to obtain a 95% confidence interval (C.I.) of the means. For comparison of signal changes at temporal lobe sites, we focused on the first 2.5 s following stimulus-onset, since the longest included stimuli were 2.5 s in duration. We averaged the percent gamma-augmentation, relative to the reference, across the frequency range 50 to 150 Hz. We utilized the related measures of (i) peak augmentation/attenuation, determined using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA), and (ii) area under the gamma-augmentation curve (AUC), determined using the trapezoidal numerical integration function (trapz) in MatLab (The MathWorks Inc., Natick, MA, USA). The AUC takes both augmentation amplitude as well as duration into account, making for a more complete measure of 'activity'. In comparing forward and reverse speech trials at low frequencies, we slightly modified the method of calculating the AUC described in the manuscript. We have reported previously that the alpha/beta bands undergo a brief augmentation just prior to task-related attenuation (Fukuda et al., 2010a). Thus, we rectified the signal such that only amplitude changes below 0% relative to baseline were passed prior to application of MatLab's *trapz* function. Peak amplitude change was measured as described in section 2.6 of the manuscript; for the gamma-band we were interested in peak-augmentation while in the alpha- and beta-bands we were interested in peak-attenuation. For comparison of signal changes at

frontal lobe sites, we focused on results of response-onset analysis from 2 s prior to response-onset to 1 s after; peak augmentation/attenuation but not AUC was considered for frontal lobe sites due to variability of response-times and response durations. The Wilcoxon Signed Ranks Test was applied across electrode sites in order to test the hypothesis that forward and reverse speech stimuli induce differential cortical activity. Alongside uncorrected statistical results of ECoG signal comparisons is provided the median difference between the forward and reverse speech trials; forward minus reverse.

Our forward speech trials were chosen because they have been previously validated as a means to yield language related gamma-augmentations of both the frontal and temporal lobes (Brown et al., 2008); see Chapter 2. We are familiar with the use of this task in our surgical patients and apply it routinely. However, the use of this particular task imposes the possibility of an important confound in this particular study. For example each of the forward speech stimuli begin with interrogatives; in particular, the majority of forward speech trials begin with the word ‘what’. Thus, the first sound heard is frequently the same across forward speech trials. However, the first sound heard is widely variable across reverse speech trials. Therefore, our results may be confounded by the early novelty of reverse speech trials relative to forward speech trials. Additional analyses of latency to and degree of early, during the first 300-ms following stimulus onset, gamma-augmentation were performed only upon Auditory sites. If the confound described above is influencing our ECoG data, we expect to find reverse speech trials to have significantly shorter latency to gamma-augmentation or significantly larger peak gamma-augmentation or AUC relative to forward speech trials.

## *Results*

### *Behavioral Data*

All subjects satisfying the criteria described in the 'Study patients' section were able to complete the task. Appropriate responses were recorded for both trial types. Behavioral results are summarized in Table 5. For trials included in stimulus-onset analysis, the grand-mean response-time across subjects was longer for forward speech trials (1707 ms; 95% C.I.: 1509- to 1905-ms) compared to that for reverse speech trials (1173 ms; 95% C.I.: 1029- to 1336-ms). On average, 95.9% (95% C.I.: 91.7 to 100%) of the forward speech naming questions were answered correctly while the response “I don't know” or equivalent was appropriately elicited by 98.0% (95% C.I.: 95.9 to 100%) of the corresponding reverse speech stimuli. Patient 7 chose to utter “gibberish” and patient 8 chose to utter “nothing” in response to reverse speech trials. These alternative responses to reverse speech stimuli were considered equivalent to the response “I don't know”. All other patients consistently articulated “I don't know” in response to reverse speech trials.

### *Temporal lobe*

Across all eight patients, the temporal lobe yielded a total of 34 sites with significant gamma-augmentation. Of these sites, 26 were classified as Auditory, 7 as Late Stimulus, 1 as Pre-Response, and 0 as Post-Response. The time-frequency analysis of two representative Auditory sites can be found in Fig. 4. Results from gamma-range analyses are summarized in Fig. 5.

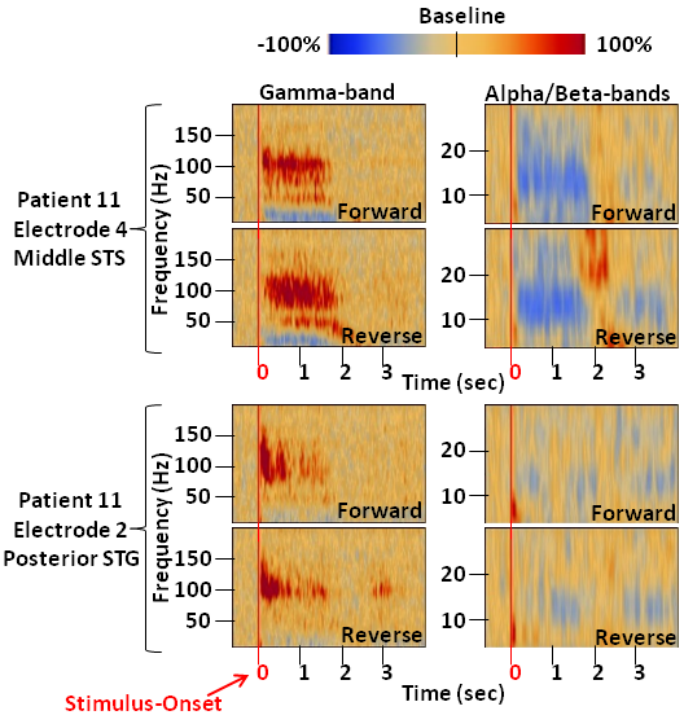


**Figure 4**: **Representative Auditory Sites.** Depicted here are the time-frequency results for both forward and reverse speech trials at two electrode sites of patient 11 classified as Auditory. Similar to our previous studies (Brown et al., 2008), task-related gamma-augmentations exhibit a broadband nature (Crone et al., 2011) largely within the range from 50 to 150 Hz. Alpha/beta-attenuations approximately correspond with gamma-augmentation. Within the Auditory category, we observed two subtypes: (i) those with gamma-augmentation extending throughout the stimulus (top electrode) and (ii) those with gamma-augmentation primarily very early in the stimulus (bottom electrode). These were not separate analyses. Baseline reference extends over a 400 ms silent period prior to stimulus onset. Stimulus questions range from 1 to 2.5 s in duration. STG = superior temporal gyrus. STS = superior temporal sulcus.

*Auditory temporal lobe sites*

Of the 26 temporal lobe sites classified as Auditory, 8 sites (2 right hemisphere and 6 left) were located over the posterior superior temporal gyrus, 6 sites (2 right hemisphere and 4 left) over the posterior superior temporal sulcus, 7 sites (2 right hemisphere and 5 left) over the middle portion of the superior temporal gyrus, and 5 sites (1 right hemisphere and 4 left) over the middle portion of the superior temporal sulcus. On stimulus-onset analysis, the reverse speech trials were associated with a gamma-band ECoG waveform possessing an AUC larger than that associated with the corresponding forward speech trials ($p<0.001$; median difference [forward−reverse]= −22.80%-s). All 8 patients exhibited at least one temporal lobe Auditory site with a gamma-augmentation of larger AUC during reverse speech compared to forward speech. No significant difference was found between the peak gamma-augmentations associated with reverse and forward speech trials ($p=0.096$;−11.44%). Analysis of the

low frequency alpha and beta range yielded no significant differences in either AUC (p=0.809; −0.07 %-s) or peak-attenuations (p=0.341; 1.26%). Representative results obtained from patient 9 can be found on electrodes 1 through 9 in Fig. 6.

In evaluating only the very early portion of the stimulus-onset response (b300 ms following stimulus onset), a significant difference was found between forward and reverse speech for neither the AUC (p=0.409; 1.13%-s) nor the peak gamma-augmentation (p=0.209; 8.24%). The difference in the latency to gamma-augmentation between forward and reverse speech trials did not reach significance (95% C.I. [forward−reverse]: −65.36 to 23.46 ms); excluding only 4 Auditory sites that were significant for only one trial type, 3 of which with reverse speech but not forward.

*Non-Auditory temporal lobe sites*

Of the 8 temporal lobe sites classified as Non-Auditory (7 Late Stimulus, 1 Pre-Response, 0 Post-Response), 1 site was located over the right anterior superior temporal gyrus, 5 sites (2 right hemisphere and 3 left) over the middle portion of the superior temporal gyrus, 1 site over the left posterior superior temporal gyrus, and 1 site over the middle portion of the left middle temporal sulcus. Stimulus-onset analysis of gamma activity revealed no significant difference between AUC measures for reverse and forward speech (p=0.674; 19.83%-s). Moreover, no significant difference was found between the peak gamma-augmentations for reverse and forward speech (p=0.674; −6.55%). Analysis of the alpha and beta range yielded a significantly increased peak attenuation during reverse speech trials (p=0.036; 2.41%) not corroborated by AUC measures (p=0.123; 2.60%-s). A representative result is found on electrode 10 in Fig. 6.

Patient 10 did have a statistically significant Pre-Response gamma-augmentation at 1 site over the medial temporal region during forward but not reverse speech, indicating that only the forward speech trials engaged the medial temporal region in this patient. This medial temporal site was not included in the comparison analysis because there remained doubt that the signal was neocortical in origin.

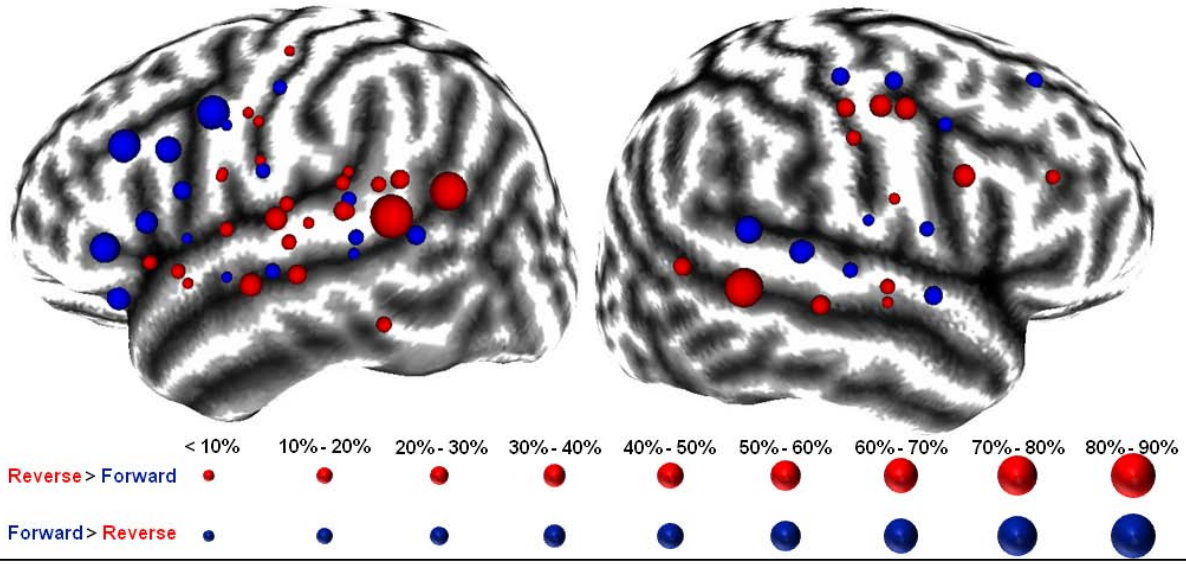


**Figure 5**: **Summary Comparison of Forward and Reverse Speech-Related Gamma Activity.** We created a combined image across all patients with a previously described landmark constrained conformal cortical mapping approach using in-house neuroimaging software (Muzik et al., 2007). The size of electrode locations depicts the difference between forward and reverse speech trials in peak gamma-augmentations, as averaged across the frequency range 50- to 150-Hz, in percent above baseline. Red electrodes are those for which reverse speech elicited the larger peak gamma-augmentation while blue electrodes are those for which that of forward speech was larger. Especially in the left hemisphere, electrodes for which reverse speech elicits a larger peak gamma-augmentation tend to cluster in the superior temporal lobe while those for which forward speech elicits a larger peak gamma-augmentation tend to cluster in the inferior-lateral frontal lobe. Only electrodes of the frontal and temporal lobes for which forward or reverse speech elicited significant gamma augmentation are displayed on this MNI152 template brain atlas.

*Frontal lobe*

Across all eight patients, a total of 31 sites with significant gamma-augmentation were noted in the frontal lobe. Of these, 4 were classified as Auditory, 4 as Late Stimulus , 10 as Pre-Response, and 13 as Post-Response. Results displayed in Fig. 7.

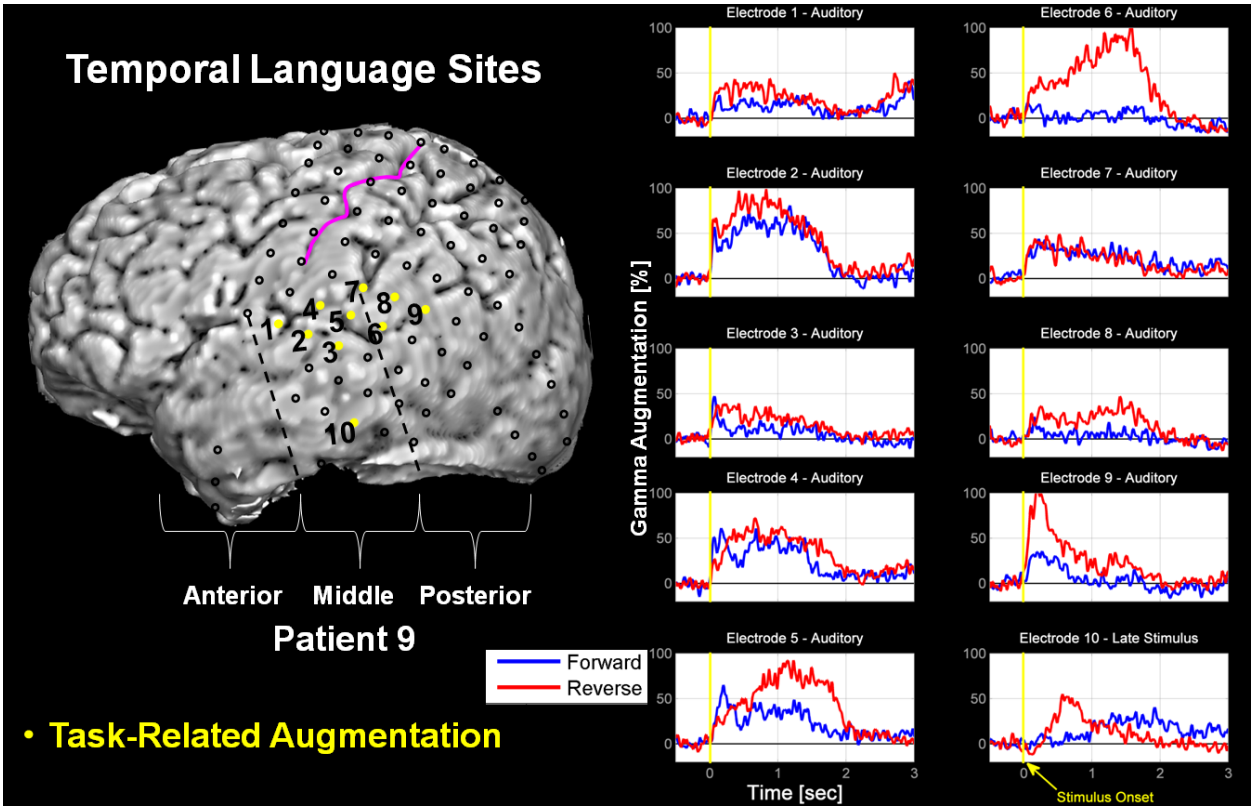


**Figure 6**: **Reverse versus Forward Speech at Temporal Sites**. Data from patient 9 presented. Complete analysis revealed 10 temporal lobe electrode sites with significant gamma-augmentation. Both quantitatively and qualitatively, it is clear that the reverse speech trials more strongly engaged these language-related temporal lobe sites. The pink curve in the figure denotes the central sulcus. The vertical, dashed black lines depict our method of dividing the temporal lobe into 'anterior', 'middle', and 'posterior' portions; each line is drawn down perpendicular to the axis of the temporal lobe from the inferior points of the pre- and post-central sulci, respectively. Results shown are those of stimulus-onset analysis. A seizure onset zone was not resolved in this patient. The tumor in this patient lies in the parietal lobe near the postcentral sulcus.

*Pre-Response frontal lobe sites*

Of the 10 frontal lobe sites classified as Pre-Response, 3 sites (1 right hemisphere and 2 left) were located over the inferior frontal sulcus, 3 sites (1 right hemisphere and 2 left) over the inferior frontal gyrus, 3 sites (1 right hemisphere and 2 left) over the precentral gyrus, and 1 site over the left precentral sulcus. Response-onset analysis based on the Wilcoxon Signed Ranks test showed that forward speech trials elicit a larger peak gamma-augmentation in these frontal Pre-Response sites as compared to

the corresponding reverse speech trials (p=0.028; 25.49%). Similarly, the low frequency alpha and beta range exhibited a greater peak-attenuation during forward speech trials compared to reverse speech trials (p=0.037;−11.97 %). Representative results from patient 6 can be found in Fig. 7.

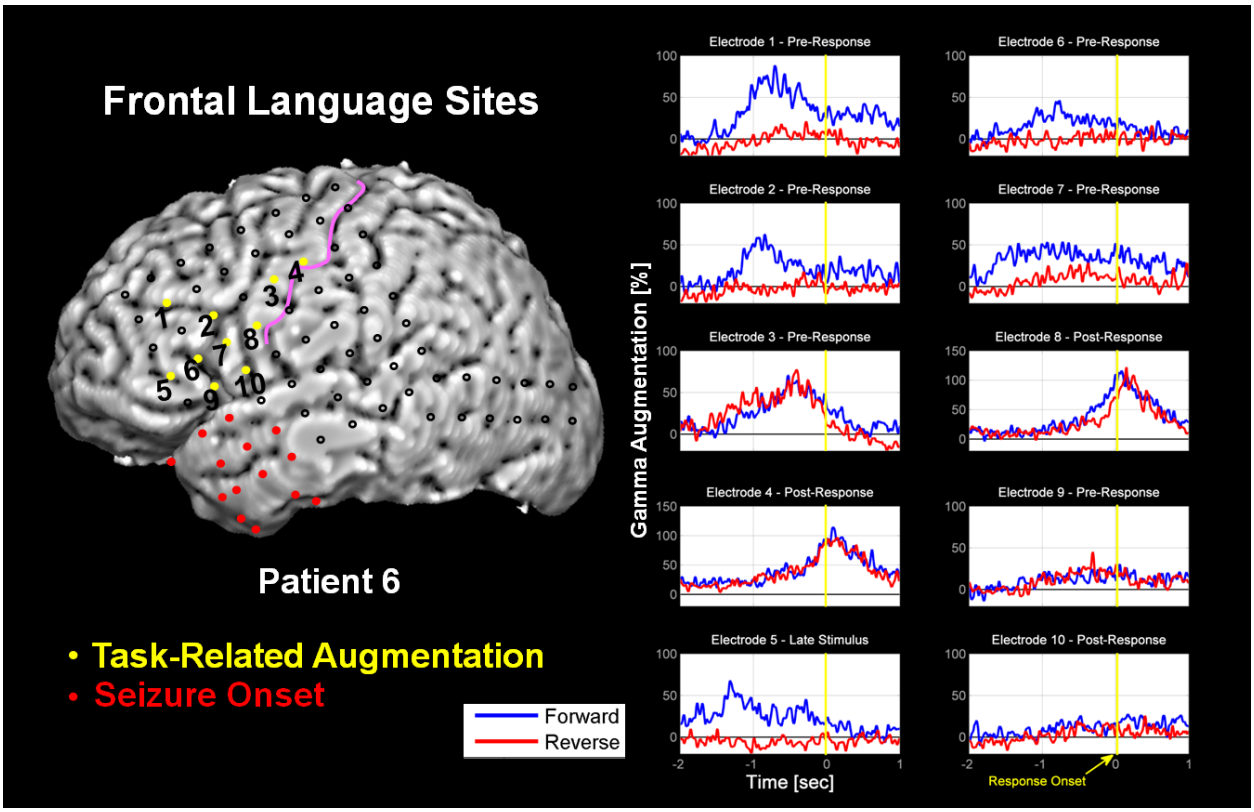


**Figure 7**: **Reverse versus Forward Speech at Frontal Sites.** Data from patient 6 presented. Complete analysis revealed 10 frontal lobe electrode sites with significant gamma-augmentation. Both quantitatively and qualitatively, it is clear that the forward speech trials more strongly engage sites classified as Pre-Response; especially those more anterior to the precentral sulcus. Also evident is the finding that sites classified as Post-Response are similarly activated by the forward and reverse speech tasks. Results shown are those of response-onset analysis. Red colored electrodes depict the seizure onset zone. The pink curve in the figure denotes the central sulcus.

*Late Stimulus frontal lobe sites*

Of the 4 frontal lobe sites classified as Late Stimulus, 1 site was located over the right middle frontal gyrus and 3 sites (1 right hemisphere and 2 left) over the inferior

frontal gyrus. Response-onset analysis based on the Wilcoxon Signed Ranks test showed no difference in the peak-augmentation of gamma activity between Forward and Reverse Speech trials (p=0.144; 34.85%). Analysis of the low frequency alpha and beta range yielded no significant difference in peak-attenuations (p=0.465; 4.51%). A representative result from patient 6 can be found in Fig. 7.

*Post-Response frontal lobe sites*

Of the frontal lobe sites classified as Post-Response, all 13 sites (5 right hemisphere and 8 left) were located over the precentral gyrus or sulcus. Response-onset analysis failed to reveal a difference between peak gamma-augmentations at these sites between the forward speech trials and the corresponding reverse speech trials (p=0.594; 2.04%). Similarly, the low frequency alpha and beta yielded no significant difference in peak-attenuation between forward and reverse speech trials (p=0.055; 4.64%). Representative results derived from patient 6 can be found in Fig. 7.

*Auditory frontal lobe sites*

Four frontal lobe sites showed very early gamma-augmentation during questions and were classified as Auditory, 1 over the right inferior frontal gyrus in patient 5, 2 over the right precentral gyrus in patient 7, and 1 over the left precentral gyrus in patient 9. Plots of the activities of these sites can be seen in Fig. 8. The frontal Auditory site found in patient 5 showed augmentation exclusively during the stimulus, whereas those of patients 7 and 9 had augmentations during both the stimulus and response. Due to the small number of frontal electrodes with Auditory activity, the apparent heterogeneity

within the group, and their analysis extending beyond the scope of this study, a comparison test of significance between the tasks was not performed.

*Correction for multiple comparisons*

The above analyses included a total of 27 statistical comparisons between forward and reverse speech trial types. After applying the conservative Bonferroni correction for multiple comparisons, only the increase in AUC of gamma-augmentations during reverse speech trials compared to forward speech at temporal lobe Auditory sites remained significant (corrected $p<0.05$).

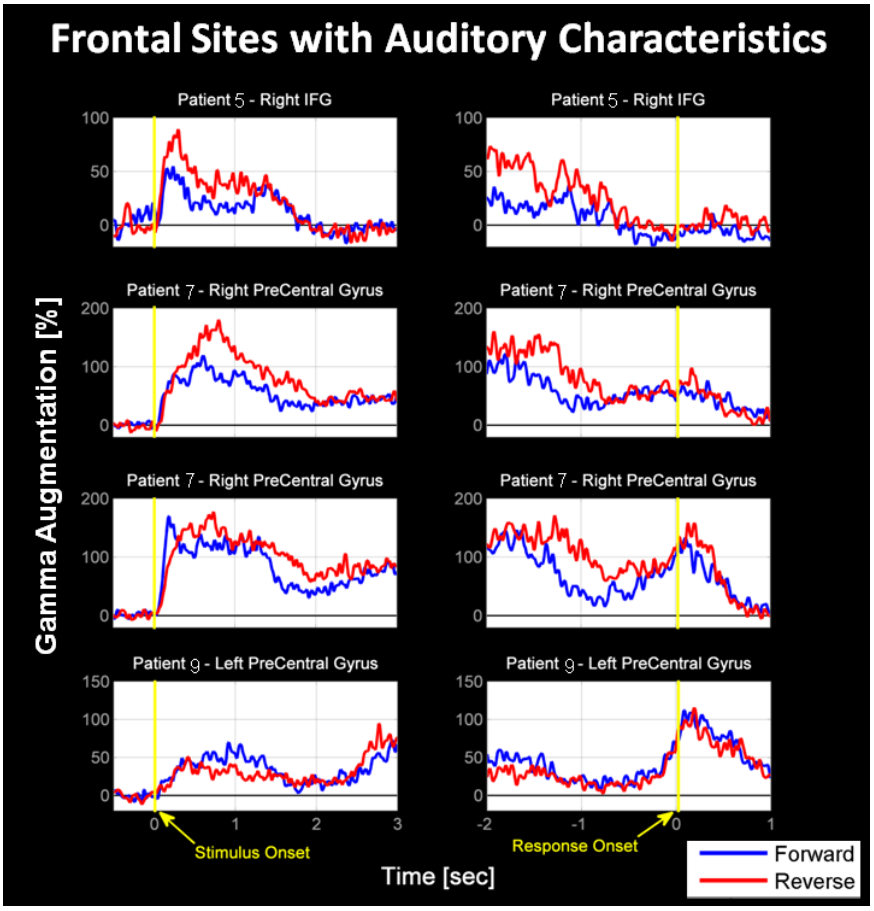


**Figure 8: Unique Frontal Auditory Sites.** Four electrode sites of the frontal lobe were unexpectedly classified as Auditory. These were observed in the right inferior frontal gyrus of patient 5 and the left precentral gyrus of patients 7 and 9; patient 7 having two such sites. In patient 5, this Auditory frontal gamma-augmentation occurred only during the stimulus. There was no significant gamma-augmentation during the response. In patients 7 and 9, augmentation occurred both during the stimulus as well as during the response. We believe that these electrodes may indicate the location of the frontal eye-field, which has recently been implicated in sensory function (Kirchner et al., 2009).

## *Discussion*

### *Primary findings*

We failed to prove the hypothesis that forward speech elicits larger augmentation of gamma activity in bilateral superior temporal regions than does reverse speech. On the contrary, we rejected the null hypothesis in favor of an opposing alternative hypothesis: reverse speech more strongly engages bilateral superior temporal regions than forward speech. It is unlikely that this finding is due to a greater cognitive demand imposed by reverse speech trials or to Type I error. Rather, our subjects were instructed to provide a generic response to the reverse speech trials while the forward speech trials required a unique and appropriate response. Supporting this notion is the fact that the forward speech trials were associated with longer response times and greater peak augmentation at frontal lobe Pre-Response sites. Thus, we have demonstrated a double dissociation between Auditory sites of the superior temporal region, responding more strongly to the reverse speech trials, and Pre-Response sites of the frontal lobe, responding more strongly to the forward speech trials. Taken together, although forward speech trials imposed a greater cognitive demand, reverse speech appeared to more strongly engage bilateral superior temporal cortices. Enhanced gamma-augmentation at Auditory sites of the superior temporal gyrus during reverse speech trials may indicate increased attention (Crone et al., 2011; Deco and Thiele, 2009). Relevant psychoacoustic reasons for why reverse speech may be a poor control for non-language auditory functions can be found in the perceptually unusual time reversal of a distinctly human voice. The idea that temporally reversing speech signals completely removes intelligibility is flawed in that the amplitude envelope and all spectral details are

otherwise intact. The authors and our patients can attest to our ability to identify reverse speech trials as originating from a human voice; one of our patients spontaneously tried to identify the reverse speech trials as being French. Indeed, it has been previously shown that even speech signals that are severely degraded in spectral detail and amplitude envelope dynamics can carry a surprising degree of intelligibility (Shannon et al., 1995). It may be more accurate to speak of the perceptual effect created by the reversing of speech signals as that of ‘confused intelligibility’ rather than ‘removed intelligibility’; the result does not lack intelligibility per se, although it cannot be understood without prior experience and practice (Cowan et al., 1982).

In the present study, the first sound in most of the forward speech stimuli was the same (/w/), and on the majority of occasions the first word was the interrogative ‘what’. In contrast, the sounds ending the forward speech stimuli were highly variable. Therefore, reverse speech stimuli began with a wide and unpredictable range of speech sounds. This creates the potential for the occurrence of a confounder which may explain our results; i.e. increased novelty of the early portion of the reverse speech trials may enhance the gamma-augmentations at Auditory sites. To search for the occurrence of such an undesirable phenomenon, we employed additional analyses at Auditory sites to address possible differences in the latency to gamma-augmentation and early gamma-augmentation peak (<300 ms post-stimulus-onset) between forward and reverse speech trials. If variability in the first sound was seriously confounding our results, we would expect to find that reverse speech would have a significantly earlier onset of gamma-augmentation following stimulus onset or elicit larger gamma-augmentation during this very early period of the stimulus. However, our analysis yielded no significant difference

between the latency to gamma-augmentation or early gamma-augmentation peak between forward and reverse speech trials. These analyses failed to account for our findings simply by variability in the first sound between stimuli and suggest that the confounding effects of such a phenomenon may be modest, if any.

Our ECoG study compared the effects of forward speech stimuli to that of corresponding reverse speech stimuli based on the frequency range from 50 to 150 Hz, as in our previous studies (Brown et al., 2008; Wu et al., 2011). This frequency range is largely out of reach of noninvasive EEG or MEG methods (Dalal et al., 2009) and is measured on a finer spatial scale with ECoG; each macro-electrode records the activities from on the order of 100,000 neurons (Modolo et al., 2010). It completely contains the recently proposed χ-band (76 to 150 Hz), which has been suggested to be the optimal range for spectral-band-based features in brain mapping (Miller et al., 2008). Additionally, our frequency range of interest is related to the LFP spectrum, defined as neurophysiological activity below 300 Hz. LFPs have been shown to “reflect cooperative activity in neuronal populations” (Logothetis, 2003). LFPs and related electrophysiological measures are known to be selectively sensitive to activity involving pyramidal cells, which are almost ideally vertically oriented in an ‘open-field’ geometrical arrangement; the apical dendrite more superficial relative to the soma, creating a cortical array of ‘dendrite-to-soma dipoles’ (Buzsáki, 2004; Logothetis, 2003). Further, computational modeling and experimental data have shown that the dominant mechanism of generation of gamma activity above 50 Hz involves reciprocal interactions between pyramidal cells and certain classes of locally-projecting, inhibitory interneurons (Whittington et al., 2011). Specifically, fast-spiking inhibitory interneurons

generate high frequency oscillations in concert with rhythmic feedback from pyramidal cells in order to ‘gate’ synaptic inputs and synchronize pyramidal cell output (Cardin et al., 2009). In short, our ECoG methods represent a validated, reliable, and direct measure of task-related cortical activity.

*Secondary findings*

In addition to gamma range high-frequency activity, we considered low frequency oscillations across the alpha and beta ranges. Attenuations at these frequencies were originally described as being closely related to gamma-augmentations (Crone et al., 1998b; Crone et al., 2011; Pfurtscheller and Lopes da Silva, 1999). However, the underlying functional meaning of amplitude changes in these low frequency components is less well understood compared to that of high frequency gamma (Engel and Fries, 2010). More recently, activity at these low frequencies has generally been found to be more spatially distributed and less dynamic than those of the gamma range (Crone et al., 2006a; Crone et al., 2011; Fukuda et al., 2010a; Hermes et al., 2011) and such low frequency changes may be functionally independent of those in the gamma range (Cardin et al., 2009; Conner et al., 2011). Indeed, at temporal lobe sites classified as Auditory, we found that low frequency oscillations in the alpha/beta range exhibited similar attenuations between forward and reverse speech trials even though the gamma-band was more strongly augmented during reverse speech stimuli.

Regarding the beta range, emerging theories suggest a role in maintenance of the ‘status quo’ (Engel and Fries, 2010). This might explain the enhanced attenuation of low frequency oscillations we observed at Non-Auditory sites of the temporal lobe during

reverse speech trials, where gamma augmentations were not seen to differ from those of forward speech: reverse speech trials may have required additional flexibility in language comprehension processes in an attempt to decode meaning from an unusual but clearly human-speech-related stimulus. Relevant to the double-dissociation we observed, the opposite occurred at frontal lobe sites classified as Pre-Response where forward speech trials elicited both increased gamma-augmentation as well as alpha/beta-attenuation: forward speech trials may have required additional cognitive flexibility in preparing a unique and relevant response. Finally, the lack of a difference in low frequency attenuations at Auditory sites of the superior temporal lobes suggests that the enhanced gamma-augmentation observed during reverse speech trials is not simply due to increased novelty of the reverse speech stimuli, which would be expected to increase relative attenuation, nor to auditory imagery of the repetitive response “I don't know”, which would represent a type of ‘status-quo-maintenance’ and elicit a decreased relative attenuation.

*ECoG and fMRI*

Task-related measures obtained using methods such as fMRI are currently widely employed and reported in the neuroscience literature. Such methods have the strong benefit of being noninvasive, enabling data collection from normal subjects. Additionally, fMRI possesses a spatial resolution exceeding that of all other functional mapping modalities as well as the ability to obtain measures from both superficial as well as deep brain structures. The disadvantages of fMRI include poor temporal resolution and reliance upon indirect measures of cortical activity, i.e. the BOLD effect which is more

directly related to cortical blood flow and metabolism than to the electrophysiological activity of neurons. Nevertheless, it is thought that “the BOLD-fMRI signal will always reflect the input and intracortical processing taking place in an imaged cortical area” (Logothetis, 2003). PET and NIRS rely upon biophysical mechanisms that are similar but not identical to that of BOLD-fMRI (Perani et al., 1996; Sato et al., 2011).

Without doubt, our results derived from invasive ECoG measurements are inconsistent with the broader literature based on noninvasive methods, such as fMRI, PET, and NIRS. As non-invasive neuroimaging represents an important tool in the study of brain function, an appraisal of possible reasons for the observed discrepancy is warranted. One possibility may be differences in the applied tasks between studies. However, the difference between forward and reverse speech observed in the non-invasive neuroimaging literature does not appear to be highly task-specific, as indicated by the following three complimentary studies: In one fMRI study involving passive listening, simple or complex audio stories represented the forward speech trials while time reversal of the simple stories generated the reverse speech trials (Redcay et al., 2008). Another fMRI study described a lexical–semantic decision task as the forward speech trials, during which both child and adult subjects were to determine the appropriateness of a noun that followed a descriptive sentence (Moore-Parks et al., 2010). To their reverse speech control trials, subjects were to always select the answer ‘incorrect’ in response; this is similar to our requirement to always respond with “I don't know” when a stimulus is incomprehensible. In an NIRS study, a female Japanese voice was used to read children's stories to Japanese infants and compare the oxygenated hemoglobin ([Oxy-Hb]) response to the same voice played in reverse (Sato et al., 2011).

In all the above studies, a larger response to forward speech was demonstrated in temporal neocortices. Differences in task details do not appear important when comparing forward to reverse speech.

This is not the first instance in which a discrepancy between results of electrophysiological and fMRI studies has been reported. In monkeys, the visual area known as V4, along with V1, V2, V3, and V5/MT, was shown on fMRI to be strongly activated by a visual motion processing task (Tolias et al., 2001). However, electrophysiological methods consistently showed that V1, V2, V3, and V5/MT but not V4 were involved in motion processing (Logothetis, 2003). Logothetis has proposed that this discrepancy is due to fMRI's sensitivity to the metabolic activity of all classes of cortical interneurons, not just the fast-spiking inhibitory type, in addition to that of pyramidal cells. It is speculated that distant brain regions may mediate “some kind of modulatory function” that is insufficient to drive pyramidal cells, creating the opportunity for local intracortical processing to proceed undetected by electrophysiology (Logothetis, 2003). Such ‘modulatory function’ has yet to be clearly described. We speculate that the ECoG data presented here indicates a stronger engagement of temporal language neocortex by a reverse speech stimulus, perhaps indicating increased attention (Crone et al., 2011; Deco and Thiele, 2009) in an attempt to decode meaning from an incomprehensible but distinctly human sound; human speech can be accurately recognized even with severely degraded detail in both amplitude envelope and spectral information (Shannon et al., 1995), both of which are left intact by reverse speech tasks, albeit with reversed temporal dynamics. Using the same reasoning as Logothetis, the increased activation to forward speech observed on fMRI may be

caused by an enhanced ‘modulation’ (rather than engagement) of superior temporal language areas in response to what is being perceived and decoded as normal human language. This ‘modulation’ of temporal language cortices during processing of the native language may involve interneuronal cell types beyond fast-spiking inhibitory interneurons or, potentially, cortical astrocytes, which have been shown to be intimately associated with both normal synaptic functions (the ‘tripartite synapse’) and the regulation of cortical blood flow (Iadecola and Nedergaard, 2007; Wieronska and Pilc, 2009). Understanding of this ‘modulation’ clearly requires further multimodal investigation.

*Studying language function in patients with epilepsy*

As can be observed from the behavioral and neuropsychological data provided, there is little reason to believe that our study cohort deviates significantly from ‘normal’ individuals with intact language function. All patients were able to satisfactorily complete our auditory naming task along with the corresponding reverse speech trials. The findings from this study can be considered to represent ‘approximately normal’ brain function and may be applied to the broader population.

*Conclusion*

The purpose for the use of a reverse speech task in neuroimaging studies of language is to control for auditory and motor processing (Moore-Parks et al., 2010). Although the non-invasive neuroimaging literature is quite consistent across modalities in showing that the superior temporal regions are more strongly engaged by forward

speech compared to reverse speech, we have observed the opposite effect using invasive ECoG methods. Whether this indicates a true discrepancy between metabolic and electrophysiologic measures is a question that must be reserved for future studies combining noninvasive neuroimaging with invasive electrophysiology for simultaneous recordings. While reverse speech may ideally control for the physical aspects of spoken language, more needs to be learned about the functional cortical events related to hearing reverse speech before it can be effectively incorporated into studies of language as a control or contrast task for auditory processing. Further studies using other auditory baselines such as spectrally-rotated speech, signal-correlated noise, noise-vocoded speech, ‘musical rain’, or other stimuli of non-human origin are warranted to determine a control task to better segregate neural activation for general auditory perception from that specific to linguistic function (Mottonen et al., 2006; Scott et al., 2009).

*Synthesis*

With our ECoG-based study of reverse speech, we attempted to enhance our language-mapping methodology while also validating findings from fMRI regarding the relative cortical activities associated with hearing forward and reverse speech. We failed to reach our clinical aims with this approach and inadvertently yielded data that contradicted the widely reported findings of fMRI. The discrepancy between the two modalities still needs to be validated in a study that directly compares them. We attempted to start such a study at our institution but the frequency with which our patients receive clinical fMRI evaluation is low and sporatic; fMRI is currently not

considered a valuable method of pre-surgical language mapping (Spritzer et al., 2012). We can report that we did attempt such a study in one patient as a pilot attempt, but this patient was found to possess a tumor of the posterior portion of the superior temporal gyrus and we could not reliably compare our measurements. It is likely that Investigational Review Board approval and additional funding will be required to begin such a study so that a free, research-oriented fMRI dataset can be collected from every epilepsy surgery patient that we interact with. It is of interest to note that the location of the most increased gamma augmentations with reverse speech were observed in these posterior superior temporal regions because this region is often included as part of Wernicke's region (Bogen and Bogen, 1976; Harpaz et al., 2009; Simos et al., 2005). The next subsection presents the follow-up to this study as we continue our search for a potential control task and yield data that allows us to make further comments on this topic.

## Subsection 3.1B: Validation of the Signal-Correlated Noise Control Task

*Introduction*

Auditory language function is studied with a range of methodologies in humans (McNelly et al., 2009), including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), scalp electroencephalography (EEG), and magnetoencephalography (MEG). A well designed task to elicit cortical activity, including a control task to isolate task-specific activity, is critical. We previously attempted to validate reverse speech as a control task in studies of auditory language with electrocorticography (ECoG) (Brown et al., 2012b), the intracranial counterpart to EEG. In many fMRI studies, reverse speech is utilized to control for non-language-specific auditory functions (Gherri and Eimer, 2011; Moore-Parks et al., 2010; Perani et al., 1996; Redcay et al., 2008; Redcay and Courchesne, 2008; Sato et al., 2011). These studies commonly report that the blood-oxygen-level-dependent signal detected by fMRI is enhanced within peri-Sylvian regions during forward speech compared to reverse speech, supporting the notion that reverse speech controls for non-language-specific auditory functions. However, with ECoG we found that language-related activations of the temporal lobe, in particular those of the superior temporal gyrus with early-onset gamma (50-150Hz) activity, showed similar or even greater augmentation during reverse speech compared to forward speech (Brown et al., 2012b). Taking into account that gamma-augmentation is generally considered as an excellent summary measure of cortical activation (Kojima et al., 2013b; Lachaux et al., 2012; Ray et al., 2008), this ECoG observation suggests that reverse speech is a rather poor control for non-language-specific auditory function in the brain. We hypothesized

that the problem lies in the fact that reverse speech is still perceived as originating from a human voice, although it is largely unintelligible.

Various other types of control tasks have also been described in the literature and used for similar purposes. Several of these can be generated to match normal speech sounds for certain characteristics, such as duration or amplitude envelope, but do not retain those essential to create the perception of a human voice. These are considered as non-speech sounds. Noise-vocoded speech is essentially a normal speech signal with reduced spectral complexity generated by restricting the output sound to a finite set of frequency components without altering the amplitude envelope (Davis and Johnsrude, 2003; Millman et al., 2011; Shannon et al., 1995). Noise-vocoded speech shows the curious effect of enhancing the blood-oxygen-level-dependent signal on fMRI relative to normal speech when the degree of frequency degradation is not severe (Davis and Johnsrude, 2003). Musical rain can be generated from frequency formants otherwise used to produce synthetic voice sounds but with a randomly varying carrier frequency and formant onset to produce a rapid spatter of 'pips' with a pleasant, rain-like quality (Uppenkamp et al., 2006). Signal-correlated noise (SCN) is essentially a noise signal that is modulated by the amplitude envelope of the original speech signal (Davis and Johnsrude, 2003; Schroeder, 1968). Both musical rain and SCN have been shown on fMRI to activate superior temporal regions less robustly than normal speech sounds, suggesting that they may control for non-language-specific auditory function.

We set out to determine whether a sound that did not create the perception of a human voice may better control for non-language-specific auditory processing as measured on ECoG in the temporal lobe compared to reverse speech. We chose to test

SCN because it can be generated directly from the original forward speech sound (Davis and Johnsrude, 2003). Like reverse speech, SCN retains the same duration and intensity. However, unlike reverse speech, SCN is not perceived as a human voice. While reverse speech does retain some potential for intelligibility (Cowan et al., 1982), SCN cannot be understood in any circumstance (Davis and Johnsrude, 2003).

In our previous study comparing ECoG activities associated with forward and reverse speech, we noted two distinct sub-classes within the class of sites showing augmentation of gamma activity during auditory stimuli (Brown et al., 2012b). In one sub-class, gamma-augmentation was restricted to only the earliest portions of the auditory stimulus. In the other sub-class, gamma-augmentation extended throughout the stimulus from beginning to end. In this follow-up study, we distinguished these sub-classes as ‘Early Auditory’ and ‘Full Auditory’ and analyzed them separately. We tested the following hypotheses for ECoG sites of the temporal lobe: 1) ECoG sites with augmented gamma activity spanning the entire duration of an auditory stimulus (i.e.: ‘Full Auditory’ sites) will show enhanced augmentation during reverse speech compared to forward speech and reduced augmentation during SCN. Such sites are responding to the entirety of the language stimuli and may be involved in the initial extraction of language-related auditory information prior to semantic processing. 2) ECoG sites with augmented gamma activity occurring only very early during an auditory stimulus (i.e.: ‘Early Auditory’ sites) will not show any preference for sounds perceived as human speech. Because these sites show only brief auditory responses upon stimulus delivery, they are not likely to be involved in the extraction of language-related auditory information.

## *Methods*

### *Study Patients*

Patients were selected by using the following inclusion criteria: (i) a history of intractable focal epilepsy scheduled for extraoperative subdural ECoG recording as part of presurgical evaluation at Children's Hospital of Michigan or Harper University Hospital, Detroit, between December 2011 and March 2013, (ii) age of 5 years or older, and (iii) measurement of ECoG amplitude augmentations driven by a language task described in section 2.3. Our ECoG study performed prior to the current study period reported that even a 4-year-old child cooperatively and accurately named objects in an auditory-naming task and naming-related gamma-augmentation was observed in both temporal and frontal regions (Kojima et al., 2013b).

Exclusion criteria consisted of: (i) presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and Sylvian fissure, (ii) history of hearing impairment, (iii) right language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left-handedness when Wada test results are not available (Knecht et al., 2000a), (iv) multiple seizure foci involving both hemispheres, (v) Verbal Comprehension Index (VCI) or Verbal Intelligence Quotient (VIQ) less than 70, (vi) inability to complete the language task described in section 2.3 due to lack of adequate vocabulary or cooperation, and (vii) history of previous neurological surgery. We studied a consecutive series of 10 patients satisfying all criteria (age range: 5 - 30 years; five females; Table 7). This study has been approved by the Institutional Review Board at

Wayne State University, and written informed consent was obtained from all patients or their legal parent or guardian.

Subdural platinum grid electrode (10 mm inter-contact distance; 4 mm diameter; Adtech, Racine, WI, USA) placement was as described previously by our team (Kojima et al., 2013b). Extraoperative video-ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc., Foothill Ranch, CA, USA) at a sampling frequency of 1000 Hz as previously described (Kojima et al., 2013b). Total electrode contact number ranged from 86 to 128 (Table 6). Seizure onset zones were clinically determined (Asano et al., 2009a) and excluded from subsequent analysis.

**Table 6**
**Summary of Clinical Information**

| Pt | Gdr | Age at surgery (years) | Dom. Hand | Age at epilepsy onset | Antiepileptic medications | PSI† | VCI† | VIQ† | Schooling | Wada test† | Sz type | ECoG electrode coverage | Seizure onset zone | ECoG contacts (total) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | M | 28 | Rt | 27 | CBZ | N/A | N/A | 99 | College Degree | Both | Complex Focal Sz | Rt FPT | Rt medial T | 86 | Tumor |
| 14 | F | 27 | Rt | 26 | LEV | N/A | N/A | 100 | High School Diploma | Lt | Complex Focal Sz | Lt FPT | Lt F | 86 | Tumor |
| 15 | F | 12 | Rt | 9 | LAM, LAC | 97 | 98 | N/A | Normal 7th Grade | N/A | Complex Focal Sz | Lt FPTO | Lt anterior medial T | 112 | Gliosis |
| 16 | F | 5 | Rt | 1 | LEV, LAC | 97 | N/A | 129 | Normal Kinder-garten | N/A | Complex Focal Sz | Lt FPTO | Lt medial T | 108 | Gliosis |
| 17 | F | 9 | Rt | 8 | OXC | 112 | 91 | N/A | Normal 4th Grade | N/A | Focal Sz | Lt FPTO | Lt anterior medial T | 108 | Tumor |
| 18 | M | 30 | Rt | 29 | CBZ, LAC | N/A | N/A | 108 | College | Lt | Focal Sz w/ sGTC | Lt & Rt FPTO | Rt inferior T | Rt 94 Lt 30 | Tumor |
| 19 | F | 21 | Rt | 19 | LEV, Phenytoin | N/A | N/A | 83 | High School Diploma | Lt | Complex Focal Sz | Lt FPTO | Lt medial T | 98 | Gliosis |
| 20 | M | 28 | Rt | 5 | CBZ, VAL | N/A | N/A | 95 | College | Lt | Complex Focal Sz | Rt FPT | Rt medial T | 112 | Gliosis and Dysplasia |
| 21 | M | 13 | Rt | 9 | LEV, OXC | 115 | 114 | N/A | Normal 8th Grade | N/A | Complex Focal Sz | Rt FPT | Rt F | 128 | Dysplasia |
| 22 | M | 12 | Rt | 7 | LEV, VAL | 73 | 73 | N/A | Homebound Normal 7th Grade | N/A | Focal Sz w/ sGTC | Lt FPTO | Lt Inferior P | 104 | Dysplasia and gliosis |

Pt: patient. Gdr: gender. LEV: levetiracetam. LAM: lamotrigine. LAC: lacosamide. CBZ: carbamazepine. OXC: oxcarbazepine. TPM: topiramate. VAL: valproate. Rt: right. Lt: left. Sz: seizure. sGTC: secondarily generalized tonic-clonic sz. F: frontal. T: temporal. O: occipital. P: parietal. † PSI: processing speed index. VCI: verbal comprehension index. VIQ: verbal intelligence quotient.

*Coregistration of Electrodes on Individual Three-Dimensional MRI*

MRI, including a volumetric-T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image of the entire head, was obtained preoperatively using a previously described protocol (Nagasawa et al., 2010a). Planar X-ray images (lateral and antero-posterior) were acquired with subdural electrodes in place for localization on the brain surface; three metallic fiducial markers at anatomically well-defined locations aided coregistration with MRI. A three-dimensional MRI brain surface image was created with electrode sites delineated (Alkonyi et al., 2009b; Muzik et al., 2007; von Stockhausen et al., 1997). Accuracy was confirmed by intraoperative digital photographs showing *in situ* electrode locations (Asano et al., 2005; Nagasawa et al., 2010a; Wu et al., 2011).

*Auditory Naming Task*

Language mapping by measurement of auditory naming-related gamma activity was performed using an auditory naming task similar to that previously reported (Brown et al., 2012b; Kojima et al., 2013b); see Chapter 2. None of the patients had a seizure within two hours prior to or during task performance. While awake and comfortably seated on a bed in a room with unwanted noises minimized, patients received 30 question-and-answer trials. Question stimuli ranged from 1 to 2.5 s in duration. All questions were delivered via playback of an audio recording of the author's (E.C.B.) voice using Presentation version 9.81 software (Neurobehavioral Systems Inc., Albany, CA, USA) and were designed to elicit 1 or 2 word answers with nouns; e.g. "What flies in the sky?"

In this study, we also delivered reverse speech and SCN trials during the task. To generate reverse speech trials, audio recordings of the 30 forward speech question trials were duplicated and then reversed in time with Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA). The 30 SCN trials were generated by a method identical to that employed in previous fMRI studies (Davis and Johnsrude, 2003; Rodd et al., 2005) using a script obtained from Dr. Matt H. Davis (University of Cambridge, Cambridge, United Kingdom) for Praat version 5.3.03 software (University of Amsterdam, Amsterdam, The Netherlands). The script employs an algorithm slightly different than what was first described as SCN (Schroeder, 1968) to create a speech-spectrum SCN. Specifically, the low-frequency amplitude envelope of the forward speech trial is applied to a computer-generated noise with the same duration and frequency spectrum as the forward speech trial but with random phase. The amplitude modulated speech-spectrum noise is then scaled to match the power of the forward speech trial. The resulting SCN trial is an unintelligible noise signal with a rhythm similar to the corresponding forward speech trial, but not interpretable as originating from a human voice.

The audible session of 90 total stimuli in random order was recorded and integrated with ECoG as previously described (Brown et al., 2012b; Kojima et al., 2013b). Subsequently, the onset and offset of auditory stimuli as well as the onset of the patient's vocalization of the response were marked for each trial. Cool Edit Pro was used to visually and audibly aid in the manual determination of these time-points. The response time was defined as the period between offset of stimulus presentation and

onset of the respective overt response. Patients were instructed to answer “I don’t know” when they did not know the answer to or did not understand a stimulus.

*Evaluation of ECoG Amplitude Changes*

Each ECoG trace was transformed into the time-frequency domain, and we determined ‘when’ and ‘where’ gamma activity at 50-150 Hz was augmented. The time-frequency analysis used in the present study (Brown et al., 2012b; Hoechstetter et al., 2004) was previously validated by the results of electrical stimulation (Kojima et al., 2012; Nagasawa et al., 2010a; Nagasawa et al., 2010b) as well as postoperative functional impairment (Kojima et al., 2013b). In short, the *primary* measures of interest were the percent change in amplitude of gamma activity relative to that during the reference period (i.e.: the resting baseline) as well as statistical significance of task-related augmentation of gamma activity. The details of analytic methods are described below. The *secondary* measures included evaluation of low frequency band oscillations at 8-24 Hz (Brown et al., 2012b; Miller et al., 2007a), as described in this Chapter's subsection 3.1A.

*Analysis of ECoG Amplitude Changes Relative to Stimulus Onset*

A maximum of 90 trials were considered for analysis: 30 forward speech trials, 30 corresponding reverse speech, and 30 corresponding SCN trials. Forward speech, reverse speech, and SCN trial sets were analyzed separately. The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) a period of silence serving as a reference period of 400 ms duration was available between 600 to

200 ms prior to the onset of stimulus presentation. The exclusion criteria included: (i) ECoG trace was affected by movement artifacts, (ii) ECoG trace was affected by electrographic seizures, (iii) the corresponding forward speech, reverse speech, or SCN trial was excluded due to failure to satisfy criteria, and (iv) ECoG trace from the superior temporal gyrus affected by runs of epileptiform discharges lasting 3 seconds or longer.

Time-frequency analysis was performed using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany). Each suitable ECoG trial was transformed into the time-frequency domain using a previously described complex demodulation technique (Hoechstetter et al., 2004; Papp and Ktonas, 1977). A given ECoG channel was assigned amplitude values as a function of frequency and time. For evaluation of high frequency gamma activity, time-frequency transformation was performed for frequencies between 10 and 200 Hz and latencies between -600 ms and +4,000 ms relative to the onset of stimulus presentation, in steps of 5 Hz and 10 ms as previously reported (Brown et al., 2008); the method used to evaluate low frequency alpha- and beta-range oscillations is also previously described, presented herein as a *secondary* measure. At each time-frequency bin, we analyzed the percent change in amplitude (averaged across trials) relative to the grand mean amplitude of the reference period for each frequency epoch. Results are referred to as “event-related synchronization and desynchronization” (Pfurtscheller and Lopes da Silva, 1999) or “temporal spectral evolution” (TSE) (Salmelin and Hari, 1994).

To test for statistical significance in obtained TSE values, a two-step statistical analysis was performed using BESA software (Brown et al., 2012b; Kojima et al., 2013b; Nagasawa et al., 2010a). Initially, a studentized bootstrap statistic (Davidson

and Hinkley, 1999) was applied to obtain an uncorrected p-value independently for each time-frequency bin. In a second step, correction for multiple testing was performed, accounting for the partial correlation between neighboring TSE values. The following modified Bonferroni correction was used (Auranen, 2002; Simes, 1986): p-values derived for a particular frequency band were sorted in ascending order ($p_i$ , $i$ = 1, ... , N, where N is the number of bins) and the maximum index, $m$, for which $p_i < \alpha * i/N$ was determined. The corrected significance level, $\alpha$, was set to 0.05. All TSE values corresponding to indices $i < m$ were considered statistically significant. This is less conservative than classical Bonferroni correction but well suited for multiple correlated items (Simes, 1986).

As described previously (Asano et al., 2009b; Brown et al., 2012b; Fukuda et al., 2010a; Nagasawa et al., 2010b; Nagasawa et al., 2010a), an additional manual correction was employed. TSE values in a given electrode were declared significant only if, after the modified Bonferroni correction, a minimum of eight time-frequency bins contained within the gamma range from 50 to 150 Hz were arranged in a continuous array spanning (i) at least 20 Hz in width and (ii) at least 20 ms in duration. All electrodes identified herein have exhibited statistically significant augmentation by this method for the forward speech, reverse speech or SCN trials. In all charts of the present study, a positive deflection indicates augmentation.

*Analysis of ECoG Amplitude Changes Relative to Stimulus Offset*

We maintained a pre-stimulus reference period that was jittered based upon stimulus duration but always within a silent period. For each patient, we determined the

longest stimulus duration, referred to here as $t_{stim}$ in milliseconds (ms). The inclusion criteria for defining trials suitable for this time-frequency analysis included: (i) patient provides a correct response and (ii) a period of silence serving as a reference period lasting 400 ms immediately preceding the time point $-t_{stim} - 200\ ms$, with stimulus-offset defined as 0 ms. Time-frequency transformation was performed for latencies between $-t_{stim} - 200\ ms$ and $-t_{stim}$ + 5,000 ms relative to the offset of stimulus presentation. The exclusion criteria, waveform evaluation, and statistics were as described above.

*Analysis of ECoG Amplitude Changes Relative to Response Onset*

We maintained a pre-stimulus reference period that was jittered based upon the combined stimulus and response-time duration, but likewise within a silent period. For each patient, we determined the longest stimulus + response time, here referred to as $t_{resp}$ in milli-seconds. The inclusion criteria for defining ECoG epochs suitable for this time-frequency analysis included: (i) patient provided a correct response, (ii) the response-time variability must be within 1000 ms across trials (Brown et al., 2008), and (iii) a period of silence serving as a reference period of 400 ms immediately preceding the time point $-t_{resp} - 200\ ms$, with response-onset defined as 0 ms. Time-frequency transformation was performed for latencies between $-t_{resp} - 200\ ms$ and $-t_{resp}$ + 5,000 ms relative to the offset of stimulus presentation. The exclusion criteria, waveform evaluation, and statistics were as described above.

*Categorization of Electrode Sites with Significant Gamma-Augmentation*

We utilized an algorithm for classification similar to what we have previously published (Brown et al., 2012b); see this Chapter's subsection 3.1A. Specifically, we categorized electrode sites based solely on the temporal characteristics of gamma-augmentations. A given electrode is defined as an Auditory site if (i) significant gamma-augmentation begins within 300 ms following stimulus onset (Flinker et al., 2010) and (ii) ends prior to 300 ms following stimulus offset (Brown et al., 2012b) during forward speech, reverse speech, or SCN trial sets. Thus, Auditory sites are those that are temporally 'locked' to the stimuli; a stimulus refers to the entire auditory question.

In this study, we further subdivided Auditory sites into Early-Auditory and Full-Auditory sites based upon our observations in a previous dataset (Brown et al., 2012b). Full Auditory sites are those that possess significant gamma augmentation extending past 850 ms after stimulus-onset on any of the forward, reverse, or SCN trial sets; with '850 ms' representing half of the average duration of stimulus trials. All other Auditory sites are defined as Early Auditory, since the gamma-augmentation is restricted to only the earliest portions of the auditory stimuli. All other sites with significant gamma-augmentation were treated as 'Non-Auditory' sites. These Non-Auditory sites were further sub-categorized based upon the temporal domain in which peak gamma augmentation occurred. That is, 'Late Stimulus' sites exhibited peak augmentation during the stimulus, 'Pre-Response' sites exhibited peak augmentation after stimulus-offset but prior to response-onset, and 'Post-Response' sites exhibited peak augmentation following response-onset.

This analytic approach does not suffer from circular analysis (Kriegeskorte et al., 2009), since the aforementioned ECoG site classification was developed based upon observations from other datasets (Brown et al., 2012b), rather than the current dataset. Furthermore, classification was not exclusively driven by the temporal pattern of gamma activity elicited by a 'specific' auditory stimulus type, but fairly performed according to the systematic rule treating the three stimulus types equally.

*Comparing Outcome Measures between Task Types*

We compared forward speech, reverse speech, and SCN stimulus sets with identical durations and overall auditory characteristics (e.g., volume). Statistics were generated using IBM SPSS Statistics version 20 software (SPSS Inc., Chicago, IL, USA). For behavioral measures, an ANOVA was performed to obtain a 95% confidence interval (C.I.) of the means. For comparisons of electrographic activity, we considered sites of the temporal and frontal lobe classified as described above. Electrodes ambiguously located over the Sylvian fissure were determined to be sampling temporal cortex if classified as Auditory; otherwise, surgical photographs were inspected to determine if an electrode was associated more with the temporal or frontal cortex. If a patient contributed more than one site to a classification within the temporal or frontal lobe, the values associated with those sites were averaged such that each patient contributed only one sample for each classification. For comparison of signal changes at temporal lobe sites, we focused on the first 2.5 s following stimulus-onset, the longest stimulus duration. We averaged the percent gamma-augmentation, relative to the reference, across the frequency range 50 to 150 Hz, as described previously (Brown et al., 2012b).

We utilized the related measures of (i) peak augmentation/attenuation, and (ii) area under the gamma-augmentation curve (AUC), determined using the trapezoidal numerical integration function (*trapz*) in MatLab (The MathWorks Inc., Natick, MA, USA); this procedure for calculating the AUC was also done similarly for low frequency alpha- and beta-attenuations, 8 to 24 Hz, as described previously (Brown et al., 2012b). The AUC takes both augmentation amplitude as well as duration into account, thus creating a more complete measure of 'activity'. For comparison of signal changes at frontal lobe sites, we focused on results of response-onset analysis from 2 s prior to response-onset to 1 s after; peak augmentation/attenuation but not AUC was considered for frontal lobe sites due to variability of response-times and response durations (Brown et al., 2012b). Friedman's Test was applied across patients in order to test the hypothesis that forward speech, reverse speech, and SCN stimuli elicit differential distributions of cortical activity within a given classification. Any significant result yielded by this nonparametric analysis of variance by ranks was followed by pairwise *post-hoc* comparisons between trial sets. Uncorrected p-values are presented for Friedman's tests. Pairwise *post-hoc* comparisons were corrected by Bonferroni's method. Alongside *post-hoc* comparison statistics is provided the pairwise median difference; forward minus reverse, forward minus SCN, or reverse minus SCN.

## *Results*

### *Behavioral Data*

All subjects satisfying the criteria described in section 2.1 were able to complete the task. Appropriate responses were recorded for both trial types.

Behavioral results are summarized in Table 7. For trials included in stimulus-onset analysis, the grand-mean response-time across subjects was not significantly different (ANOVA p-value=0.500) between forward speech trials (1304 ms; 95% C.I.: 1171 to 1436 ms), reverse speech trials (1198 ms; 95% C.I.: 1094 to 1303ms), and SCN trials (1251 ms; 95% C.I.: 1118 to 1384 ms).

On average, 95.3% (95% C.I.: 91.0 to 99.7%) of the forward speech naming questions were answered correctly while the response “I don’t know” or equivalent was appropriately elicited by 95.7% (95% C.I.: 91.9 to 99.4%) of the corresponding reverse speech stimuli and by 92.3% (95% C.I.: 84.7 to 100%) of the corresponding SCN stimuli. Patients occasionally chose to say "no idea" or "I don't understand". These alternative responses to reverse speech and SCN stimuli were considered equivalent to the response “I don’t know” (Brown et al., 2012b).

*Temporal Lobe*

Over the temporal lobe, 9 patients contributed a total of 38 sites with significant gamma-augmentation. Of these sites, 15 were classified as Early-Auditory, 15 were classified as Full-Auditory, 6 as Late Stimulus, 2 as Pre-Response, and 0 as Post-Response. The time-frequency analysis of representative Early-Auditory and Full-Auditory sites can be found in Figure 9.

*Early-Auditory Temporal Lobe Sites*

Of the 15 temporal lobe sites classified as Early-Auditory, 8 sites (3 right hemisphere and 5 left) were located over the posterior superior temporal gyrus, 2 sites over the left posterior superior temporal sulcus, 3 sites (2 right hemisphere and 1 left) over the

middle portion of the superior temporal gyrus, and 1 site over the middle portion of the left superior temporal sulcus. These sites were contributed by 7 different patients; sites contributed by the same patient were averaged together such that each patient contributed only one sample to statistical analysis. On stimulus-onset analysis, no significant difference in the distributions of gamma-band AUC measures was observed (Friedman's p=0.066). No significant difference was found between the distributions of peak gamma-augmentations (Friedman's p=0.867). Analysis of the low frequency alpha and beta range yielded no significant differences in either AUC (Friedman's p=0.180) or peak-attenuations (Friedman's p=0.565). Representative results obtained from patient 22 can be found on electrodes 8, 9, and 10 in Figure 9.

**Table 7**
**Behavioral Results**

| Patient | Response Time Forward Speech Trials mean (95% CI) | Response Time Reverse Speech Trials mean (95% CI) | Response Time Signal Correlated Noise mean (95% CI) | Correct responses %forward,%reverse,%SCN |
|---|---|---|---|---|
| 13 | 719 (603-836) ms | 648 (587-708) ms | 1079 (436-1721) ms | 97%,93.3%,96.7% |
| 14 | 1276 (977-1574) ms*,** | 760 (649-871) ms* | 595 (513-678) ms** | 96.7%,100%,100% |
| 15 | 932 (791-1074) ms | 893 (781-1006) ms | 856 (713-998) ms | 96.7%,100%,96.7% |
| 16 | 2019 (1526-2512) ms | 1611 (1373-1848) ms | 1570 (1011-2129) ms | 90%,90%,86.7% |
| 17 | 1621 (1049-2194) ms* | 611 (504-718) ms* | 989 (645-1332) ms | 96.7%,100%,96.7% |
| 18 | 1271 (1007-1534) ms | 1618 (1414-1821) ms | 1458 (1242-1674) ms | 100%,100%,100% |
| 19 | 1436 (989-1883) ms | 1910 (1287-2532) ms | 1744 (1251-2237) ms | 96.7%,90%,96.7% |
| 20 | 1610 (1023-2197) ms | 1844 (1371-2317) ms | 2182 (1648-2717) ms | 100%,96.7%,66.7% |
| 21 | 617 (540-694) ms* | 931 (848-1015) ms*,*** | 730 (622-838) ms*** | 100%,100%,100% |
| 22 | 1809 (987-2630) ms | 1358 (848-1867) ms | 1603 (1022-2183) ms | 80.0%,86.7%,83.3% |
| Grand average | 1304 (1171-1436) ms | 1198 (1094-1303) ms | 1251 (1118-1384) ms | 95.3%,95.7%,92.3% |

All response times averaged from stimulus onset analysis trials. *t-Test indicates difference between forward and reverse speech trials; **difference between forward speech and SCN; ***difference between reverse speech and SCN. α = 0.05.

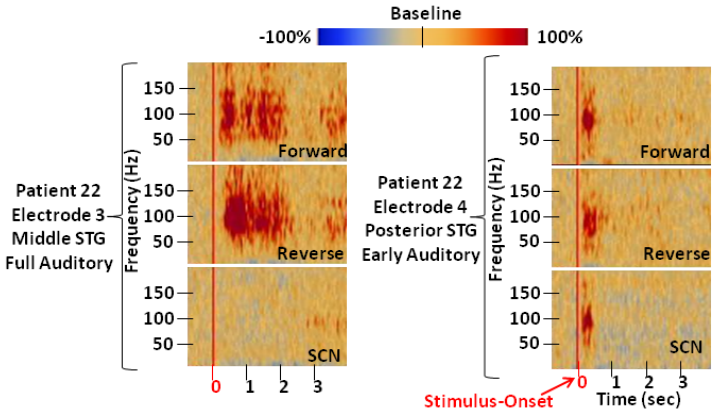


**Figure 9: Example of Different Types of Auditory Activity.** Depicted are time-frequency results for forward speech, reverse speech, and SCN trials at two electrode sites of Patient 23 classified as Auditory; one further classified as Full Auditory (left) and the other as Early Auditory (right). Differences in activity between stimulus types are apparent in the Full sub-classification, but not Early. Stimuli range from 1 to 2.5 s duration. STG = Superior Temporal Gyrus.

*Full-Auditory Temporal Lobe Sites*

Of the 15 temporal lobe sites classified as Full-Auditory, 3 sites (1 right hemisphere and 2 left) were located over the posterior superior temporal gyrus, 1 site (left) over the posterior superior temporal sulcus, 10 sites (3 right hemisphere and 7 left) over the middle portion of the superior temporal gyrus, and 1 site (right) over the middle portion of the superior temporal sulcus. These sites were contributed by 7 different patients. On stimulus-onset analysis, a significant difference in the distributions of gamma-band AUC measures was observed (Friedman's p=0.002). The SCN trials were associated with a gamma-band ECoG waveform possessing an AUC smaller than that associated with the corresponding reverse speech trials ($p_{corr}$=0.003; median difference [reverse - SCN] 108.91%-s) but not forward speech ($p_{corr}$=0.099; [forward – SCN] = 82.56%-s). Differences between forward speech and reverse speech trials failed to reach significance ($p_{corr}$=0.543; [forward - reverse] -26.35%-s). A significant difference in the distributions of peak gamma-augmentation was also observed (Friedman's p=0.004). The SCN trials were associated with a gamma-band ECoG waveform possessing a peak smaller than that associated with either the corresponding forward speech ($p_{corr}$=0.048; 67.65%) or reverse speech trials ($p_{corr}$=0.003; 96.90%). Difference between forward speech and reverse speech trials failed to reach significance ($p_{corr}$=1; -29.25%). Analysis of the low frequency alpha and beta range yielded no significant differences in either AUC (Friedman's p=0.156) or peak-attenuations (Friedman's p=0.565). Representative results obtained from patient 15 can be found on electrodes 2 through 4 and 6 and 7 in Figure 10.

*Non-Auditory Temporal Lobe Sites*

Of the 8 temporal lobe sites classified as Non-Auditory (6 Late Stimulus, 2 Pre-Response, 0 Post-Response), 2 sites (1 right hemisphere and 1 left) were located over the anterior superior temporal gyrus, 3 sites over the middle portion of the left superior temporal gyrus, 1 site over the right posterior superior temporal gyrus, and 2 sites over the left posterior middle temporal gyrus. These sites were contributed by 6 different patients. On stimulus-onset analysis, a significant difference in the distributions of gamma-band AUC measures was observed (Friedman's p=0.009). The SCN trials were associated with a gamma-band ECoG waveform possessing an AUC smaller than that associated with the corresponding forward speech ($p_{corr}$ = 0.012; 42.38%-s) but not reverse speech trials ($p_{corr}$ = 0.063; 40.69%-s). No significant difference was observed between forward speech and reverse speech trials ($p_{corr}$ = 1; 1.69%-s). A significant difference in the distributions of peak gamma-augmentation was observed (Friedman's p = 0.009). The SCN trials were associated with a gamma-band ECoG waveform possessing a peak smaller than that associated with the corresponding forward speech ($p_{corr}$ = 0.012; 33.31%) but not reverse speech trials ($p_{corr}$ = 0.063; 32.78%). No significant difference was observed between forward speech and reverse speech trials ($p_{corr}$ = 1; 0.53%). Analysis of the low frequency alpha and beta range yielded no significant differences in either AUC (Friedman's p = 0.607) or peak-attenuations (Friedman's p = 0.513). A representative result from patient 12 can be found on electrodes 1 and 5 in Figure 11.

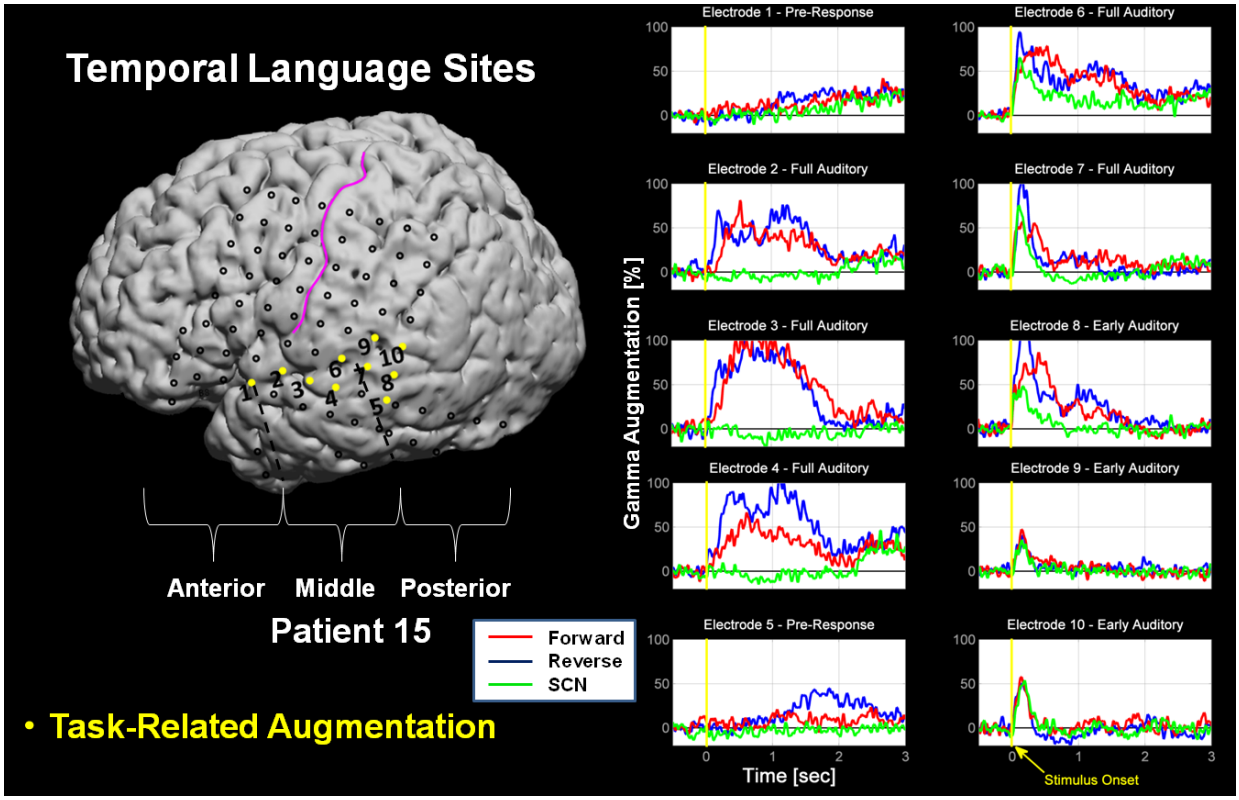


**Figure 10: Reverse Speech, Forward Speech, and SCN at Temporal Sites.** Complete analysis revealed 10 temporal lobe electrode sites with significant gamma-augmentation. Both quantitatively and qualitatively, it is clear that the SCN trials less strongly engaged language-related temporal lobe sites classified as Full Auditory compared to either forward or reverse speech trials. The pink curve in the figure denotes the central sulcus. The vertical, dashed black lines depict our method of dividing the temporal lobe into 'anterior', 'middle', and 'posterior' portions; each line is drawn down perpendicular to the axis of the temporal lobe from the inferior points of the pre- and post-central sulci, respectively. Results shown are those of stimulus-onset analysis. The seizure onset zone of this patient resided in the medial temporal regions.

*Frontal Lobe*

Across all 11 patients, a total of 42 sites with significant gamma-augmentation were noted in the frontal lobe. Of these, 5 were classified as Early-Auditory, 4 as Full-Auditory, 5 as Late Stimulus, 14 as Pre-Response, and 14 as Post-Response.

*Pre-Response Frontal Lobe Sites*

Of the 14 frontal lobe sites classified as Pre-Response, 3 sites were located over the left inferior frontal gyrus, 4 sites over the left precentral gyrus, 3 sites (1 right

hemisphere and 2 left) over the precentral sulcus, 2 sites (1 right hemisphere and 1 left) over the middle frontal gyrus, 1 site over the left orbital frontal region, and 1 site over the right medial superior frontal gyrus. These sites were contributed by 6 different patients. On response-onset analysis, a significant difference in the distributions of peak gamma-augmentation was observed (Friedman's p=0.009). Forward speech trials elicited a larger peak gamma-augmentation in these frontal Pre-Response sites as compared and corresponding SCN trials ($p_{corr}$=0.012; 32.87%) but not to the corresponding reverse speech trials ($p_{corr}$=0.063; 21.26%). No difference was observed between reverse speech and SCN trials ($p_{corr}$=1; 11.61%). Analysis of the low frequency alpha and beta range showed a significant difference in the distributions of peak-attenuation (Friedman's p=0.042). However, none of the *post-hoc* comparisons reached significance (all $p_{corr}$>0.05). Representative results from patient 11 can be found in Figure 11.

*Late Stimulus Frontal Lobe Sites*

Of the 5 frontal lobe sites classified as Late Stimulus, 1 site over the left precentral sulcus, 1 site over the left medial superior frontal gyrus, 1 site over the right middle frontal gyrus, 1 site over the right inferior frontal gyrus, and 1 site over the right inferior frontal sulcus. These sites were contributed by 4 different patients. On response-onset analysis, a significant difference in the distributions of peak gamma-augmentation was observed (Friedman's p=0.039). Forward speech trials elicited a larger peak gamma-augmentation in these frontal Late Stimulus sites as compared to the corresponding reverse speech trials ($p_{corr}$=0.039; 48.93%) but not corresponding SCN trials

($p_{corr}$=0.231; 40.96%). No difference was observed between reverse speech and SCN trials ($p_{corr}$=1; -7.97%). Analysis of the low frequency alpha and beta range yielded no significant difference in peak-attenuations (Friedman's p=0.779). A representative result from patient 15 can be found in Figure 11.

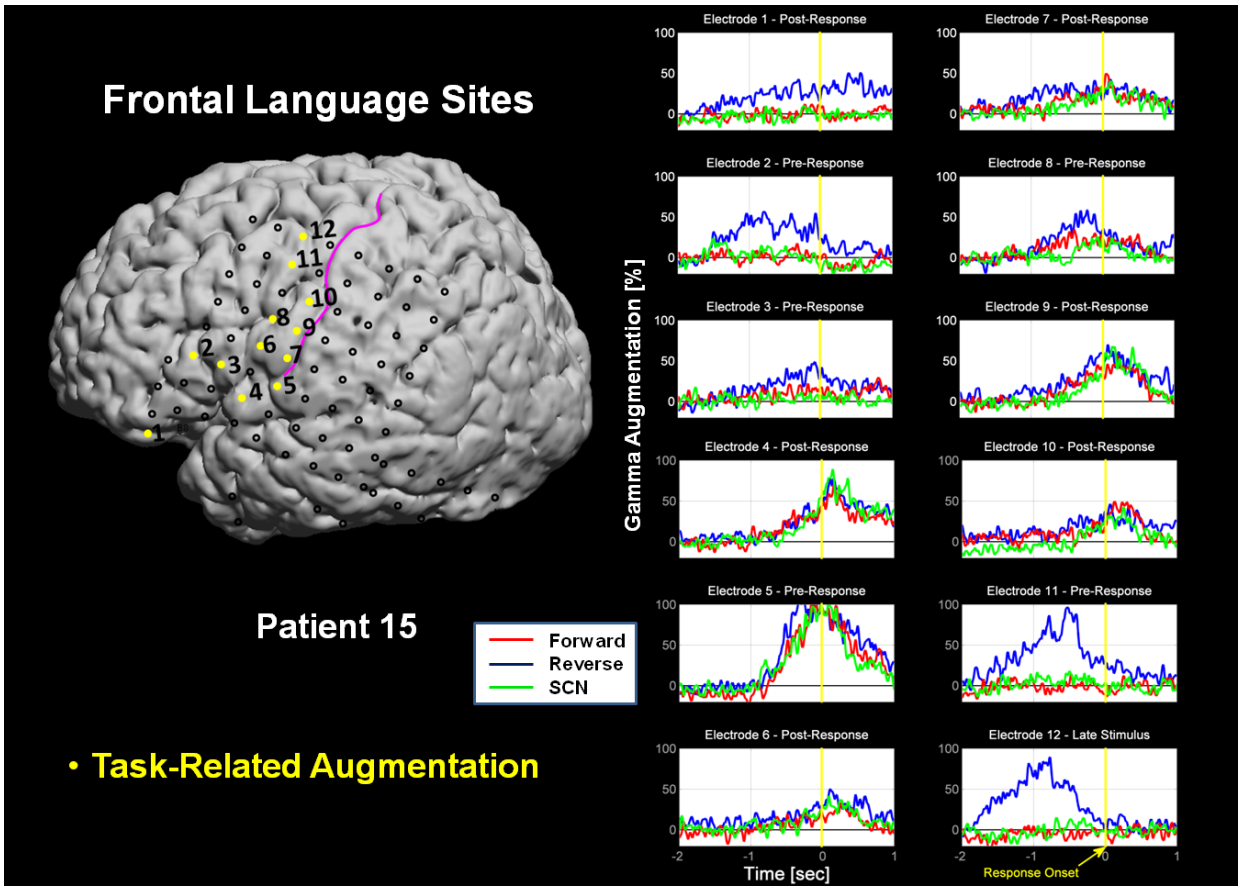


**Figure 11: Reverse Speech, Forward Speech, and SCN at Frontal Sites.** Complete analysis revealed 12 lateral frontal lobe electrode sites with significant gamma-augmentation. Both quantitatively and qualitatively, it is clear that the forward speech trials (blue lines) more strongly engage sites Non-Auditory sites classified as Pre-Response or Late Stimulus. Also evident is the finding that sites classified as Post-Response are similarly activated by the forward and reverse speech tasks; with the exception of electrode 1 which is the only Post-Response site not associated with the precentral gyrus or sulcus. Results shown are those of response-onset analysis; with a vertical yellow line identifying onset of overt responses. The pink curve denotes the central sulcus.

*Post-Response Frontal Lobe Sites*

Of the 14 frontal lobe sites classified as Post-Response, 13 sites (3 right hemisphere and 10 left) were located over the precentral gyrus or sulcus while 1 sites were located

over the left orbitofrontal cortex. These sites were contributed by 5 different patients. On response-onset analysis, no significant difference in the distributions of peak gamma-augmentation was observed (Friedman's p=0.549). Similarly, the low frequency alpha and beta analysis yielded no significant difference in peak-attenuation between forward and reverse speech trials (Friedman's p=0.247). Representative results derived from patient 15 can be found in Figure 11.

*Auditory Frontal Lobe Sites*

A total of 9 sites of the frontal lobe were classified as Auditory; 5 as Early Auditory and 4 as Full Auditory. Of the 5 Early Auditory sites found across 4 different patients, 3 sites (1 right hemisphere and 2 left) were located over the inferior frontal gyrus, 1 over the right precentral sulcus, and 1 over the medial surface of the right superior frontal gyrus. Of the 4 Full Auditory sites found across 3 different patients, 3 sites (1 right hemisphere and 2 left) were located over the precentral gyrus and 1 site over the right precentral sulcus. Due to the small number of frontal electrodes with Auditory activity and the apparent heterogeneity in spatial-temporal profiles within the groups, comparison tests of significance between the tasks were not performed. Results from each of these sites are displayed in Figure 12.

*Correction for Multiple Comparisons*

The above analyses included a total of 18 Friedman's tests comparing the distributions in gamma activity of forward speech, reverse speech and SCN trials. After applying a modified Bonferroni correction for multiple comparisons more suitable for

highly correlated data, i.e. Simes correction (Simes, 1986), only the findings related to the AUC of gamma-augmentations at temporal lobe Full-Auditory sites remained significant (corrected $p<0.05$), where both forward and reverse speech were associated with greater augmentation than was SCN.

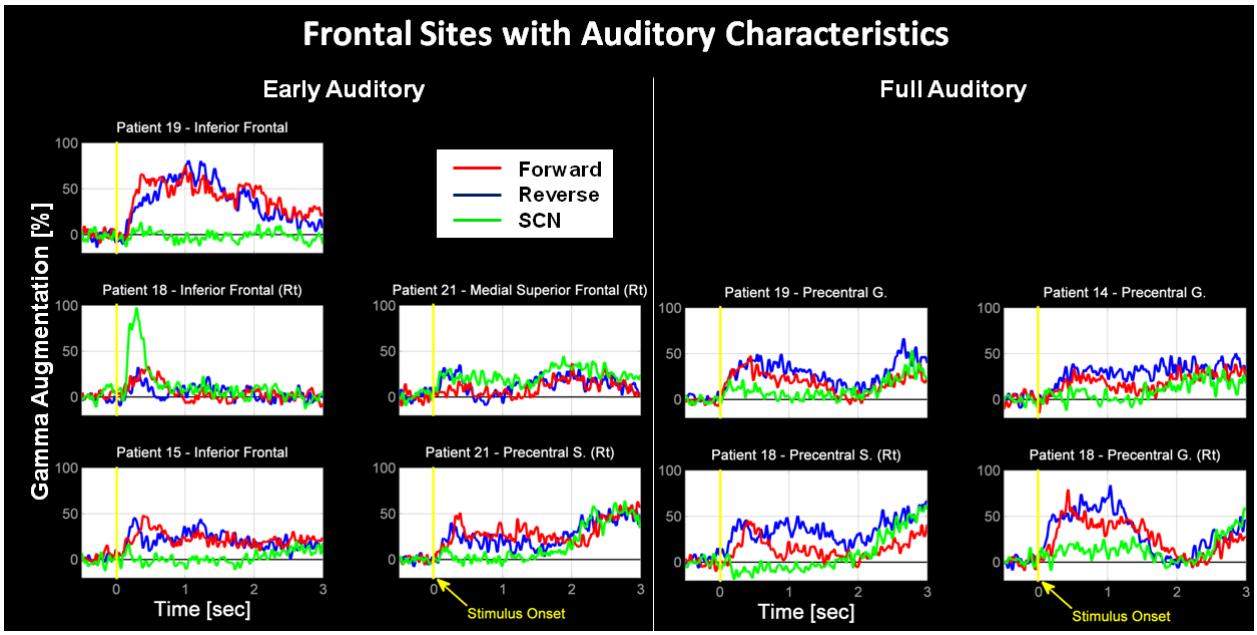


**Figure 12: Frontal Auditory Sites with SCN.** Several frontal sites exhibited Auditory activity, similar to that observed in the preceding study. In this study, we further divided Auditory sites into Early and Full Auditory. Frontal sites classified as Early Auditory (left) appeared highly variable and it difficult to draw conclusions regarding their nature; they appear quite different than similarly classified sites of the temporal lobe. However, frontal sites classified as Full Auditory exhibited a pattern of activity resembling that of similarly classified sites of the temporal lobe. Furthermore, three of the four sites classified as Full Auditory residing in a region midway up the lateral surface of the precentral gyrus near what is known as the frontal eye field. Language-specific processing may occur at such sites.

## *Discussion*

### *Primary Findings*

We were able to validate findings from non-invasive imaging studies suggesting SCN to less intensely engage temporal lobe sites associated with language processing (Davis and Johnsrude, 2003; Rodd et al., 2005). This was not simply due to a general lack of engagement of temporal lobe sites. Indeed, SCN augmented gamma activity in temporal sites classified as Early Auditory to a degree similar to that of forward as well

as reverse speech. Only temporal lobe sites classified as Full Auditory or Non-Auditory displayed evidence of reduced gamma-augmentation during SCN trials. It is unlikely that this finding is simply due to a lesser cognitive demand imposed by SCN trials or due to Type I error. Rather, while the forward speech trials required a unique and appropriate response, our subjects were instructed to provide a generic response to both reverse speech and SCN trials. Indeed, reverse speech was not associated with such a reduced gamma-augmentation at Full Auditory and Non-Auditory sites of the temporal lobe, supporting our previously published findings suggesting reverse speech to be a poor control task for non-language-specific auditory function (Brown et al., 2012b). SCN trials were also associated with response times similar to both forward speech and reverse speech. Thus, we have demonstrated on ECoG that a control task not perceivable as a human voice (i.e. SCN) will engage language-related temporal lobe sites to a lesser degree than stimuli that are perceived as such (i.e., forward and reverse speech). Taken together, temporal lobe sites classified as Early Auditory may be associated with a non-specific auditory process that can be engaged by either stimuli perceived as a human voice or stimuli not perceivable as such.

Sites of the lateral temporal lobe classified as Full Auditory may be associated with a language-specific auditory process engaged only by stimuli perceived as a human voice (i.e., forward and reverse speech). Lateral temporal sites classified as Non-Auditory may provide further analysis of voice characteristics even when language information is confused (Brown et al., 2012b). Reduced gamma-augmentation at Full-Auditory sites of the superior temporal gyrus and sulcus during SCN trials may indicate decreased attention to stimuli not perceived as human (Crone et al., 2011; Deco and Thiele, 2009).

Our ECoG study compared the effects of forward speech stimuli to that of corresponding reverse speech and SCN stimuli based on the frequency range from 50 to 150 Hz, as in our previous studies (Brown et al., 2012b); a well validated, reliable, and direct measure of task-related cortical activity (Crone et al., 2006a; Kojima et al., 2013b). We reproduced our previous result that reverse speech may engage language-specific cortex of the lateral temporal lobe, whereas the difference in the magnitude of gamma augmentation elicited by reverse and forward speech stimuli failed to reach significance in the present study. This may be related to a reduced power in the present study due to two differences between the present and our previous study of this Chapter's subsection 3.1A: 1) in the present study, we split the Auditory category into Early Auditory and Full Auditory categories based upon the temporal profiles of gamma augmentation observed in our previous study (Brown et al., 2012b); and 2) our statistical analysis in the present study was more rigorous in that each subject was permitted to contribute a maximum of one sample to each classification whereas the previous study considered each individual electrode site as a separate and independent sample point (Brown et al., 2012b). Even at the reduced statistical power of the present study, we were able to identify a robust finding suggesting SCN to have reduced activation at Full-Auditory sites of the lateral temporal lobe relative to reverse speech.

*Secondary Findings*

In addition to gamma range high-frequency activity, we considered low-frequency oscillations across the alpha and beta ranges at 8-24 Hz. Attenuations at these frequencies were originally described as being closely related to gamma-augmentations

(Crone et al., 1998b; Crone et al., 2011; Pfurtscheller and Lopes da Silva, 1999). However, the underlying functional meaning of amplitude changes in these low frequency components is less well understood compared to that of high frequency gamma (Brown et al., 2012b; Engel and Fries, 2010). Activity at these low frequencies has generally been found to be more spatially distributed and less dynamic (e.g.: lingering) than those of the gamma range (Brown et al., 2012b; Crone et al., 2006b; Crone et al., 2011; Fukuda et al., 2010a; Hermes et al., 2011; Miller et al., 2007a) and such low frequency changes may be functionally independent of those in the gamma range (Cardin et al., 2009; Conner et al., 2011). Indeed, at temporal lobe sites classified as Full-Auditory and Non-Auditory, we found that low frequency oscillations in the alpha/beta range exhibited similar attenuations between forward speech, reverse speech, and SCN trials even though the gamma-band was less strongly augmented during SCN stimuli. The only low frequency finding of note was that of the Pre-Response sites of the frontal lobe in which low frequency attenuations were somewhat greater during reverse speech compared to the other stimuli, while the effect size was rather small (only 11% difference). This finding is difficult to interpret, as it is contrary to our previously reported findings (Brown et al., 2012b) and did not survive correction for multiple comparisons.

*Non-Language-Specific Processing in Wernicke's Region*

Posterior regions of the superior temporal gyrus are often included into a well known concept of the cortical organization of language processing known as Wernicke's region (Boatman and Krauss, 2000; Bogen and Bogen, 1976; Harpaz et al., 2009; Simos et al.,

2005). This is the brain region thought to engage in language-specific processing as it is well known historically that lesions in this region are capable of severely disrupting language comprehension. Therefore, it is interesting that many of our Early Auditory sites, which we have demonstrated here to be involved in a non-language-specific function, are located in the posterior portions of the superior temporal gyrus. At these sites, forward speech, reverse speech, and SCN were associated with similar, short augmentations of gamma activity early during the stimulus. Indeed, it is unlikely that such early ECoG gamma-augmentation reflects semantic processing at these sites since, by definition, the activity is not extending throughout the stimulus even when it is intelligible (i.e. forward speech). Rather we demonstrated human-voice-specific processing at sites classified as Full Auditory, which largely localized to middle portions of the superior temporal gyrus. This emergent pattern begs the question of how lesions to posterior superior temporal regions disrupt language when more specific language processing is not located there. A plausible hypothesis may be that some such lesions are actually disrupting a process of human voice detection, rather than language processing. That is, Early Auditory sites may engage in a process of human voice detection. If a human voice is detected, processing proceeds toward sites classified here as Full Auditory, and language-related information processing proceeds; e.g. semantic processing. Further work is needed to confirm the validity of this hypothesis.

*Conclusion*

Stimuli that cannot be perceived as a human voice may be more appropriate for the control of non-language-specific auditory function of the lateral temporal lobe. SCN is an

excellent candidate control task in the study of large-scale language networks because it can be generated directly from the corresponding speech to maintain the rhythm, duration, power, and frequency information while removing the essential characteristics of the human voice. We also found that two subclasses of activity along the superior temporal regions may carry out differential functions in the processing of speech; one being specific to human voice and the other non-specific. Reverse speech was again shown to poorly control for non-language-related activities of the lateral temporal lobe.

*Synthesis*

This follow-up study yielded results that suggest it to be possible to create an auditory descriptive naming task that allows for more precise characterization of superior temporal sites that are engaged during language performance. Indeed, with this 'dissection', we were able to propose a new concept for the language related function of the posterior portion of the superior temporal gyrus; i.e., human voice detection. Such information may further our scientific understanding of processes related to language comprehension as well as create new clinical techniques that may further enhance the prevention of post-operative deficits.

A topic of interest that spontaneously arose from these two studies of auditory language control tasks is that of the frontal eye field (FEF). In both of the above studies of this section, we were able to demonstrate 'auditory' activations of the precentral gyrus, about midway up its lateral surface. These activations look strikingly similar to those of the superior temporal gyrus in terms of onset and duration. Clearly, these sites of the precentral gyrus are engaged in some sort of early auditory processing; as has

been proposed by other investigators (Kirchner et al., 2009). In neither study did we garner enough sites to investigate this phenomenon fully, as it was not the aim. However, we may comment that there does appear to be some similarity in these sites compared to the sites of the superior temporal gyrus. For example, the difference in activations in response to forward speech, reverse speech, and SCN appears to be to those over the superior temporal gyrus. Therefore, the 'auditory' activity here does appear to be selective for human speech. Further studies will be needed with multiple modalities to further determine the significance of such activity.

This study comparing the activations associated with SCN to those with forward speech yielded results similar to what has been reported in the fMRI literature. However, this study also confirmed, albeit less dramatically, that the activities associated with reverse speech relative to those with forward speech appear different on ECoG compared to fMRI. This somewhat specific discrepancy between fMRI and ECoG is interesting because reverse speech is perceived as a human voice, much like forward speech. Combined ECoG-fMRI or even simultaneous EEG-fMRI studies utilizing reverse and forward speech task trials will be interesting as it may reveal information that will aid understanding of the blood oxygen level dependent (BOLD) signal itself.

## Section 3.2: Dissecting Frontal Lobe Language Functions from Working Memory

*Introduction*

Language sites are highly variable from person to person. Studies of fMRI report frontal lobe language activity outside of Broca's area (Gaillard et al., 2003; Schapiro et al., 2004; Szaflarski et al., 2006; Wood et al., 2004); often attributed to working memory. However, an intraoperative stimulation study suggests premotor areas to possess naming function separate from working memory (Duffau et al., 2003). In fact, some imaging research suggests premotor cortex, rather than Broca's area, to be directly connected to Wernicke's region (Bernal and Ardila, 2009). Premotor cortex has also been implicated in language using stimulation, fMRI, and Positron Emission Tomography (Brown et al., 2005; Dreyer et al., 2009; Duffau et al., 2003; Gaillard et al., 2003; Schapiro et al., 2004; Schlaggar et al., 2002; Szaflarski et al., 2006; Wood et al., 2004), with evidence it may not be attributable to working memory or motor function (Duffau et al., 2003).

This study aims to determine if language-related frontal sites outside of Broca's area are truely mediating at language-related function. We employ a working memory task alongside a well-studies naming task for contrast. We hypothesize that language-specific frontal sites, with function independent of working memory, exist outside of the traditional Broca's area.

*Methods*

*Study Patients*

Patients were selected by using the following inclusion criteria: (i) a history of intractable focal epilepsy scheduled for extraoperative subdural ECoG recording as part

of presurgical evaluation at Children's Hospital of Michigan or Harper University Hospital, Detroit, between December 2010 and March 2013, (ii) age of 5 years or older, (iii) measurement of ECoG amplitude augmentations driven by a language task described in the 'Auditory Naming Task' section below, and (iv) measurement of ECoG amplitude augmentations driven by a letter-based working memory task described in the 'Working Memory Task' section below. Exclusion criteria consisted of: (i) presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and sylvian fissure, (ii) right or bilateral language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left-handedness when Wada test results are not available (Knecht et al., 2000a), (iv) multiple seizure foci involving both hemispheres, (v) Verbal Comprehension Index (VCI) or Verbal Intelligence Quotient (VIQ) less than 70, (vi) inability to complete the tasks described in the 'Auditory Naming Task' and 'Working Memory Task' sections below due to lack of adequate vocabulary, comprehension of task instructions, or cooperation, and (vii) history of previous neurological surgery. We studied a consecutive series of 11 patients satisfying all criteria (age range: 5–44 years; six females; Table 8). This study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from all patients or their legal parent or guardian. Subdural platinum grid electrode (10 mm inter-contact distance; 4 mm diameter; Adtech, Racine, WI, USA) placement was as described previously by our team (Wu et al., 2011). Extraoperative video–ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc., Foothill Ranch,

CA, USA) at a sampling frequency of 1000 Hz as previously described (Wu et al., 2011). Total electrode contact number ranged from 86 to 120 (Table 8).

**Table 8**
**Summary of Clinical Information**

| Pt | Gdr | Age at surgery (years) | Dom. Hand | Age at epilepsy onset | Antiepileptic medications | PSI† | VCI† | VIQ† | Schooling | Wada test† | Sz type | ECoG electrode coverage | Seizure onset zone | ECoG contacts (total) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | F | 15 | Rt | 13 | LEV | N/A | N/A | N/A | Above ave., 10th grade | N/A | Focal sz w/ sGTC | Lt FPTO | Lt Anterior T | 100 | Low grade tumor & gliosis |
| 7 | M | 44 | Both | 26 | LEV, OXC | N/A | N/A | N/A | Incomplete grad school | Lt | Focal sz w/ sGTC | Rt FPTO | Rt PO | 108 | Atrophy & gliosis |
| 9 | F | 14 | Rt | 13 | LEV, OXC, LAC | 100 | 124 | N/A | Above ave, 9th grade | N/A | Focal sz w/ sGTC | Lt FPTO | Lt Lateral P | 120 | Low grade tumor |
| 12 | M | 12 | Rt | 3 | VPA, OXC, LAC | 80 | 83 | N/A | Normal 6th grade | Lt | Focal sz | Lt FPTO | Lt anterior & inferior T | 116 | Mild gliosis |
| 14 | F | 27 | Rt | 26 | LEV | N/A | N/A | 100 | High School Diploma | Lt | Cx. Focal Sz | Lt FPT | Lt F | 86 | Tumor |
| 23 | M | 17 | Rt | 5 | LEV, TPM | 85 | 103 | N/A | Normal, 12th grade | Both | Cx. Focal Sz | Rt FPTO | Rt T | 104 | Gliosis |
| 15 | F | 12 | Rt | 9 | LAM, LAC | 97 | 98 | N/A | Normal 7th Grade | N/A | Cx. Focal Sz | Lt FPTO | Lt anterior medial T | 112 | Gliosis |
| 16 | F | 5 | Rt | 1 | LEV, LAC | 97 | N/A | 129 | Normal Kinder-garten | N/A | Cx. Focal Sz | Lt FPTO | Lt medial T | 108 | Gliosis |
| 17 | F | 9 | Rt | 8 | OXC | 112 | 91 | N/A | Normal 4th grade | N/A | Focal Sz | Lt FPTO | Lt anterior medical T | 108 | Tumor |
| 18 | M | 30 | Rt | 29 | CBZ, LAC | N/A | N/A | 108 | College | Lt | Focal sz w/ sGTC | Lt & Rt FPTO | Rt inferior T | Rt 94 Lt 30 | Tumor |
| 21 | M | 13 | Rt | 9 | LEV, OXC | 115 | 114 | N/A | Normal 8th grade | N/A | Cx. Focal Sz | Rt FPTO | RT anterior F | 138 | Dyspasia & gliosis |

Pt: patient. Gdr: gender. Ave: average. LEV: levetiracetam. LAM: lamotrigine. LAC: lacosamide. CBZ: carbamazepine. OXC: oxcarbazepine. TPM: topiramate. VPA: valproate. Rt: right. Lt: left. Cx: complex. Sz: seizure. sGTC: secondarily generalized tonic-clonic sz. F: frontal. T: temporal. O: occipital. P: parietal. † PSI: processing speed index. VCI: verbal comprehension index. VIQ: verbal intelligence quotient. Neuropsychological testing was performed based on clinical necessity. Wada testing (i.e. intracarotid sodium amobarbital procedure) results are provided to indentify the language-dominant hemisphere. Due to use of an auditory language task, we include the measures VIQ and VCI, when available.

*Coregistration of electrodes on individual three-dimensional MRI*

MRI, including a volumetric-T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image of the entire head, was obtained preoperatively using previously described protocol (Nagasawa et al., 2010a). Planar X-ray images (lateral and antero-posterior) were acquired with subdural electrodes in place; three metallic fiducial markers at well-defined anatomical locations aided coregistration with MRI. A three-dimensional MRI brain surface image was created with

electrodes delineated (Alkonyi et al., 2009a; Muzik et al., 2007; von Stockhausen et al., 1997). Accuracy was confirmed by intraoperative digital photographs of *in situ* electrodes (Asano et al., 2005; Nagasawa et al., 2010a; Wu et al., 2011).

*Auditory Naming Task*

Language mapping by measurement of auditory naming-related gamma activity was performed using an auditory naming task similar to that of Chapter 2 (Brown et al., 2008). None of the patients had a seizure within two hours prior to or during task performance. While awake and comfortably seated on a bed in a room with unwanted noises minimized, patients received up to 85 question-and-answer trials. All questions were delivered via playback of an audio recording of the author's (E.C.B.) voice using Presentation version 9.81 software (Neurobehavioral Systems Inc., Albany, CA, USA) and were designed to elicit 1 or 2 word answers with nouns; e.g. “What flies in the sky?”. The audible session was recorded and integrated with ECoG as in Chapter 2 (Brown et al., 2008; Wu et al., 2011). Subsequently, onset and offset of auditory stimuli as well as onset of the patient's vocalization of responses were marked for each trial. Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA) was used to aid manual determination of time-points. Response time was defined as the period between stimulus offset and overt response onset.

*Working Memory Task*

The working memory task employed in this study represents a letter-based, auditory variation on the Sternberg task (Sternberg, 1966) not unlike working memory tasks of

other ECoG studies (Raghavachari et al., 2001; Tertel et al., 2010); our task described in Figure 13. Task administration was similar to that of the auditory naming task. Patients received 60 question-and-answer trials. Auditory stimuli consisted of a set of 2 letters for 'low load' trials or 4 letters for 'high load' trials. After delivery of the final letter in a set, a 2 s delay preceded delivery of a target letter. Patients were instructed to answer 'yes' or 'no' regarding whether the target letter was in the set for that trial. All letters were delivered via playback of an audio recording of the author's (E.C.B.) voice using Presentation version 9.81 software. Each letter was delivered over 500 ms with 200 ms between each letter in a set. All consonants of the English alphabet were used, excluding 'w' because it is verbalized as a three syllable word. Since the sound of some letters is similar, such as 'd' and 'p' or 'f' and x', care was taken to ensure that two similar sounding letters were never delivered in succession. As the target letter is a repeat of one of the letters in a set in half of the trials, letters were recorded in three different intonations: rising, falling, and flat. Target letters in such 'yes' trials were never an exact replica of the remembered letters in the set since the intonation was always made to be different. The audible session was recorded and integrated with ECoG as described above. Subsequently, onset and offset of a stimulus set, onset and offset of the target letter, and onset of the patient's response were marked for each trial. Response time was defined as the period between target letter offset and overt response onset.

*Evaluation of ECoG amplitude changes*

Each ECoG trace was transformed into the time-frequency domain, and we determined ‘when’ and ‘where’ gamma activity was augmented. The time-frequency

analysis used in the present study was previously validated (Brown et al., 2008; Hoechstetter et al., 2004; Nagasawa et al., 2010a; Wu et al., 2011). In short, the primary measures of interest were the percent change in amplitude of gamma activity relative to that during the reference period (i.e. the resting baseline) as well as statistical significance of task-related augmentation of gamma activity. The details of analytic methods are described below.

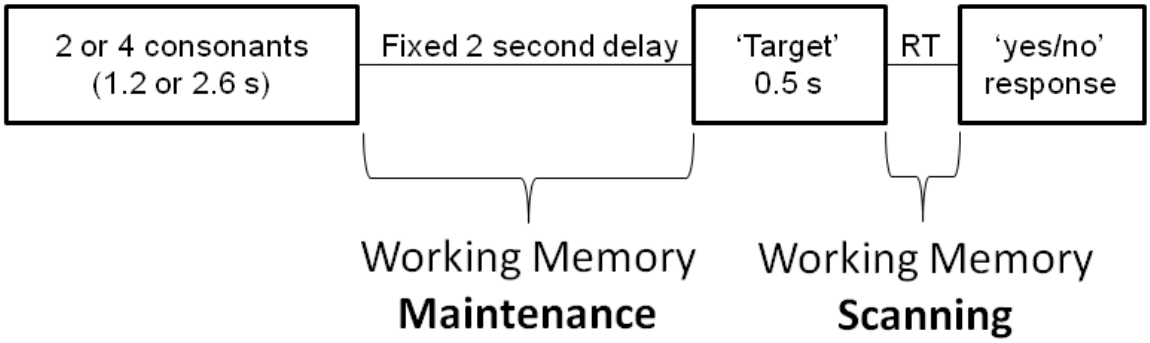


**Figure 13: Modified Sternberg Task of Working Memory.** Via pre-recording of the same voice and volume as the naming task, trials present 2 or 4 letter stimuli the patient must remember; inter-consonant-interval of 200 ms. A two second delay follows, after which a target letter is provided. The maintenance phase occurs during the two second delay. The scanning phase follows receipt of the target, prior to response generation. Patients state "yes" or "no" indicating if the target was in the stimulus. RT = response time. WM = working memory.

*Analysis of ECoG changes relative to stimulus onset - Naming task only*

The auditory naming trial set was analyzed in part based on stimulus onset. The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) a period of silence serving as a reference period of 400 ms duration was available between 600 and 200 ms prior to the onset of stimulus presentation. The exclusion criteria included: (i) ECoG trace was affected by movement artifacts, (ii) ECoG trace was affected by electrographic seizures, (iii) the corresponding forward or reverse speech trial was excluded due to failure to satisfy criteria, and (iv) ECoG traces were affected by runs of interictal epileptiform discharges lasting 3 s or longer.

Time-frequency analysis was performed using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany). Each suitable ECoG trial was transformed into the time-frequency domain using a previously described complex demodulation technique (Hoechstetter et al., 2004; Papp and Ktonas, 1977; Wu et al., 2011). For evaluation of high frequency gamma activity, time-frequency transformation was performed for frequencies between 10 and 200 Hz and latencies between −600 ms and +4000 ms relative to the onset of stimulus presentation, in steps of 5 Hz and 10 ms as previously reported (Brown et al., 2008). Details of the statistical approach to determine significance of gamma-augmentation is described in Chapter 2.

*Analysis of ECoG changes relative to stimulus offset - Naming task only*

We maintained a pre-stimulus reference period that was jittered based upon stimulus duration. For each patient, we determined the longest stimulus duration, referred to here as $t_{stim}$ in milli-seconds. The inclusion criteria defining trials suitable for this time-frequency analysis included: (i) patient provides a correct response and (ii) a period of silence serving as a reference period lasting 400 ms immediately preceding the time point $-t_{stim}$ - 200 ms, with stimulus-offset defined as 0 ms. The exclusion criteria, waveform evaluation, and statistics were as described in the 'Analysis of ECoG amplitude changes relative to stimulus onset' section.

*Analysis of ECoG changes relative to target onset - Working memory task only*

Since the stimulus set and delay periods prior to target onset of working memory trials were standardized, stimulus onset and offset analyses were not warranted.

Instead, we performed a target onset analysis. We maintained a pre-stimulus reference period. The inclusion criteria defining trials suitable for this time-frequency analysis included: (i) patient provides a correct response and (ii) a period of silence serving as a reference period lasting 400 ms immediately preceding the time point -4800 ms, with target-onset defined as 0 ms. The exclusion criteria, waveform evaluation, and statistics were as described in the 'Analysis of ECoG changes relative to stimulus onset' section.

*Analysis of ECoG changes relative to response onset - both tasks*

We maintained a pre-stimulus reference period that was jittered based upon the combined stimulus and response-time duration. For each patient, we determined the longest stimulus + response time, referred to here as $t_{resp}$ in milli-seconds. The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) patient provided a correct response, (ii) the response-time variability must be within 1000 ms across trials (Brown et al., 2008), and (iii) a period of silence serving as a reference period of 400 ms immediately preceding the time point $-t_{resp}$ − 200 ms, with response-onset defined as 0 ms. Time-frequency transformation was performed for latencies between $-t_{resp}$ - 200 ms to the duration of the longest included trial. The exclusion criteria, waveform evaluation, and statistics were as described in the 'Analysis of ECoG changes relative to stimulus onset' section.

*Categorization of electrode sites with significant gamma-augmentation*

We used a categorization scheme similar to that more thoroughly described in this Chapter's subsection 3.1A (Brown et al., 2012b). Categorization is based entirely upon

findings from language mapping with the auditory naming task. A given electrode is defined as an ‘Auditory’ site if significant gamma-augmentation begins within 300 ms following stimulus onset (Flinker et al., 2010). All other sites with significant gamma-augmentation were treated as ‘Non-Auditory’ sites. These Non-Auditory sites were further subcategorized by the temporal domain in which peak gamma-augmentation occurred. That is, ‘Post-Response’ sites exhibited peak augmentation following response-onset. In this study, we do not further classify other Non-Auditory sites.

*Comparing Language-related to Working Memory-related Activities*

We performed a straightforward comparison of activations generated by the naming task or by the working memory task. We identified and classified working memory activations as 'Maintenance' and 'Scanning'. Working memory Maintenance sites were defined as those sites with i) significant gamma-augmentation during the delay period of the working memory task, excluding the first 500 ms of the delay period if the site was identified as Auditory with the auditory naming task to avoid any effects of anticipation (duration of individual working memory stimuli was 500 ms), and ii) a 'dose effect' in which this activation possessed a higher peak augmentation associated with the 4 letter, high dose trials compared to that with the 2 letter, low does trials. Working memory Scanning sites were subjected to a more rigorous criteria in order to ensure they are separable from sites associate with auditory processing of the target. Scanning sites were identified when i) significant gamma-augmentation followed onset of the target stimulus but peaked prior to response onset, ii) the site was not classified as Auditory or Post-Response by the classification criteria associated with the auditory

naming task, and iii) a 'dose effect' was suggested by a peak gamma-augmentation greater during the 4 letter, high does trials than during the 2 letter, low dose trials. The localization of such activity was compared with a search for trends across patients.

## *Results*

### *Behavioral Results*

All patients were able to participate in both tasks until completion. On average, 92.1% (±8.5% standard deviation) of all working memory trials were correctly answered. There was no significant difference in the average percentage of correct responses between the 4 and 2 letter working memory trials (90.3% and 93.9%, respectively; p-value = 0.224). Across patients, the 'high dose' 4 letter working memory trials were associated with a significantly longer average response time relative to that of the 'low dose' 2 letter working memory trials (279 ms and 263 ms, respectively; $p<0.001$).

### *Frontal Lobe*

The naming and working memory tasks elicited significant gamma-augmentation at many sites of the frontal lobe. Working memory scanning was observed at many sites including 3 sites of the precentral gyrus or sulcus (2 right hemispheric), 2 sites over the inferior frontal gyrus or sulcus, 2 sites over medial frontal cortex, 1 site over the cingulate, and 1 site over the frontal pole (1 right hemispheric). Each of these working memory scanning sites were also activated by the naming task except for 1 site of the right medial frontal cortex, 1 site of the inferior frontal sulcus, 1 site of the precentral sulcus, and 1 site of the frontal pole. Working memory maintenance sites were

observed over restricted distributions with 8 sites over the precentral gyrus or sulcus (1 right hemispheric) and 3 over medial frontal cortex. Each of these working memory maintenance sites were also activated by the naming task except for 1 site over the right precentral sulcus. In particular, of the working memory maintenance sites of the precentral gyrus, 4 were classified as Auditory, 2 as Pre-Response, and 1 as Post-Response based on the naming task. Of the working memory maintenance sites of medial frontal cortex, 1 was classified as Late Stimulus and 2 as Pre-Response based on the naming task; data from the 5 patients with these sites are displayed in Figure 14 with an example from patient 9 in Figure 15. Naming was uniquely associated with gamma-augmentation at 8 sites over the middle frontal gyrus, 3 sites over the superior frontal gyrus, 20 sites (1 right hemispheric) over the inferior frontal gyrus, 24 sites (4 right hemispheric) over the precentral gyrus or sulcus, 4 sites (2 right hemispheric) over the central sulcus, 5 over orbital frontal cortex, and 1 over medial frontal cortex.

## *Discussion*

### *Primary Findings*

We set out to determine if language-related sites of the frontal lobe outside of Broca's area could be attributed to the non-language-specific function of working memory. We found that several such sites could be attributed to such a non-language-specific process, but this was a minority of sites. Regarding the inferior frontal gyrus, including Broca's area, nearly all sites engaged during performance of the naming task were not engaged by the working memory task. Similar language-specific sites were observed over orbital frontal cortex, medial frontal cortex, superior and middle frontal

gyri, and the precentral gyrus and sulcus. Sites mediating a working memory scanning function appeared to be sporadically localized across patients and it is difficult to condense this information into a concise interpretation. We leave such investigation of working memory scanning functions to future studies with higher statistical power, in terms of both task design as well as patient sample size. Regarding working memory maintenance function, we obtained a result that was otherwise unexpected. Working memory maintenance activity appeared to be highly localized to the precentral gyrus and medial frontal cortex.

*Frontal Eye Field*

It is a finding of interest that the majority of sites of the precentral gyrus or sulcus identified as involved in working memory maintenance were classified as having an Auditory function with the naming task. These sites are similar to those that we have previously reported (Brown et al., 2012b) in section 3.1 of this Chapter. Indeed, all of the working memory maintenance sites of the precentral gyrus or sulcus that were not classified as Auditory with the naming task were next to at least one such electrode of the precentral gyrus that was classified as such. Due to the association with auditory function, we believe that these sites may be over or near to the frontal eye field (Kirchner et al., 2009). Only in patient 6 can we report the instance of eye deviation upon electrical brain stimulation; the electrode pair was adjacent to the electrode associated with maintenance.

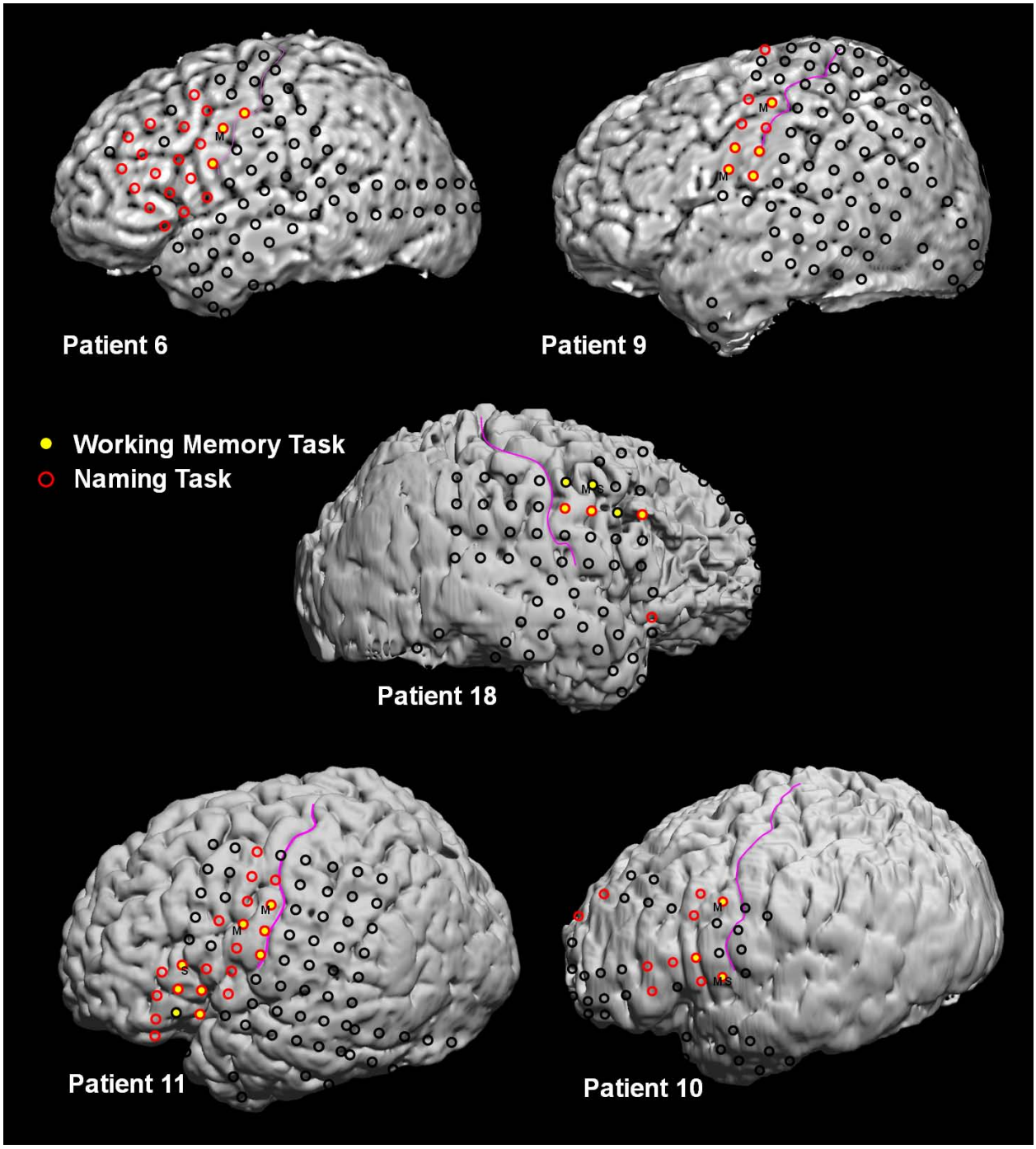


**Figure 14: Working Memory and Naming Sites.** Displayed are the MRI images of the brains of the 5 patients with working memory maintenance function observed over the precentral gyrus or sulcus. Working memory maintenance is identified by the letter 'M' near a red-yellow electrode; 'S' for scanning. Interestingly most maintenance sites cluster midway up the precentral gyrus.

The frontal eye fields, identified by lateral eye deviation toward the contralateral side upon electrical brain stimulation, have been shown to be involved in both fast auditory

and visual processing (Kirchner et al., 2009). However, our findings presented in section 3.1 suggest some language-specific processing. We identify here a role for the frontal eye field in working memory maintenance, which has never been reported previously. This particular region of cortex midway up the lateral surface of the precentral gryus appears to be rich with various functions. While this study was not designed to explore this region specifically, we believe that further study of the frontal eye fields may yield new insights into the cortical function of language, working memory, and beyond. The clinical significance of these sites also requires further investigation.

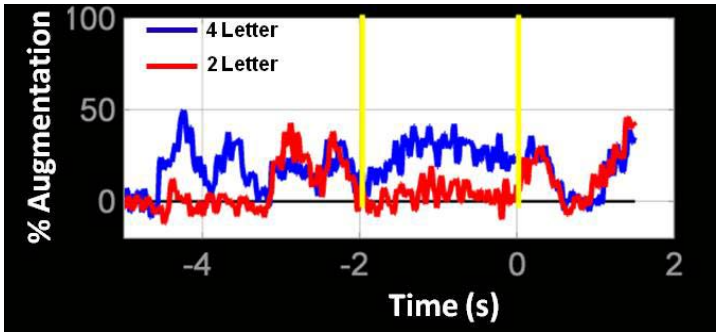


**Figure 15: Working Memory Maintenance.** Displayed is an example of a working memory maintenance site from patient 9; vertical axis is percent above baseline, horizontal axis is time in seconds with 0 as the onset of the target letter. Blue tracing represents gamma activity for the 4-letter trials, red for the 2-letter trials. Working memory maintenance with dose response occurs between -2 and 0 s. Note the auditory activity.

*Synthesis*

While this study failed to meet its original goal of determining which naming sites of the frontal could be attributed to working memory function, it inadvertently allowed for the observation of working memory maintenance functions which may reside within a region known as the frontal eye fields. Such a finding has not been previously reported with any other modality. Indeed, ECoG may be an essential modality for this initial observation of such a phenomenon due to its excellent signal-to-noise ratio and temporal resolution.

## CHAPTER 4: Structural Connectivity of Language Areas Defined by ECoG

*This chapter is modified from the original publication in the scientific journal Human Brain Mapping - (Brown et al., 2013)*

### *Introduction*

The Wernicke-Lichtheim model, formulated by 1885, was the first to suggest a direct anatomical connection between Wernicke's region of the posterior left temporal lobe and Broca's area of the left inferior frontal gyrus (Graves, 1997). This model laid out the origins of our modern understanding of language in a diagrammatic form that was both easy to understand and predictive of what type of lesion might lead to what type of symptom (Graves, 1997; Lichtheim, 1885). Geschwind's work in the 20th century is well known for advancing the idea that the arcuate fasciculus represented the physical manifestation of the concept of a direct connection between Wernicke's region and Broca's area (Geschwind, 1970). Even after recent reconsideration of the model (Catani and Mesulam, 2008; Friederici, 2012; Poeppel et al., 2012), these two cortical regions and the associated white matter tract have constituted our understanding of language-related structure and localization in the left hemisphere.

It is interesting that a review of the literature back to the 19th century does not yield a single study that clearly demonstrates the arcuate fasciculus' assumed termination within Broca's area (Martino et al., 2012); with Broca's area strictly defined as the lateral surface of the combination of *pars triangularis* (Brodmann Area [BA] 45) and *pars opercularis* (BA 44) of the left inferior frontal gyrus (Dronkers et al., 2007; Strotzer, 2009). In many studies utilizing diffusion-weighted imaging tractography, a termination of the arcuate fasciculus within Broca's area is assumed, often by seeding fibers directly from Broca's area (Brauer et al., 2011; Ellmore et al., 2009). A lack of fibers associated

with portions of Broca's area, *pars triangularis* in particular, is often interpreted as an imaging shortfall rather than a reflection of actual connectivity (Diehl et al., 2010). Indeed, several studies have provided new evidence that the anterior terminations of the arcuate fasciculus, the cytoarchitecture traditionally associated with Broca's area, and the functional correlates of language often extend outside the anatomically defined boundaries of Broca's area (Dronkers et al., 2007), with a notable extension into the inferior precentral gyrus (Amunts et al., 2003; Amunts and Zilles, 2012; Bizzi et al., 2012; Catani and Mesulam, 2008); the new term 'Broca's territory' (Catani et al., 2005) has even been proposed to encompass cortex adjacent to the historically relevant Broca's area. Functional data generated by a study of patients with gliomas located in the inferior precentral gyrus and the inferior frontal gyrus of the left hemisphere suggest that essential language function can be located within the inferior precentral gyrus (Bizzi et al., 2012); out of 19 patients, the only case of Broca (expressive) aphasia was associated with a glioma in the inferior precentral gyrus that compressed but spared *pars opercularis* of the inferior frontal gyrus.

The signals detected and routinely analyzed by ECoG methods fall within a class of electrophysiological activities known as local field potentials (LFP), which have been shown to correlate well with the blood-oxygen-level-dependent (BOLD) signal detected by fMRI (Logothetis, 2003). Task-related amplitude augmentation of broadband gamma-range signals in excess of 50 Hz has been shown to accurately localize cortical function (Crone et al., 2011; Jerbi et al., 2009; Miller et al., 2008). We utilize a well validated auditory descriptive naming task to elicit gamma (50 to 150 Hz) augmentation in

cerebral regions mediating language (Brown et al., 2008; Brown et al., 2012b; Cervenka et al., 2013; Kojima et al., 2012; Kojima et al., 2013b).

The aim of the present study involved the utilization of language-related electrocorticography (ECoG) results to generate temporal lobe seed and supra-Sylvian target regions for tractographic analysis. Such an approach provides the ability to avoid specific anatomical assumptions about the localization of Wernicke's region. While seeding tractrography from language-related gamma sites of the temporal lobe, indicated by ECoG analysis to be involved in language-related processing, we hypothesized that fibers would track predominantly to the inferior frontal gyrus rather than the precentral gyrus. Further, we hypothesized that fibers would track more frequently to frontal lobe sites showing gamma-augmentation during a language task compared to those that do not. We expected that testing these hypotheses would provide additional evidence to validate the aforementioned model of language-related brain structure (Graves, 1997).

## *Materials and Methods*

### *Study Patients*

Patients were selected by using the following inclusion criteria: (i) a history of left-hemispheric focal epilepsy scheduled for extraoperative subdural ECoG recording as part of presurgical evaluation at Children’s Hospital of Michigan or Harper University Hospital, Detroit, (ii) age of 5 years or older, (iii) measurement of ECoG amplitude augmentations driven by a language task described in Chapter 2, and (iv) preoperative magnetic resonance imaging (MRI), including 55-direction diffusion-weighted imaging.

Our recent ECoG study demonstrated that language-related gamma sites were identified in patients at 4 years and older and that resection of such sites predicted postoperative language deficits with statistical significance (Kojima et al., 2013b). Exclusion criteria consisted of: (i) the presence of physical deformities of the brain, including tumor or malformation, that disrupt the normal structure of the left superior temporal region, inferior parietal region, postcentral gyrus, precentral gyrus, or inferior frontal gyrus, (ii) history of hearing impairment, (iii) right language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left- or ambiguous-handedness when Wada test results are not available (Knecht et al., 2000b; Moddel et al., 2009), (iv) multiple seizure foci involving both hemispheres, (v) documented history of language delay represented by Verbal Comprehension Index (VCI) or Verbal Intelligence Quotient (VIQ) less than 70, and (vi) history of previous neurological surgery. We studied a series of five patients satisfying all criteria (age range: 6 - 21 years; four females; Table 9). This study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from all patients or their legal parent or guardian.

Subdural platinum grid electrode (10 mm inter-contact distance; 4 mm diameter) placement was performed as described previously by our team (Asano et al., 2009a; Wu et al., 2011). Electrode plates were stitched to adjacent plates and/or the edge of dura mater, to avoid movement of subdural electrodes after placement. Extraoperative video-ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc., Foothill Ranch,

CA, USA) at a sampling frequency of 1000 Hz as previously described (Wu et al., 2011). Total electrode contact number ranged from 68 to 118 (Table 9).

**Table 9**
**Summary of Clinical Information**

| Pt | Gdr | Age at surgery (years) | Dom. Hand | Age at epilepsy onset | Antiepileptic medications | PSI† | VCI† | VIQ† | Schooling | Wada test† | Sz type | ECoG electrode coverage | Seizure onset zone | ECoG contacts (total) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | M | 17 | Rt | 5 | LEV,OXC | 88 | 109 | 104 | Above Ave., Normal 12th Grade | Lt | Focal Sz w/ sGTC | Lt FPTO | Lt Medial T | 112 | Gliosis & Micro-dysgenesis |
| 25 | F | 21 | Rt | 21 | LEV | N/A | N/A | N/A | High School Diploma | N/A | Focal Sz w/ sGTC | Lt PTO | Lt O | 68 | Low Grade Tumor |
| 6 | F | 15 | Rt | 13 | LEV | N/A | N/A | N/A | Above Ave., Normal 10th Grad | N/A | Focal Sz w/ sGTC | Lt FPTO | Lt Medial & Anterior T | 100 | Low Grade Tumor |
| 26 | F | 6 | Rt | 1 | VAL, LAM | N/A | N/A | 74 | Normal Kinder-garten | N/A | Focal Sz | Lt FPTO | Lt Medial T | 118 | Hippo-campal Sclerosis |
| 15 | F | 12 | Rt | 9 | LAM, LAC | 97 | 98 | N/A | Normal 6th Grade | N/A | Focal Sz | Lt FPTO | Lt Medial T | 110 | Hippo-campal Sclerosis |

Pt: patient. Gdr: gender. LEV: levetiracetam. LAM: lamotrigine. LAC: lacosamide. OXC: oxcarbazepine. VAL: valproate. Rt: right. Lt: left. Sz: seizure. sGTC: secondarily generalized tonic-clonic sz. F: frontal. T: temporal. O: occipital. P: parietal. † PSI: processing speed index. VCI: verbal comprehension index. VIQ: verbal intelligence quotient. Wada test: sodium amobarbital procedure

*Coregistration of Electrodes on Individual Three-Dimensional MRI*

MRI, including a volumetric-T1-weighted spoiled gradient echo image as well as a fluid-attenuated inversion recovery image of the entire head, was obtained preoperatively using a previously described protocol (Nagasawa et al., 2010a). Planar X-ray images (lateral and antero-posterior) were acquired with subdural electrodes in place for localization on the brain surface (Dalal et al., 2008; Miller et al., 2007b; von Stockhausen et al., 1997); three metallic fiducial markers at anatomically well-defined locations aided coregistration with MRI. A three-dimensional MRI brain surface image was created with electrode sites delineated (Alkonyi et al., 2009b; Muzik et al., 2007; von Stockhausen et al., 1997). Accuracy was confirmed by intraoperative digital photographs showing *in situ* electrode locations (Asano et al., 2005; Nagasawa et al., 2010a; Wu et al., 2011). Figure 16 shows typical electrode coverage.

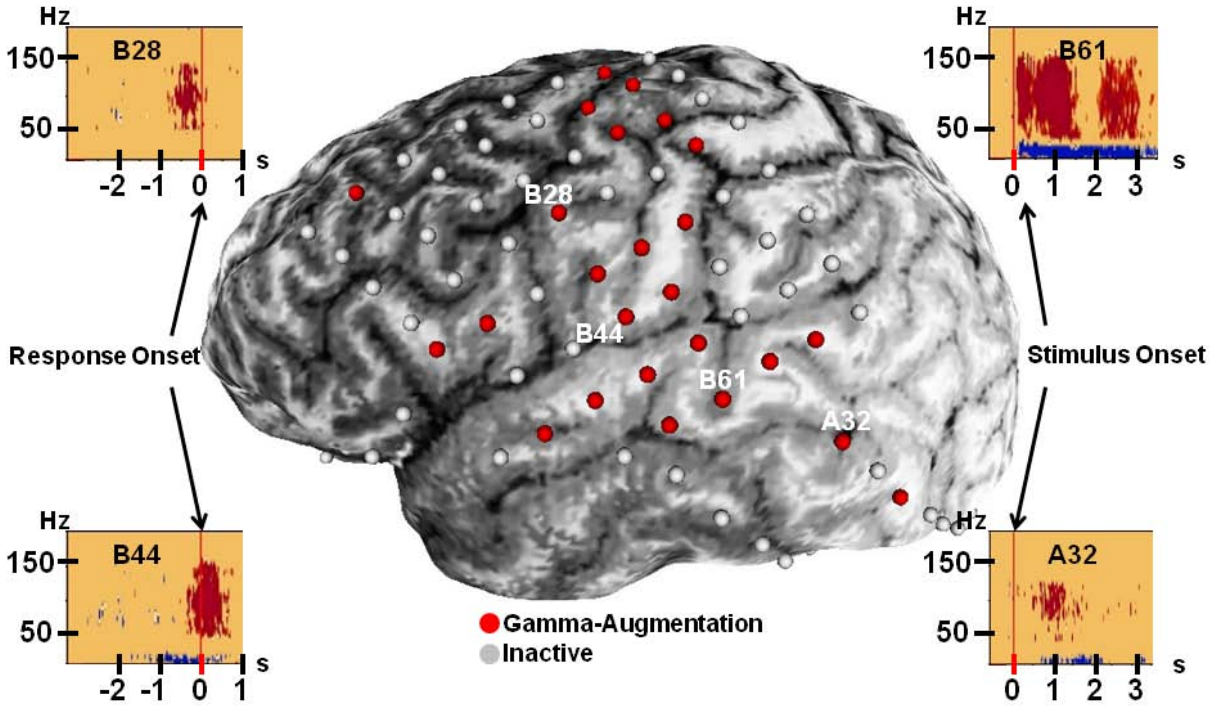


**Figure 16: Typical Electrode Coverage.** Data from patient 24. In four of the five patients, with patient 25 as the exception, an 8x8 grid of electrodes covered portions of the lateral frontal, parietal, and temporal lobes. Variably, electrode strips extended coverage, as seen here in inferior temporal region. Electrodes with 'red' color represent those with significant gamma-augmentation between 50 and 150 Hz. Results from stimulus-onset analysis are shown for electrodes A32 and B61; B61 exhibits Auditory activity as previously described (Brown et al., 2012b). These two temporal lobe electrode sites were among those used to generate tractography seed regions. Electrodes B28 and B44 are over the inferior portion of the precentral gyrus and results from response-onset analysis are displayed. Note that B28 exhibits augmentation largely prior to response-onset.

*Auditory Naming Task*

Language mapping by measurement of auditory naming-related gamma activity was performed using an auditory naming task similar to that described in Chapter 2 (Brown et al., 2008; Kojima et al., 2012); more specifically described as an auditory descriptive naming task (Cervenka et al., 2013). None of the patients had a seizure within two hours prior to or during task performance. While awake and comfortably seated on a bed in a room with unwanted noises minimized, patients received up to 100 question-and-answer trials. Question stimuli ranged from 1 to 2.5 s in duration. All questions were delivered via playback of an audio recording of the author's (E.C.B.) voice using

Presentation version 9.81 software (Neurobehavioral Systems Inc., Albany, CA, USA) and were designed to elicit 1 or 2 word answers with nouns; e.g., “What flies in the sky?”

The audible session was recorded and integrated with ECoG as previously described (Brown et al., 2008). Subsequently, the onset and offset of auditory stimuli as well as the onset of the patient's vocalization of the response were marked for each trial. Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA) was used to visually and audibly aid in the manual determination of these time-points. The response time was defined as the period between offset of stimulus presentation and onset of the respective overt response. Patients were instructed to answer “I don’t know” when they did not know the answer to or did not understand a stimulus.

*Evaluation of ECoG Amplitude Changes*

Each ECoG trace was transformed into the time-frequency domain, and we determined ‘when’ and ‘where’ gamma activity was augmented. The time-frequency analysis used in the present study was previously validated (Brown et al., 2008; Hoechstetter et al., 2004; Nagasawa et al., 2010a; Wu et al., 2011). In short, the *primary* measures of interest were the percent change in amplitude of gamma activity relative to that during the reference period (i.e.: the resting baseline) as well as statistical significance of task-related augmentation of gamma activity. The details of the analytic methods are described below.

Stimulus onset, stimulus offset, and response onset analyses were carried out across all suitable trials as described in Chapter 2 and Chapter 3's subsection 3.1A

(Brown et al., 2012b). Briefly, inclusion criteria ensure that a period of silence serving as a reference period of a minimum of 400 ms duration prior to the onset of stimulus presentation was present for each trial. For response-onset analysis, a maximum variation in reaction time of 1 s was imposed across included trials. Exclusion criteria removed EMG/EOG and movement artifacts as well as data associated with runs of repetitive spike-wave discharges lasting longer than 3 s from analysis. Trials in which the stimulus was not heard were excluded from all analyses. Trials with incorrect answers were excluded from stimulus offset and response onset analyses. Time-frequency analysis and statistic were performed as described in Chapter 2 and Chapter 3's subsection 3.1A. All electrodes identified herein as 'activated' have exhibited significant gamma augmentation by this method; selected examples can be seen in Figure 16. The precise anatomical location of each language-related gamma site was defined as described in this Methods section below.

*Diffusion Tensor Imaging*

*Image Acquisition*

MRI scans were performed with a 3T Twin-Speed GE Scanner using an 8-channel head coil; patient 5 was instead scanned on a 1.5T GE Scanner. Diffusion-weighted images were acquired with multi-slice single shot diffusion weighted echo-planar-imaging (EPI) sequence at TR = 12,500 ms, TE = 88.7 ms, FOV = 24 cm, 128x128 acquisition matrix (nominal resolution = 1.89 mm), contiguous 3 mm thickness in order to obtain axial slices of the whole brain using 55 isotropic, non-collinear gradient directions with b=1000 s/mm$^2$, one b=0 acquisition, and number of excitations (NEX)=1.

Approximate scanning time for the acquisition was 12 minutes using double refocusing pulse sequence and parallel imaging capability (ASSET factor of 2) to reduce eddy current artifacts and geometric distortion artifacts derived from echo-planar imaging. Because the scans were clinical MRI studies, sedation was used as necessary by the sedation team at Children's Hospital of Michigan according to standard clinical protocols. However, younger children were scanned while sleeping, and all patients were monitored for movement during scanning.

*Image Processing and Analysis*

SPM 8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) was utilized for eddy current correction of diffusion-weighted images. Freesurfer (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA) was utilized to reconstruct all T1 images. ECoG electrodes were represented in our processing stream by spherical masks of 8 mm radius that were placed on the T1 MRI surface using in-house software following detailed manual correction of deskulling procedures. Electrode spheres were transferred into Freesurfer to generate corresponding white matter surface labels including those voxels of the white matter surface that coincide with any portion of a sphere; an example can be seen in Figure 17B. A white matter mask, generated by Freesurfer reconstruction, was grown by 1 mm and inverted using in-house software to generate an exclusion mask for tractographic analysis in each subject.

In the present study, anatomical regions were defined with standardized, reproducible methodology. Broca's area was defined as the combination of the *pars*

*opercularis* and *pars triangularis* (Dronkers et al., 2007) of the left inferior frontal gyrus with boundaries determined by Freesurfer's parcellation algorithm; widely used and available. Precentral and postcentral gyri were defined similarly. Wernicke's region, which lacks an anatomical definition (Bogen and Bogen, 1976), was not limited to any specific cortical location. Instead, we utilized the location of language-related gamma sites of the lateral temporal lobe to define our posterior language sites; utilized here as an approximation of Wernicke's region. The specific anatomical location associated with each ECoG electrode was defined by the Freesurfer cortical parcellation containing at least 50% of the voxels associated with a particular electrode's white matter surface label. The only exception to this rule occurred when an ECoG electrode was resting upon the Sylvian fissure, since it is possible that such an electrode may detect neural activities derived from either infra- or supra-Sylvian structures. Individual white matter surface labels were not allowed to include areas on both sides of the Sylvian fissure. If such an electrode showed 'Auditory' activity, that which has an onset of gamma-augmentation within 300 ms of stimulus-onset and an offset of gamma-augmentation prior to 300 ms after stimulus-offset (Brown et al., 2012b), only the voxels of the temporal lobe were chosen to remain within the label. Otherwise, the side containing at least 50% of the voxels associated with the label was kept.

*Tractography*

Probabilistic tractography was based upon constant solid angle orientation distribution functions (Aganj et al., 2010) as implemented in FSL (FMRIB Centre, Oxford, United Kingdom). White matter surface labels associated with language-related

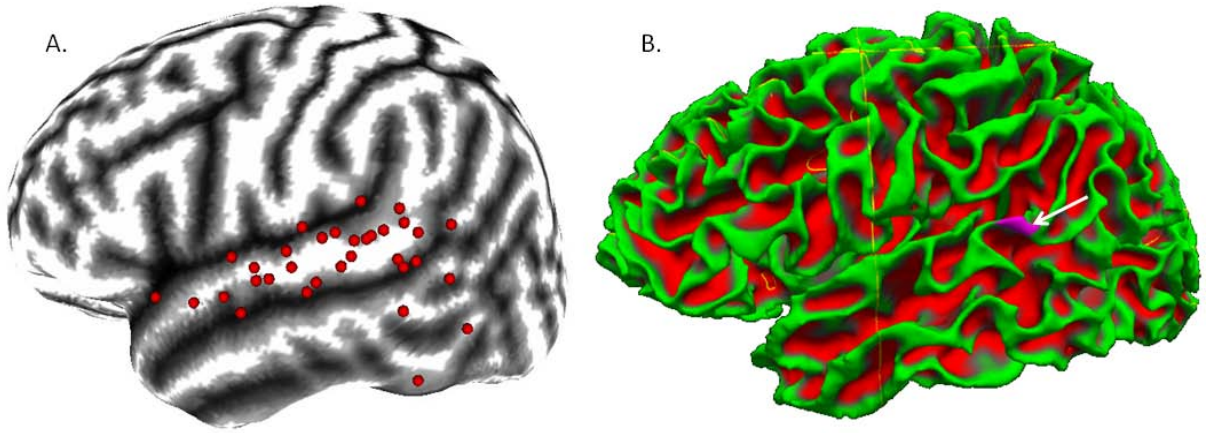


**Figure 17: Temporal Lobe Tractography Seed Sides.** Lateral temporal seed masks were generated from electrodes exhibiting language-related gamma-augmentation on ECoG. A.) Utilizing an in-house conformal cortical mapping technique (Brown et al., 2012b; Muzik et al., 2007), we mapped language-related temporal lobe electrode sites utilized in the generation of tractography seed regions in individual patients to the surface of an MNI-152 brain atlas. Sites shown here to lie over the Sylvian fissure were required to have either 50% extension of the mask into the temporal lobe white matter or to exhibit an Auditory type of activity (Brown et al., 2012b) with any amount of mask extension into the temporal lobe white matter. It can be seen that most language-related sites of the lateral temporal lobe were along the surface of the superior temporal gyrus; indeed this is our temporal region of best electrode coverage across patients. There appears to be some clustering over the posterior superior temporal region. A few sites over the posterior middle and inferior temporal gyri were also found to exhibit language-related gamma-augmentation and their associated seed masks were included. B.) A seed mask (purple region identified by white arrow) associated with one language-related temporal lobe ECoG site is displayed upon the white matter surface of patient 24, as generated by Freesurfer reconstruction; superficial white matter in green with deeper white matter in red. Only voxels associated with the white matter surface within 8mm of the electrode center are included in seed and target masks.

gamma sites of the lateral temporal lobe were used as seed regions to initiate fiber tracking into the white matter. Fibers were restricted by probabilistic correction for fractional anisotropy and allowed to make angles of up to 90̊ To ensure convergence in the tracking algorithm, 5000 fibers were generated from each seed voxel. With specific attention to the *pars opercularis*, *pars triangularis*, precentral gyrus, and postcentral gyrus, tractographic analysis was performed in three stages: 1) We determined whether anatomical white matter surface labels parcellated by Freesurfer revealed the favored anatomical termination of fibers from language-related gamma sites in the temporal lobe, 2) we determined whether tractography from temporal language-related gamma sites could predict language-related gamma sites within these

supra-Sylvian regions, and 3) tractography was performed in the reverse direction for qualitative verification of findings.

*Statistical analysis*

All statistical tests were conducted using IBM SPSS Statistics version 20 software (SPSS Inc., Chicago, IL, USA). The Generalized Estimating Equations framework was used to account for repeated measures within individuals. The first tractographic analysis compared the degree of white matter connectivity with language-related gamma sites of the lateral temporal lobe between the supra-Sylvian target regions delineated by Freesurfer parcellation: *pars opercularis*, *pars triangularis*, precentral gyrus, and postcentral gyrus. Here, after accounting for repeated measures within patients, the aim was to determine whether supra-Sylvian target region could predict tractography fiber counts from seeds in the language-related gamma sites of the lateral temporal lobe; this serves to compare the level of connectivity between the language-related temporal lobe sites and each supra-Sylvian anatomical target. A negative binomial distribution link was utilized to test this while assuming independent correlations between the regions. Parameter estimates for each region were then compared to that of the postcentral gyrus (negative control) to determine pair-wise differences.

In the second analysis, we determined whether or not the occurrence of a fiber termination associated with a supra-Sylvian target electrode could predict the occurrence of significant language-related gamma-augmentation during the language task at that electrode, even after accounting for anatomical region and within-patient

repeated measures. Additionally, we assessed for an interaction between anatomical region and diffusion-weighted tractography fiber termination. With ECoG and tractography variables expressed in binary form, a binomial logistic model was utilized with an exchangeable correlation matrix.

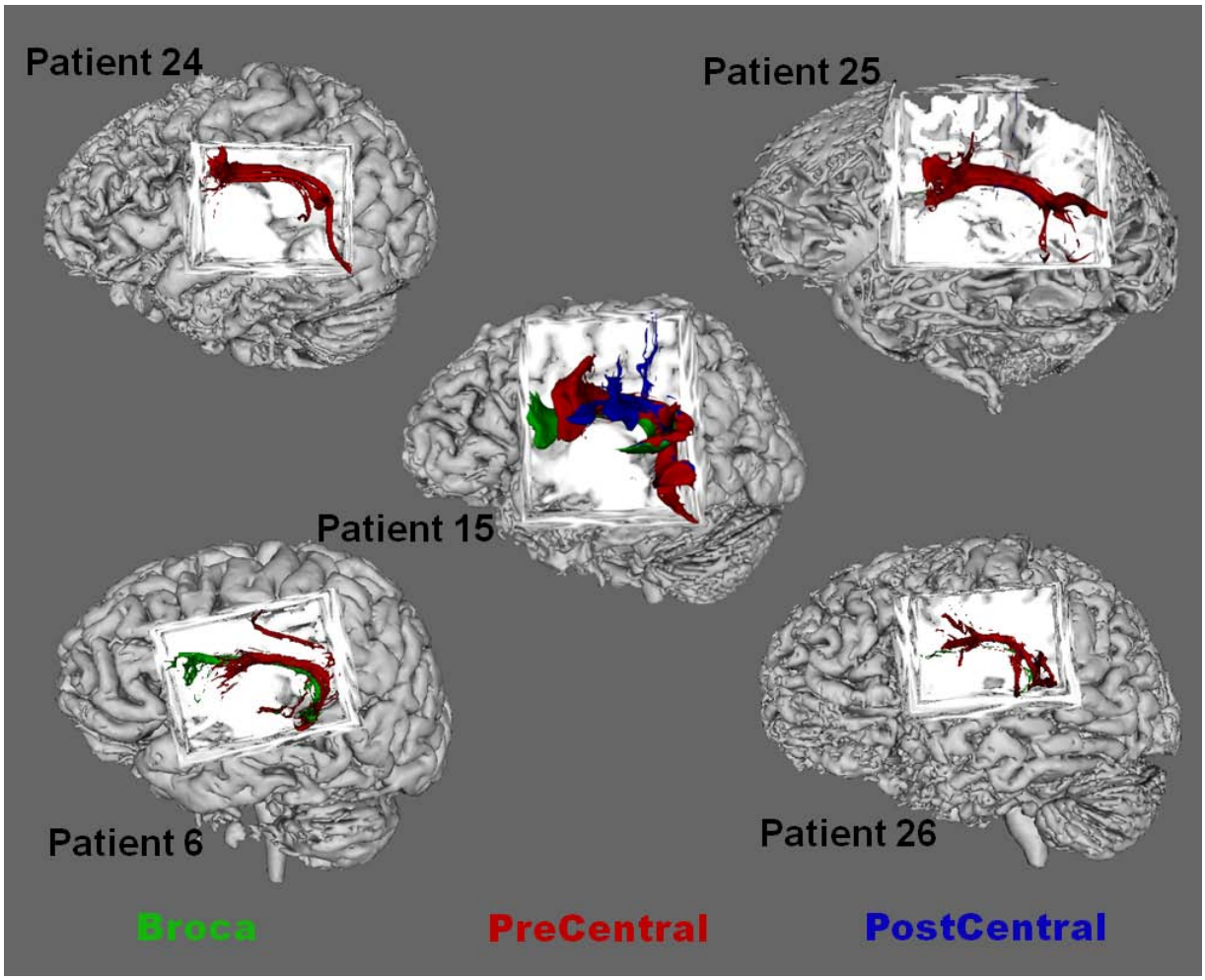


**Figure 18: Tractography Distribution.** The connectivity distribution of all fibers from each temporal seed is shown in composite for each patient. In each patient, the dominant fiber pathway resembles that of the traditional arcuate fasciculus and its primary termination in all subjects is within the precentral gyrus. In each case of fibers arriving to Broca's area, termination is within the *pars opercularis* of the inferior frontal gyrus; no fibers were found to terminate within *pars triangularis* in any patient. The precentral gyrus had a greater fiber count than the postcentral gyrus; Broca's area did not.

## *Results*

### *Supra-Sylvian Anatomical Targets*

All five subjects were included in the analysis of anatomical targets for language-related temporal seeds. The *pars triangularis* of the inferior frontal gyrus did not receive diffusion-weighted tractography fibers in any subject. Therefore, the *pars triangularis* and *pars opercularis* were combined into one region, referred to here as Broca's area, to facilitate statistical comparison. Across 33 temporal lobe seeds showing language-related gamma-augmentation in these five patients (Figure 18), supra-Sylvian anatomical target region was found to be a significant predictor of tractography fiber counts (p-value<0.001). Comparisons of the parameter estimates revealed that the precentral gyrus received a larger tractography fiber count than the postcentral gyrus (p-value<0.001); fiber counts to Broca's area did not differ from those to the postcentral gyrus (p-value=0.424). Figure 18 depicts the dominance of the precentral gyrus termination in each subject. All fibers followed a counter-clockwise path involving temporal, parietal, and frontal lobes; reminiscent of the traditional arcuate fasciculus.

### *Region Specific Association with Gamma Activity on ECoG*

Of the five subjects, only four of them received ECoG electrode coverage that included the precentral gyrus or Broca's area. In these four subjects, we evaluated whether the occurrence of a diffusion-weighted tractography fiber termination predicted the occurrence of significant language-related gamma-augmentation on ECoG. We found that, even after accounting for both patient and anatomy, the presence of a fiber termination was a significant predictor of language-related gamma sites (p-

value=0.027). Furthermore, an interaction between tractography fiber termination and anatomy was found (p-value<0.001), suggesting that fiber occurrence is a better predictor of language-related gamma sites within at least one of the three tested anatomical regions as compared to the others. Figure 19 depicts, by anatomical region, the percentage of active and non-active supra-Sylvian ECoG targets receiving at least one tractography fiber from language-related ECoG sites of the temporal lobe. It can be observed that the greatest predictive value of diffusion-weighted tractography for language-related gamma activity was within the precentral gyrus (positive predictive value [PPV]=0.89; negative predictive value [NPV]=0.76), the lowest predictive value in the postcentral gyrus (PPV=0.45; NPV=0.57), and an intermediate predictive value in Broca's area (PPV=0.78; NPV=0.52). This suggests diffusion-weighted tractography seeded from left temporal language-related gamma sites to have made a good overall prediction of language-related gamma-augmentation only within the precentral gyrus.

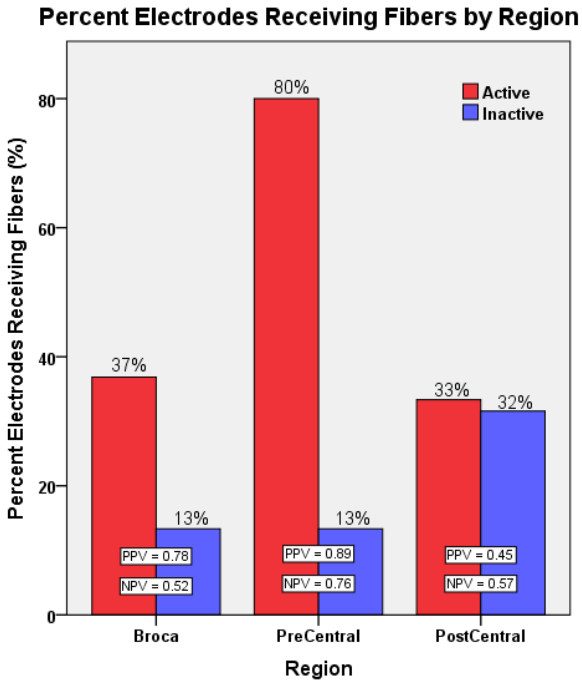


**Figure 19: Tractography-ECoG Relationship.** The percentage of active or inactive anterior electrodes receiving at least one tractography fiber from language-related gamma sites of the temporal lobe is displayed by region. The overall predictive value scores suggest that diffusion-weighted tractography from posterior language-related sites shows the greatest discrimination for anterior language-related sites within the precentral gyrus. Within Broca's area, only the positive occurrence of a nearby fiber termination exhibited an appreciable predictive value for whether or not a particular ECoG site would show language-related gamma-augmentation; the lack of a nearby fiber termination provided no predictive value. As expected, fiber terminations within the postcentral gyrus provided no predictive value for associated language-related ECoG sites.

*Tractography Seeded from Anterior Regions*

As a purely qualitative validation step, we performed tractographic analysis in the reverse direction using seeds in the anatomical regions of the precentral gyrus and within Broca's area. Within each patient, we found that more fibers from the precentral gyrus compared to those from Broca's area arrived at the targets here defined as language-related gamma sites of the lateral temporal lobe. Indeed, no fibers seeded from *pars triangularis* of the inferior frontal gyrus reached these temporal targets. Figures 20A and 20B depict fibers seeded from Broca's area and precentral gyrus to language-related sites of the lateral temporal lobe, respectively, in patient 11. Strong U-fiber tracks could be isolated between the precentral gyrus and both *pars opercularis* and *pars triangularis* within Broca's area. Although no fibers seeded from *pars triangularis* reached any of the language-related temporal lobe sites, fibers were found to reach the inferior portion of the precentral gyrus; this is depicted in Figure 20C. Overall, diffusion-weighted tractography in the reverse direction, from frontal to temporal, supported our other findings.

## *Discussion*

*Primary Findings*

We failed to find evidence in our analyses that posterior language-related cortices of the left temporal lobe possess direct white matter connections to Broca's area in the inferior frontal gyrus that are more developed than those to the precentral gyrus. This by no means indicates that Broca's area is completely devoid of arcuate fasciculus terminations. However, the fibers generated from posterior language areas failed to

exhibit any significant preference for Broca's area above that for the postcentral gyrus, a region utilized here as a negative control.

Our approach showed that diffusion-weighted tractography connectivity patterns may be related to the results of language-related ECoG analysis. It is shown here that tractographic connectivity with posterior language-related sites was best at predicting language-related gamma sites of the precentral gyrus. This finding suggests that tractography fibers from posterior language-related sites had some appreciable ability to discriminate between specific sites within the precentral gyrus that may or may not possess language-related function. Indeed, this ability for language-related functional discrimination was greater within precentral gyrus than within Broca's area in our study.

These results contribute to the growing literature suggesting that the arcuate fasciculus, arising from the left lateral temporal region showing language-related gamma-augmentation, has an anterior termination that is best approximated as the inferior portion of the precentral gyrus. In our small cohort, a well developed pathway could be traced from posterior language-related areas to the precentral gyrus in each subject. Within Broca's area, fibers could only be occasionally traced to the *pars opercularis* of the inferior frontal gyrus. In none of the patients could fibers be traced to the *pars* triangularis; a finding repeated elsewhere with various diffusion-weighted tractography and anatomical dissection methods (Bernal and Altman, 2010; Brauer et al., 2011; Diehl et al., 2010; Martino et al., 2012; Perani et al., 2011).

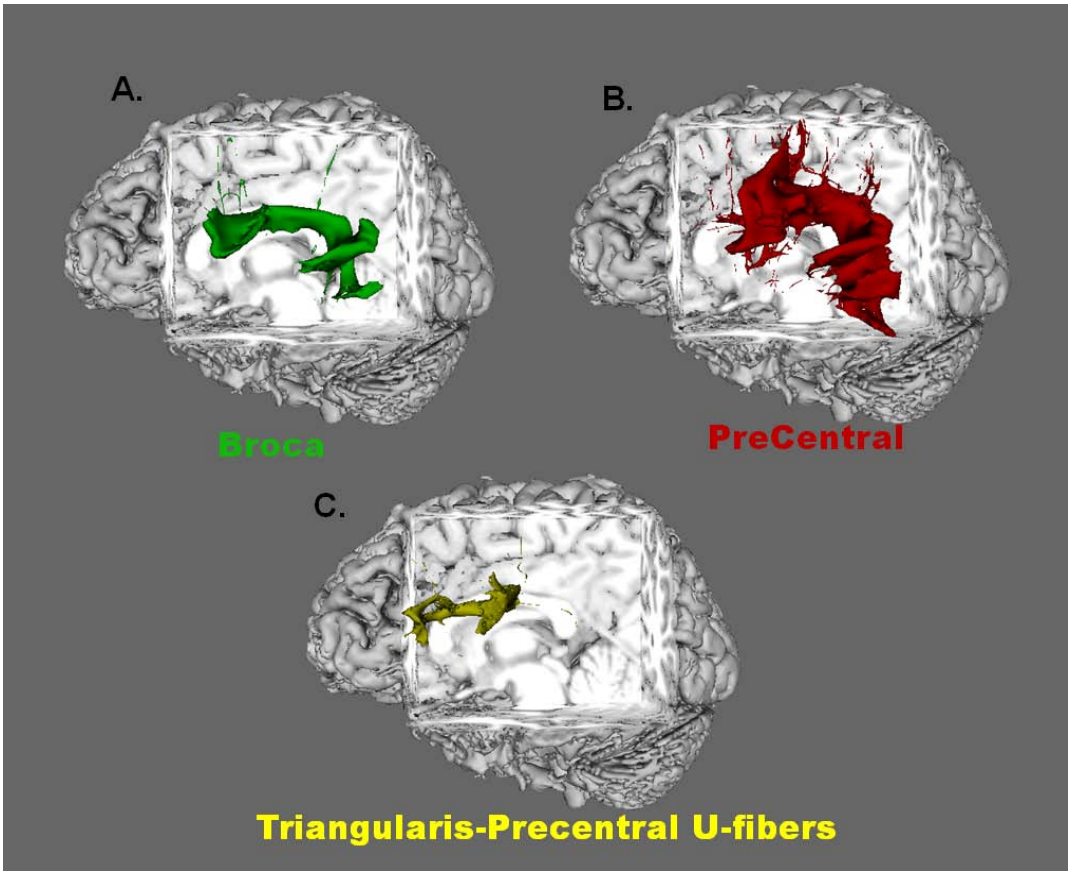


**Figure 20: Validation by Reverse Tractography.** Selected results from tractography seeded from the anterior anatomical sites in patient 6 are shown. A.) and B.) display connectivity maps of fibers seeded from Broca's area and precentral gyrus, respectively, to language-related gamma sites of the lateral temporal lobe. All fibers from Broca's area that reach the posterior language sites originated specifically from *pars opercularis* of the inferior frontal gyrus; no fibers from *pars triangularis* reached the temporal language sites. The overall tract seeded from the precentral gyrus is qualitatively larger and more robust than that from Broca's area. Although the entire precentral gyrus was used as the seed region, only those fibers originating from the inferio-lateral portion tracked through the arcuate fasciculus to the temporal language sites. Fibers shown in C.) depict U-fibers that were seeded from *pars triangularis* and reached the inferior portion of the precentral gyrus. This finding occurred even though no fibers seeded from *pars triangularis* reached the temporal language sites. Similar U-fibers were observed between *pars opercularis* and the precentral gyrus, regardless of which region was used as the seed.

*A New Model for Language Connectivity*

The Wernicke-Lichtheim model, proposed over one century ago, was powerful in that it allowed for the prediction of language-related functional deficits from lesion location in the brain (Graves, 1997; Lichtheim, 1885). This model was the first to

propose a direct anatomical communication between posterior language sites of the temporal lobe, Wernicke's region, and anterior language sites within Broca's area (Graves, 1997). Indeed, a particular set of symptoms was attributed to lesions of this tract, later identified as the arcuate fasciculus (Geschwind, 1970), in which the ability of speech repetition is compromised (Bernal and Ardila, 2009; Lichtheim, 1885); this is known today as conduction aphasia. In essence, the model describes that Wernicke's region provides the processes required for comprehension of auditory language and Broca's area, receiving this essential information via the arcuate fasciculus, provides the cortical machinery to code language into its articulatory forms (Geschwind, 1970). Such a model not only predicts conduction aphasia, but it also predicts the long-term occurrence of disturbances in speech output that can occur with Wernicke's aphasia (Geschwind, 1970), described as a lesion to Wernicke's region primarily affecting the processes of comprehension (Lichtheim, 1885). The idea that the primary purpose of the arcuate fasciculus is to provide a direct link between Wernicke's region and Broca's area in order to mediate a language-specific function has dominated both scientific and clinical thinking as a persistent dogma about the function of language even to the present time (Brauer et al., 2011; Henning Stieglitz et al., 2012; Kwon and Jang, 2011; Mohades et al., 2012).

Our study showed a primary anterior termination of the arcuate fasciculus, specifically the portions arising from lateral temporal sites showing language-related gamma-augmentation, within the inferior precentral gyrus and failed to support the conventional model of language connectivity within the brain (Geschwind, 1970). The inferior portion of the precentral gyrus possesses both premotor (BA 6) and primary

motor (BA 4) cortex (Strotzer, 2009); primary motor cortex residing largely along the central sulcus with the premotor cortex lying more laterally on the gyrus. Others have yielded similar findings regarding the anterior termination of the arcuate fasciculus with diffusion MRI methods (Anwander et al., 2007; Catani et al., 2005; Perani et al., 2011), structural MRI of lesion locations (Bizzi et al., 2012), and cadaver dissection (Martino et al., 2012). New models of language are beginning to incorporate the premotor cortex of the inferior portion of the lateral precentral gyrus (Amunts and Zilles, 2012; Friederici, 2012). One well developed model incorporating recent findings from imaging and lesion studies regarding language-related structural connectivity, presented by Bernal and Ardila [2009], hypothesizes that the arcuate fasciculus mediates a direct communication between Wernicke's region and premotor (BA 6) cortex of the inferior precentral gyrus. Regarding both Broca's area and primary motor cortex for the face and mouth, this portion of premotor cortex is hypothesized to serve as a bidirectional relay station coordinating the language-related processes among these frontal and temporal language-related regions (Bernal and Ardila, 2009). Further studies are warranted to confirm this bi-directional connectivity between the two regions using techniques such as measurement of cortico-cortical evoked potentials (Matsumoto et al., 2004).

It is hypothesized that the arcuate fasciculus may serve a supportive, language-related role that is more crucial during language development in childhood but nonessential for language maintenance in adulthood (Bernal and Ardila, 2009; Bernal and Altman, 2010). Indeed, classical conduction aphasia is so rare that some have been prompted to suggest it is not associated with the arcuate fasciculus at all (Anderson et al., 1999); the literature presents a case of complete recovery from

aphasia associated with complete and permanent disruption of the arcuate fasciculus of the dominant hemisphere only thirty months after injury and with only three months of therapy in a middle-aged adult (Kwon and Jang, 2011). Diffusion MRI of left hemisphere stroke patients (22 months post-stroke, on average) showed that reduced fractional anisotropy of the arcuate fasciculus correlates with decreased repetition ability (Breier et al., 2008). However, in such a study it is nearly impossible to exclude cortical involvement; thus, it is difficult to prove with such findings that the arcuate fasciculus is itself essential for repetition. This was acknowledged in a separate MRI study involving patients with Broca-like or Wernicke-like conduction aphasia, where the location of reduced anisotropy, anterior or posterior, was related to the type of conduction aphasia that can present (Song et al., 2011). Recovery with time, a common characteristic of conduction aphasia, suggests that the brain is able to compensate for loss of the arcuate fasciculus, either within or between the hemispheres (Berthier et al., 2011). It is more likely that permanent conduction aphasia is due to a cortical dysfunction than to any lesion in the white matter (Hickok, 2012).

*Clinical Significance*

While not the goal of this study, it is difficult to ignore the potential clinical application of this simple methodology. Our results suggest that diffusion-weighted tractography from posterior language-related electrode sites may be capable of predicting language-related sites of the precentral gyrus. This is a promising finding in which a non-invasive modality might have some, albeit limited, value in predicting invasive results. Within Broca's area, only positive prediction of language-related gamma sites was adequate. It

is well known that ECoG coverage is often very limited. A method such as this could be useful when ECoG samples the posterior superior temporal region but not the inferior portions of the precentral gyrus, as was the case with patient 25 in this study. Surface tracking from language-related sites of the lateral temporal lobe may serve to 'fill in the gap' to some extent for pre-surgical language mapping in such cases. Further validation of this finding is necessary. Applicability to language-related sites of the right hemisphere should also be investigated.

*Methodological issues*

When evaluating cortical terminations of white matter tracts, diffusion-weighted tractography has several limitations. Indeed, the spatial resolution of images used for diffusion-weighted tractography is limited. Further, we were limited to the use of clinical scans. For example, in this study, the spatial resolution was on the millimeter scale, which is no better than a gross anatomical dissection study (Martino et al., 2012); the value of diffusion-weighted tractography lies in its ability to enable *in vivo* study. Using 55-direction scans we were able to generate a probability distribution function that considered information about diffusion in many directions. We employed a nonparametric probabilistic tractography method that should have improved our ability to compensate for situations in which fibers cross (Aganj et al., 2010) or make sharp turns. Further compensation of crossing fibers from the corticospinal tract was provided by inclusion of the postcentral gyrus as a control, or reference, target region. The postcentral gyrus also provided a reference for the effect of proximity to the tractography seeds, since shorter distance may increase the likelihood of apparent

tractographic connectivity. Even so, our tractography fibers will have the general tendency to follow the path that is dominated by the greatest number of axons oriented in a common direction. Therefore, our findings suggest only that it is more likely (Jones, 2008) that more of the axons associated with the arcuate fasciculus are terminating within the precentral gyrus. It may be that there exist other axons associated with the arcuate fasciculus that extend to Broca's area or to other nearby areas of the frontal lobe, such as BA 8 (Frey et al., 2008), that are simply hidden due to partial volume effects associated with relatively low spatial resolution. Indeed, it has been shown that the actual tractography method employed can change the depicted shape of cerebral tracts, including the arcuate fasciculus (Dell'Acqua and Catani, 2012). It is impressive that we were able to find a good predictive value for ECoG results in the precentral gyrus even in the setting of such limited diffusion-weighted tractography information.

We applied several strict parameters to our tractography analysis including an exclusion mask preventing the traversal of gray matter, probabilistic anisotropy correction, and the restriction of seed and target regions of the gray-white interface to 8mm from the cortical surface associated with a specific anatomical region or ECoG electrode. Beyond these restrictions however, we allowed for any path between the seeds and targets; that is, no assumptions about or 'dissections' of the dominant fiber path were applied. This approach allowed fibers to be influenced greatly by individual variability between patients. Even so, nearly all fibers in each patient appeared to follow a path resembling that of the arcuate fasciculus (Catani and Thiebaut de Schotten, 2008). It may be that our strict tractography parameters have prevented the visualization of other potential tracts that may provide a direct connection between

posterior and anterior language sites; for example, the extreme capsule fiber system (Frey et al., 2008). As our seed and target regions did not include the inferior parietal lobe, only the direct, long segment of the arcuate fasciculus could be evaluated (Catani et al., 2005; Catani et al., 2007). We did not have consistent coverage of the inferior parietal lobe, sometimes referred to as Geschwind's territory (Catani et al., 2007), in our patients and thus left ECoG-constrained analysis of the indirect segments to future work. Indeed, we were primarily interested in the direct segment of the arcuate fasciculus at the onset of this study and, in particular, to determine where the dominant physical termination may be. Within anterior regions, other tracts may exist that interact with portions of the arcuate fasciculus. The corticospinal tract is well known to cross the arcuate fasciculus along the central sulcus. The frontal aslant tract, which may possess some function in language (Catani et al., 2012), appears to connect *pars opercularis* to supplementary motor and pre-supplementary motor areas; thus potentially interacting physically with the more anterior portions of the arcuate fasciculus. We constructed a simple method to account for problems that may arise from such crossing fibers as described above. Further evaluation of these pathways with ECoG-constrained tractography is warranted for future studies.

We did not employ electrical brain stimulation to define posterior language sites serving as seed regions. This is because stimulation is insensitive to language mapping in children (Kojima et al., 2012; Schevon et al., 2007). Our recent study of 77 patients who underwent epilepsy surgery showed that the mapping of language-related gamma-augmentation on ECoG, utilizing the naming task employed herein, was capable of predicting post-surgical language-impairment better than electrical stimulation (Kojima

et al., 2013b). Nonetheless, we can report that clinically-oriented stimulation was able to confirm left-hemispheric essential language sites in all five patients under study.

All findings present herein were generated from a data set based upon patients with focal epilepsy and may be influenced by such a disease process. However, there is no objective evidence that epileptiform discharges, structural lesions, antiepileptic drugs, or ECoG sampling limitations have a differential affect upon termination patterns of the arcuate fasciculus. All patients had the seizure onset zone and interictal epileptiform discharges recorded away from the inferior frontal region. It has been reported that antiepileptic drugs reduced the duration of interictal epileptiform high-frequency oscillations at >80 Hz in only 3% of patients (Zijlmans et al., 2009); we successfully found language-related gamma sites of the temporal lobe highly concordant with language-related temporal lobe sites on functional neuroimaging (Brown et al., 2012b). The left superior temporal gyrus, especially in the posterior portion traditionally considered a part of Wernicke's region (Bogen and Bogen, 1976), was well sampled by our ECoG electrodes.

Since our study included a small cohort of children ranging from 6 to 21 years in age, we cannot rule out an effect of patient age upon our findings. A volumetric MRI study reported that the white matter volume in the frontal lobes continues to increase until age 12 (Giedd et al., 1999). Myelination of language-related pathways, the arcuate fasciculus in particular, is known to be relatively protracted. Indeed, at age 5, myelination of the arcuate fasciculus remains detectably incomplete compared to that of adults (Su et al., 2008); although having progressed through more than 80% of change from newborn to adult values, based on structural MRI measures. Diffusion MRI

imaging is not completely dependent upon myelination (Berman et al., 2005), as anisotropic diffusion can be observed in three day old newborns in whom major portions of the arcuate fasciculus can be studied despite a general lack of myelination (Perani et al., 2011). Comparing to adults (age 24.4 to 32.4 years), tractography has yielded evidence that the portion of the direct segment of the arcuate fasciculus connecting Wernicke's region to *pars opercularis* (within Broca's area) may be underdeveloped in children (age 7) (Brauer et al., 2011); this conclusion was based on reduced fractional anisotropy and the apparent utilization of alternative pathways in children. In the present study, the dominant termination of the arcuate fasciculus residing within the inferior precentral gyrus was seen not only in a 6-year-old child, but also in the remaining four patients older than 12 years. In three out of our five patients (including the youngest one at age 6), we could demonstrate a component of the arcuate fasciculus connecting lateral temporal language-related sites to *pars opercularis* of the inferior frontal gyrus in addition to precentral gyrus.

*Conclusion*

The purpose of this study was to constrain diffusion-weighted tractography with language-related functional information from ECoG measures in order to evaluate the anterior termination of language-related white matter connectivity. Even though no assumptions about 'correct' fiber pathways were applied, a tract resembling the traditional arcuate fasciculus vastly dominated the results. It was shown that the dominant anterior termination of this tract was within the inferior portion of the precentral gyrus and could best predict the result of language-related gamma measures within that

region. Our findings contribute to mounting evidence that the traditional view of language organization within the brain requires some modification. This, along with other scientific and clinical data regarding the arcuate fasciculus, suggests that the arcuate fasciculus might be best thought of as a language-related structure providing support for the development of effective auditory communication. New models of language structure and function may benefit from incorporating the robust termination of the arcuate fasciculus within the inferior precentral gyrus.

*Synthesis*

This truly multi-modal study of language combines measures of structure and function to yield scientific information regarding connectivity between relevant brain regions and highlights a potential clinical application. Although we have demonstrated ECoG to yield important data regarding language localization, the modality suffers from the important limitation of limited cortical coverage. Tractographic analysis of diffusion weighted MRI (DW-MRI) data may be capable of filling in some of these gaps when ECoG electrodes cover either the precentral or superior temporal gyri but not the other. Indeed, electrical brain stimulation suffers from a similar drawback that can be similarly remedied, in part.

The study further demonstrates the power of ECoG language mapping for scientific study. With ECoG, we can know 'where' and 'when' activations occur. Combining this information with tractography of white matter pathways can provide not only a sense of which sites are directly connected but also of the directionality of that connection. In all cases of connectivity described here, the information appears to flow from posterior to

anterior along the arcuate fasciculus. Further studies to validate and build upon this data are necessary. Our team plans further studies following this dissertation that employ cortico-cortical evokes potentials in order to validate our tractographic findings. We also hope that studies combining language-related ECoG with tractography in patients with lesions of the arcuate fasciculus may shed light onto the changes in cortical functions that may accompany such a structural insult. Such findings will create further clarity regarding the role of the arcuate fasciculus in language and benefit patients both directly through the application of these techniques and indirectly through enhanced knowledge of the mechanisms that may underlie certain language deficits.

## CHAPTER 5: The Effect of Epilepsy upon Language

*This chapter is modified from the original publication in the clinical journal Epilepsy & Behavior - (Brown et al., 2012a)*

### *Introduction*

The presumption of a deleterious impact of focal epileptic spike-and-wave activity has been held for some time (Van Bogaert et al., 2012). Indeed, a landmark study by Shewmon and Erwin demonstrated that posteriorly localized spike-and-wave activity was capable of transiently increasing reaction time and error rate in a visual reaction time task (Shewmon and Erwin, 1989). Many studies have also described countless cases of patients exhibiting epileptiform activity in brain regions that appear to correlate with other non-epileptic neuro- or psycho-pathologic phenomena (Massa et al., 2001; Shewmon and Erwin, 1989; Van Bogaert et al., 2012; Volkl-Kernstock et al., 2009). Patients with interictal spikes involving the left hemisphere are reported to have a greater risk of language-related deficits (Bedoin et al., 2011; Binnie and Marston, 1992). Studies combining electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) provide findings that suggest spike-related changes in hemodynamic activity around the seizure focus and beyond (Jacobs et al., 2008; Moeller et al., 2010; Rathakrishnan et al., 2010; Zijlmans et al., 2007). The use of a modality with more direct and specific measures to determine the dynamics of transient spike-induced functional deficits is warranted. Since 2007, we have been collecting data regarding the functional modulation of gamma activity (>50 Hz) associated with an auditory naming task from patients with focal epilepsy undergoing resection of the presumed epileptic zone following electrocorticography (ECoG) recording (Brown et al., 2008; Kojima et al.,

2012). This presents a unique opportunity to explore the direct effect of spontaneous interictal spike activity upon task-based language functions. We aimed to explore the effects of interictal spikes from a well-defined single frontal lobe focus upon higher order language functions. Similar to the method of Shewmon and Erwin, we attempted to group our task trials into 'Spike' and 'Non-Spike' trials. Our hypothesis upon initiation of the study was that 'Spike' trials would be associated with a decrease in subsequent task-related gamma activity in brain regions involved in higher order language function.

*Methods*

We retrospectively searched our patient cohort using the following inclusion criteria: (i) intractable focal epilepsy with an ECoG-defined seizure focus of the left frontal lobe and (ii) mapping of naming-related gamma-augmentation via ECoG using an auditory naming task (Brown et al., 2008; Kojima et al., 2012). In this preliminary study, we selected patients with a frontal lobe focus since our measurements of interest were not early gamma-modulation elicited by acoustic stimuli but those elicited by higher order language function. The following exclusion criteria were applied: (i) multiple seizure foci either within or outside of the frontal lobe, (ii) presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and sylvian fissure, or (iii) right language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left-handedness when Wada test results are not available (Knecht et al., 2000b). We discovered four patient data sets fitting these strict criteria; see Table 10 for details.

All four patients had undergone a period of chronic subdural implantation of electrodes over the left hemisphere, including portions of the frontal lobe anterior to the precentral sulcus, as described previously (Brown et al., 2008; Brown et al., 2012b; Kojima et al., 2012). The seizure onset zone was visually determined from EEG data, as previously described (Asano et al., 2009a). An auditory naming task was performed with subsequent evaluation of task-related gamma-augmentations, as described in Chapters 2 and 3 (Brown et al., 2008; Brown et al., 2012b; Kojima et al., 2012). In short, task trials are designed to elicit one- or two-word overt responses; e.g. 'What flies in the sky?' In each trial, we measured the response time as defined by the period between stimulus offset and response onset. Time-frequency analysis and statistics were as described in Chapter 2. In this study, we selectively focused on sites that could be classified as Pre-Response based on a previously described categorization scheme described in Chapter 3's section 3.1 (Brown et al., 2012b); those sites at which peak average gamma-augmentation occurs following stimulus-offset but prior to response-onset, the delay period, as seen in the example provided in Figure 21.

In this study, we grouped trials based on the spontaneous occurrence of interictal spikes during auditory naming task trials. Spikes were detected with the aid of a MatLab-based spike detection algorithm under default settings that have been previously described and validated (Barkmeier et al., 2011). This spike detection algorithm was used to aid in the manual detection of individual spikes as well as to automatically quantify spike counts at individual electrode sites across the time period of the recording during which the language task was performed; about 8 to 14 minutes in duration. Only trials for which a correct answer was provided were included. 'Spike'

trials were defined with the following criteria: interictal spike(s) originating from the seizure onset zone occurs (i) during the audible question stimulus but (ii) not during the delay period, defined as the time between stimulus-offset and response-onset (Figure 22-A). 'Non-spike' trials were defined as those during which no spike originating from the seizure onset zone is detected at any time point between the onset of the audible question stimulus and the onset of the patient's overt response (Figure 22-B). Spikes occurring at any other time point (e.g. after onset of the patient's overt response) were disregarded. Due to the spike detection algorithm's inherent oversensitivity (Barkmeier et al., 2011), when evaluating for Spike and Non-Spike trials, the authors only removed invalid spike markers (such as sharply contoured deflections due to artifacts), never manually searching for undetected spikes.

**Table 10**
**Summary of Clinical Information**

| Pt | Gdr | Age at surgery (years) | Dom. Hand | Age at epilepsy onset | Antiepileptic medications | PSI† | VCI† | VIQ† | Schooling | Wada test† | Sz type | ECoG electrode coverage | Seizure onset zone | ECoG contacts (total) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | F | 10 | Rt | 10 | LEV | 112 | 85 | N/A | Ave., Normal 6th Grade | N/A | Focal Sz w/ sGTC | Lt FPT | Lt dorso-lateral F | 74 | Low Grade Tumor |
| 27 | F | 17 | Rt | 0 | LAM | 99 | 96 | 97 | Ave., Normal 12th Grade | N/A | Complex Focal Sz | Lt FPTO | Lt medial F | 102 | Mild gliosis |
| 28 | M | 17 | Rt | 6 | OXC, LAM | 56 | 78 | N/A | Special Education, 10th Grade | Lt | Complex Focal Sz | Lt FPTO | Lt dorsal F | 116 | Gliosis |
| 29 | M | 23 | Rt | 10 | LEV, LAC | N/A | N/A | 77 | Post Normal Secondary School | Lt | Focal Sz w/ sGTC | Lt FPT | Lt lateral F | 110 | Mild Gliosis |

Pt: patient. Gdr: gender. LEV: levetiracetam. LAM: lamotrigine. LAC: lacosamide. OXC: oxcarbazepine. VAL: valproate. Rt: right. Lt: left. Sz: seizure. sGTC: secondarily generalized tonic-clonic sz. F: frontal. T: temporal. O: occipital. P: parietal. † PSI: processing speed index. VCI: verbal comprehension index. VIQ: verbal intelligence quotient. Wada test: sodium amobarbital procedure

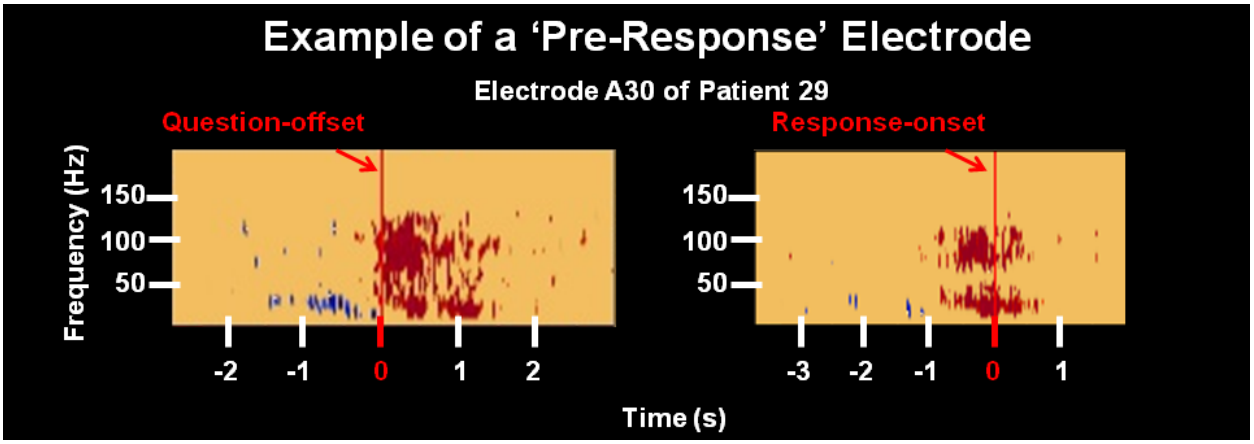


**Figure 21: Pre-Response Example.** Data from electrode A30 over the ventral inferior frontal gyrus of patient 29 during performance of the auditory naming task is represented here. As seen, the peak gamma-augmentation during the auditory naming task occurs during the delay period of the task. This type of site is classified as Pre-Response, as previously described (Brown et al., 2012b).

For time-frequency analysis of Spike and Non-Spike trials, all trials included were referenced to a common grand-averaged pre-stimulus baseline period. For each electrode site classified as Pre-Response, we determined the peak gamma-augmentation across the frequency range of 80 to 100 Hz (Kojima et al., 2012) during the delay period for each Spike and Non-Spike trial; we wish to highlight that this time period does not contain interictal spikes in either Spike or Non-Spike trials, as seen in Figure 22. At all sites classified as Pre-Response, we compared the mean peak gamma-augmentation between Spike and Non-Spike trials using a two-sided Independent Samples T-test with no assumption of equal variance, as implemented in IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY, USA). In order to assess more subtle global effects of interictal spikes upon language-related gamma-activity, we compared mean peak gamma-augmentation between Spike and Non-Spike trials at all Pre-Response electrodes across all patients using the Wilcoxon Signed-Ranks test; a non-parametric test of paired samples used when the assumption of a normal distribution is not tenable. All p-values and confidence intervals (C.I.) shown are

uncorrected, with 0.05 as the threshold for significance. A Bonferroni correction was employed to account for Type I Error due to multiple comparisons.

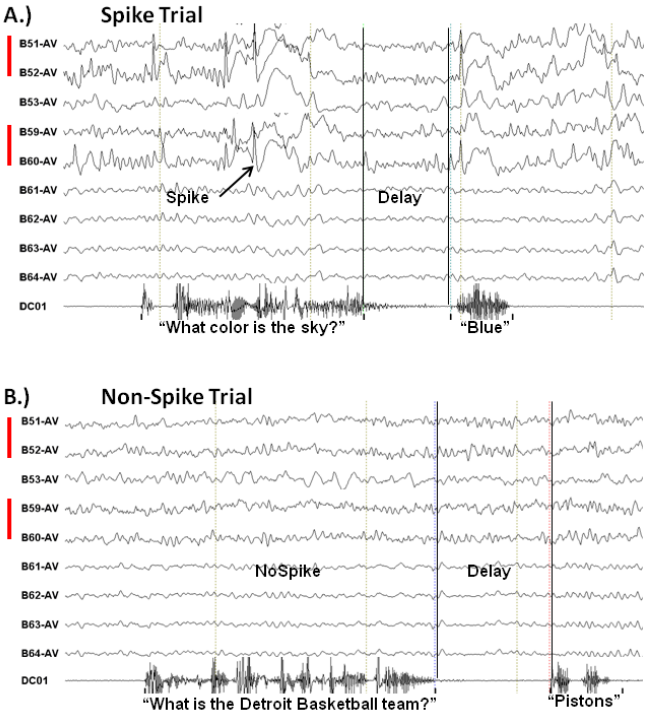


**Figure 22: (Non)Spike Trials.** Data from patient 29 are presented. (A) displays a Spike trial in which an interictal spike occurs during presentation of the question. No interictal spike occurs during the delay period. (B) displays a Non-Spike trial in which no interictal spike occurs during the trial. Red bars indicate electrodes over the seizure onset zone; electrodes B51, B52, B59, and B60. Channel DC01 represents the audio waveform of the task with subtitles. Vertical lines delineate the beginning and end of the delay period during which peak gamma-activity was evaluated. Sites showing significant gamma-augmentation during the delay period between offset of the stimulus and onset of the patient's response were defined as Pre-Response sites in the present study.

*Results*

Spike trials and Non-Spike trials could be identified in three of the four subjects. We failed to identify Spike trials during the task in patient 2, who had sparse interictal spike activity. Only data from patients 27, 28, and 29 were included in subsequent analysis. In patient 27, 16 Spike trials and 13 Non-Spike trials were identified. In patient 28, 4 Spike trials and 8 Non-Spike trials were identified. In patient 29, 10 Spike trials and 65 Non-Spike trials were identified; representative examples of a Spike trial and a Non-Spike trial from patient 29 can be seen in Figure 22. Response times did not differ significantly between Spike and Non-Spike trials, either within or across patients. The grand-average

response time was 980 ms for Non-Spike trials and 1105 ms for Spike trials (p-value=0.375).

A total of 15 sites were identified as Pre-Response in patient 27; 11 in the frontal lobe, 2 in the parietal lobe, and 2 in the temporal lobe. At no site was a significant difference in peak gamma (80-100 Hz) augmentation between Spike and Non-Spike trials discovered. Likewise, no significant difference was observed in patient 28, in whom only a single site of the frontal lobe was identified as Pre-Response. According to the spike-detection algorithm, the interictal spike counts during recording at these sites were much less than that within the seizure onset zone in both of patients 27 and 28; see Table 11 for complete data.

A total of 12 sites were identified as Pre-Response in patient 29; 10 in the lateral frontal lobe and 2 in the medial frontal lobe. Two sites showed a significantly reduced peak gamma augmentation during Spike trials; one site over the posterior middle frontal gyrus (p-value=0.01) and one site over the dorsal portion of the superior frontal gyrus (p-value=0.000078). Only the site over the dorsal portion of the superior frontal gyrus survived Bonferroni correction; reduction in mean peak amplitude was 58.4% of common baseline reference (95% C.I.: 31.6% to 85.1%). Compared to all other 11 Pre-Response sites, this superior frontal site was associated with the largest spike count during the recording, as estimated by the spike-detection algorithm. In fact, the spike count at this electrode was similar to that of the seizure onset zone; see Table 11 for complete data.

Across all electrodes classified as Pre-Response from all patients, we failed to find a significant difference in mean peak gamma augmentation (p-value=0.219; by Wilcoxon Signed-Ranks Test). See Figure 23 for electrode-level detail.

**Table 11**
**Spike Trials vs. Non-Spike Trials at Pre-Response Naming Sites**

| Patient | Electrode | Average Peak Gamma of Delay | | Difference (95% C.I.) | Spike Count† | Location |
|---|---|---|---|---|---|---|
| | | Non-Spike | Spike | | | |
| 27 | Seizure Onset | N/A | N/A | N/A (N/A) | 320 (max) | medial frontal |
| | B10 | 210.4% | 194.5% | 15.9% (-55.8% to 87.6%) | 131 | posterior IFG |
| | A56 | 214.5% | 218.6% | -4.1% (-82.9% to 74.6%) | 130 | superior parietal |
| | A42 | 210.2% | 213.6% | -3.5% (-60.2% to 53.3%) | 99 | posterior MFG |
| | A50 | 247.1% | 240.1% | 7.0% (-65.9% to 80.0%) | 93 | posterior MFG |
| | B1 | 185.5% | 190.2% | -4.7% (-60.2% to 50.9%) | 83 | posterior MFG |
| | A41 | 209.0% | 185.0% | 2.4% (-29.8% to 77.7%) | 72 | posterior MFG |
| | A49 | 120.3% | 136.5% | -16.1% (-61.0% to 28.7%) | 62 | posterior MFG |
| | A33 | 161.7% | 179.7% | -17.9% (-72.2% to 36.4%) | 61 | posterior MFG |
| | A58 | 137.3% | 138.9% | -1.5% (-34.9% to 31.8%) | 38 | posterior MFG |
| | B2 | 167.9% | 187.2% | -19.3% (-75.0% to 36.4%) | 32 | posterior MFG |
| | B47 | 146.0% | 149.3% | -3.2% (-42.9% to 36.4%) | 26 | posterior MTG |
| | B11 | 172.2% | 203.6% | -31.4% (-75.6% to 12.8%) | 17 | inferior PreCG |
| | B16 | 168.8% | 167.3% | 1.5% (-50.8% to 53.8%) | 15 | inferior parietal |
| | B25 | 199.6% | 224.6% | -2.5% (-89.1% to 39.2%) | 9 | posterior IFG |
| | A26 | 169.0% | 162.5% | 6.5% (-36.8% to 49.8%) | 2 | medial temporal |
| 28 | Seizure Onset | N/A | N/A | N/A | 197 (max) | SFG & MFG |
| | B20 | 260.3% | 230.4% | 29.9% (-85.1% to 144.8%) | 1 | posterior MFG |
| 29 | Seizure Onset | N/A | N/A | N/A | 519 (max) | posterior MFG |
| | A56 | 181.2% | 122.8% | 58.4% (31.6% to 85.1%) ** | 538 | middle dorsal SFG |
| | B42 | 129.2% | 140.9% | -11.7% (-51.1% to 27.7%) | 486 | posterior MFG |
| | B18 | 150.7% | 164.6% | -13.9% (-47.6% to 19.8%) | 429 | medial frontal |
| | A8 | 148.5% | 156.4% | -7.9% (-37.3% to 21.5%) | 380 | posterior IFG |
| | A40 | 159.9% | 168.4% | -8.5% (-40.5% to 23.5%) | 375 | anterior MFG |
| | B43 | 124.3% | 196.5% | -72.3% (-254.4% to 109.8%) | 368 | posterior MFG |
| | B17 | 258.4% | 269.8% | -11.4% (-82.7% to 59.8%) | 351 | medial frontal |
| | B49 | 208.9% | 164.0% | 44.9% (12.4% to 77.5%) * | 235 | posterior MFG |
| | A31 | 149.3% | 166.4% | -1.7% (-54.0% to 19.9%) | 226 | middle IFG |
| | B35 | 141.0% | 132.7% | 8.3% (-31.7% to 48.4%) | 170 | posterior IFG |
| | A30 | 192.6% | 193.6% | -1.0% (-33.9% to 32.0%) | 93 | ventral IFG |
| | A57 | 69.5% | 75.7% | -6.2% (-33.1% to 20.7%) | 77 | frontal pole |

MTG: Middle Temporal Gyrus. IFG: Inferior Frontal Gyrus. MFG: Middle Frontal Gyrus. SFG: Superior Frontal Gyrus. PreCG: Pre-Central Gyrus. N/A: Not Applicable. C.I.: Confidence Interval. †Spike count is that of the entire recording. * indicates a significant (<0.05) effect of interictal spikes prior to correction. ** indicates survival of Bonferroni correction.

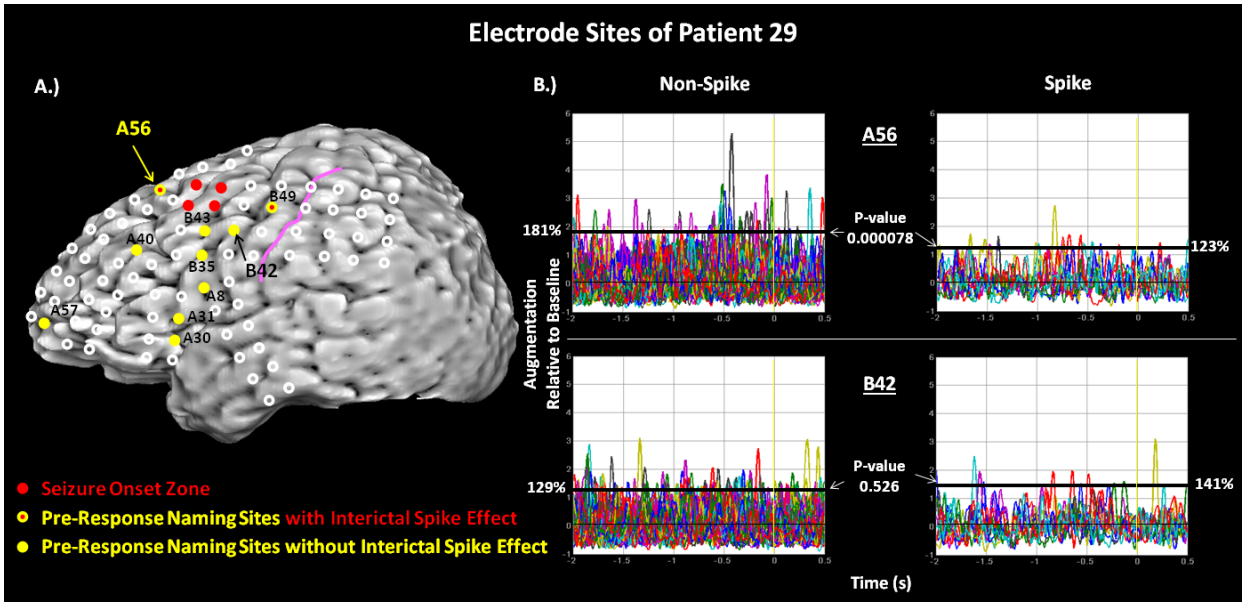


**Figure 23: Effect of Spikes upon Language-Related Gamma.** Data from patient 29 is depicted here. (A) displays the locations of electrodes associated with the seizure onset zone (solid red) and those identified as Pre-Response electrodes (yellow ring) based on evaluation of the gamma activity during an auditory naming task. Electrodes with a yellow ring and a red dot in the center depict Pre-Response electrodes at which gamma activity significantly differed between Spike and Non-Spike trials; solid yellow electrodes were not affected by interictal spikes. Electrodes over inferior and medial brain regions are not shown. (B) shows gamma activity (80Hz to 100Hz) at two sites classified as Pre-Response. In patient 29, 65 Non-Spike and 10 Spike trials were identified; different trials are represented by different color line tracings. Thick horizontal black bars depict the average peak gamma activity during the delay period across trials relative to a common pre-stimulus reference; thin horizontal black lines depict reference level activity (0%). At electrode A56, a significant difference was found that survived Bonferroni correction. Electrode B42 is a representative Pre-Response electrode that was not significantly influenced by the interictal spikes. Time zero, identified by a thin vertical yellow line, represents the onset of the patient's overt response.

## *Discussion*

### *Primary Finding*

The modern era of digital EEG/ECoG processing, long-term recordings, and (semi-) automated spike detection provides the opportunity to search for pathophysiological phenomena associated with interictal spikes on a finer temporo-spatial scale than in the past (Staley et al., 2011). We employed these tools in a simple design to retrospectively search our ECoG dataset of auditory language studies for an effect of frontal spikes upon higher order language-related activity. Even in this very limited dataset, at least

one electrode site of the frontal lobe in one patient exhibited a reduction in peak gamma activity that cannot simply be attributed to chance. Interictal spikes temporally preceded such a reduction of language-related gamma-activity, and did not contaminate the measurement of gamma-amplitudes during the delay period. This electrode site was physically located near to the seizure onset zone (Figure 23). The same site was also associated with a rate of epileptiform activity that was similar to that of the seizure onset zone, according to a validated, highly sensitive spike detection algorithm (Barkmeier et al., 2011).

Patients 27 and 28 failed to show any significant spike-related reduction in language-related gamma-activity. In both of these patients we had much lower power to find a difference due to a low number of Spike and Non-Spike trials, relative to patient 29. The Pre-Response sites of both patients 27 and 28 were associated with rates of epileptiform activity that were far lower than their respective seizure onset zones (Table 11). Also, in patient 27, the Pre-Response sites of language-related function were located a physically larger distance away from the seizure onset zone; with the seizure onset zone being medial frontal and the Pre-Response sites being either lateral frontal or in another cerebral lobe. It appears that interictal spikes of the seizure onset zone in these two patients did not have a detectable effect upon ongoing language activity.

*Interictal Spikes and Behavior*

It has long been postulated that interictal spikes can have a direct influence on normal behavior (Van Bogaert et al., 2012) although the scientific literature provides little information regarding the effects of interictal spikes upon normal

electrophysiological dynamics (Galanopoulou and Moshe, 2009). Shewmon and Erwin were able to demonstrate an increased reaction time, a behavioral measure, related to the chance occurrence of interictal spikes during a visual reaction time task (Shewmon and Erwin, 1988, 1989). However, the effect size difference in reported reaction times was on a scale of fractions of a second that would surely go unnoticed in a non-clinical, or even a clinical, setting outside of the confines of a task that demands maximal speed. Indeed, we failed to find a difference in performance between Spike and Non-Spike trials of our auditory language task, which does not demand maximal speed. The site of patient 29 at which a difference in gamma-augmentation was observed is a cortical region associated with the higher order function of 'semantic processing' (Binder et al., 2009). Our auditory naming task likely engages semantic processing networks. Thus, it is not surprising that this electrode site of the left superior frontal gyrus was activated and involved in execution of the task. It is also not surprising that task performance was not hindered by spike occurrence when it is considered that most other Pre-Response sites associated with task performance were apparently not affected by spike occurrence and that the difficulty of our auditory naming task is not great, especially for an otherwise near-normal functioning young adult. It may be that interictal spikes occurring during the delay period between question-offset and response-onset may have a more devastating effect on cortical function at Pre-Response sites. However, this is impossible to test with ECoG due to the direct effect of interictal spikes upon electrophysiological measures. In the future, it is warranted to determine whether more frequent or extensive spikes could cause a patient to take a longer time to complete the naming task.

*Conclusion*

We have demonstrated that a negative effect of interictal spikes originating from a single frontal lobe focus upon cortical language function: (i) can occur even in the absence of an observable behavioral effect, (ii) may be more prominent at sites nearer to the seizure onset zone, and (iii) may be more prominent at sites associated with epileptiform activity similar to that of the seizure onset zone. It appears that the deleterious effects of interictal spikes are more local and less global in our very small cohort. These results are strictly preliminary and require further validation in a larger cohort.

*Synthesis*

This final study included as part of this dissertation brings us full circle. Our epilepsy patients have provided such a large amount of data regarding normal language structure and function. To ensure a benefit directly to the epilepsy literature and to provide further validation to our technique, it was imperative that we study the effect of epileptic discharges upon language. We verified that it is indeed possible for interictal epileptiform discharges to impose a sub-clinical detrimental effect upon otherwise normal language function. This may partially explain how epileptic encephalopathy and other phenomena of cognitive dysfunction can arise in patients with epilepsy, especially those with frequent epileptiform activity. However, the physiological activity at such affected sites was not squelched entirely and the topographical pattern of language-related activity did not appear to be altered. The apparent robustness of language-related gamma-augmentation even in the face of interictal epileptiform discharges

supports our claim that normal language function can be studied in patients with focal epilepsy. Language mapping utilizing an auditory descriptive naming task with ECoG recording in epilepsy patients is indeed a powerful tool in presurgical mapping as well as in the scientific study of normal language structure and function.

## CONCLUSIONS AND SYNTHESES

This collection of studies has focused on cortical language function as studied with a focus on electrocorticography (ECoG) combined with other modalities such as electrical brain stimulation, neuropsychological evaluation, magnetic resonance imaging, and diffusion tensor imaging. These results demonstrate both scientific as well as clinical implications to promote further studies utilizing task-related ECoG analyses. Task-related analysis of gamma range ECoG signals shows great promise in filling gaps in clinical and scientific information gained with electrical brain stimulation. Evidence of a correlation of language-related ECoG signals with tractography of a major language-related white matter pathways lends credence both to the veracity of such ECoG utilization as well as to emergent theories considering alternative terminations of the arcuate fasciculus. Indeed, multiple tasks can be employed with ECoG, as performed herein, to perform functional 'dissections' of language-related functions. Such study can pars out, more precisely than with most other modalities, what type of underlying functional processes are engaged in a region of cortex activated during language. Finally, since nearly all subjects in ECoG studies are epilepsy patients, task-related ECoG analysis presents the opportunity to directly study the effects of interictal, and possibly ictal as well, phenomena upon the otherwise normal physiological processes mediating language. Task-related analysis of ECoG signals is a powerful clinical and scientific tool.

*Clinical Utility*

To date, language mapping utilizing task-related ECoG with an auditory descriptive naming task has been investigated across many patients and multiple investigators yielding impressive results. Our first study presented in this thesis (Brown et al., 2008) led to further investigations into the validity of language-related ECoG mapping, as compared to the clinical gold standard electrical brain stimulation. Our team later followed with studies with larger sample sizes. The first of these suggested that language-related ECoG may be capable of detecting some essential language sites of the left hemisphere of patients with confirmed left hemisphere language dominance that are missed by electrical brain stimulation (Kojima et al., 2012). This was followed by the largest of any such study to date, across 77 patients, employing multivariate analysis showing that language-related ECoG can independently predict essential language sites (Kojima et al., 2013b). More recently, a team from another institution has employed a very similar task and yielded similar findings independently (Cervenka et al., 2013).

Given mounting evidence that language mapping with task-related ECoG is beneficial and may even find essential language sites missed by electrical brain stimulation while not requiring any changes to current operating procedures or patient comfort, it would be prudent for all clinical sites performing such surgeries implement such language-related ECoG data collection. This type of pre-surgical evaluation is likely to be most fruitful for young children, in whom electrical brain stimulation has already been shown to be inadequate for language mapping (Schevon et al., 2007). We can report from our extensive experience with this technique that patients experience

neither additional discomfort nor increased invasiveness relative to the standard procedure being performed already at many institutions around the world. The technical development of dedicated, automated data collection hardware and software would enable a rapid expansion in the clinical use of this beneficial technique. It is possible that contrasting this task with other tasks, such as working memory tasks or signal-correlated noise control tasks, may yield more specific and detailed language localization; the exact benefits of which require further study. Furthermore, other modalities, such as diffusion-weighted magnetic resonance imaging tractography, may be combined with language-related ECoG to augment the enhanced presurgical mapping in certain cases; especially when cortical coverage is incomplete. The clinical potential of task-related ECoG mapping is only just being realized and tapped.

## *Future Directions of Interest*

### *Frontal Eye Fields*

A path of further study spontaneously emerging from this line of evidence regards the frontal eye fields. In each of the above studies it can be observed that the frontal eye fields, lying near to the precentral sulcus midway up the lateral surface of the precentral gyrus, are frequently activated by our naming task. In regards to temporal characteristics, these activations are often unlike those of other nearby sites of naming-related activations of the precentral gyrus. While most precentral sites activated by our task possess a peak augmentation of gamma activity within a few hundred milliseconds before or after the onset of vocalization of the response, naming-related activations of these frontal eye field regions frequently appear to come much earlier in the task.

Indeed, naming-related activity of the frontal eye fields, whether left or right hemisphere, often show significant gamma activity very early during the auditory stimulus. These activities resembled those auditory activities observed over the superior temporal regions; although there appears to be some difference in relative responses to incomprehensible stimuli such as reverse speech and signal correlated noise.

Both auditory and visual information is routinely and rapidly utilized in our navigation of the world around us. Although separate organs mediate the reception of these environmental signals, in our minds these sensations are intimately related; for example, we hear a dog bark and we look in that direction nearly involuntarily. There must be specific regions of the brain dedicated to the integration of the information gained from each of these signals. It appears convenient that the frontal eye field, a region cited as a site of higher level control of eye movement, might also mediate both auditory and visual sensory processes (Kirchner et al., 2009). Indeed, we have demonstrated an additional role for this region in working memory maintenance, particularly in the left hemisphere. It is interesting that such a small region of neocortex can have such a profound array of processes ranging from sensory to motor control to cognition.

Clinically, electrical brain stimulation of the frontal eye fields often leads to contra-lateral eye deviation; although we can report a case in which we observed vertical eye deviation, but this is not widely reported. Additionally, we have observed in our clinic that, if a language task is performed during such stimulation, the patient will often exhibit an expressive language deficit. It is unknown whether this represents an essential language function that must be preserved following epilepsy surgery. Indeed, based

upon our evidence above, this may represent a disruption of working memory maintenance processes rather than an essential language function. Temporally targeted electrical brain stimulation may further clarify the role of these sites in working memory or language. For example, following analysis of ECoG signals during a working memory task, a site of the frontal eye field found to be involved in working memory maintenance may be stimulated during the task's maintenance phase. If working memory maintenance is disrupted, such a site would be considered essential for working memory maintenance functions.

We have all observed others and ourselves looking off to the right or to the left when in deep thought. Might this expression be an epiphenomenon of engagement of memory processing being coordinated by the frontal eye fields? Further studies utilizing language-related ECoG and other modalities may provide an answer.

*Cortico-Cortical Evoked Potentials, Language-related ECoG, and Arcuate Fasciculus*

We have described here an evolution of our understanding of not only language function, but also of language networks. In particular, we presented evidence of direct language-related connectivity between posterior language sites of the superior temporal lobe and the inferior portion of the precentral gyrus. However, the methods used here, ECoG and DTI, are not widely considered to be well validated against more standard methodologies. It will be useful to follow our work with a study combining language-related ECoG with cortico-cortical evoked potentials (Matsumoto et al., 2004). Indeed, if a particular region of neocortex is stimulated with a small amount of electrical current, other neocortical regions with direct white matter connectivity will exhibit an evoked

potential upon recording. Such a methodology does not suffer from the imaging short-falls associated with crossing fibers and may confirm our findings. Furthermore, we will be able to learn the directionality of the connectivity; either equally bidirectional or favoring propagation in one direction over the other.

*Combined Functional Magnetic Resonance Imaging and Electrophysiology*

Our studies utilizing reverse speech highlighted a discrepancy between electrophysiological data measured with ECoG and the fMRI literature. Such a discrepancy may indicate a critical difference in the phenomena measured by fMRI, i.e. the BOLD signal, and that by ECoG. Because fMRI is so widely employed, it is imperative to have an understanding of the relationship between the BOLD signal that it detects and its relationship to actual cortical activity. Studies that employ simultaneous EEG-fMRI with subsequent ECoG with reverse and forward speech trials may be best suited to investigate this topic. Resolution on this particular topic may enhance our understanding of the relationship between the BOLD signal with cortical processing. In particular, we wonder whether this discrepancy between these modalities is being generated by certain neuronal populations or, possibly, by non-neuronal populations that are involved in cortical function. A multi-modal approach is critical.

*Conclusion*

Language mapping with task-related ECoG is a powerful tool. Although all subjects from whom this data is collected possess a neurological disease, appropriate application of the technique can generate interesting data regarding normal language

function. Combining ECoG with other modalities is essential and will further enhance the contributions that can be made. For the clinic, we believe that the development of dedication hardware and software to enable routine task-related ECoG data collection in the extraoperative epilepsy surgery setting is warranted. Furthermore, we generally recommend the integration of language mapping by ECoG analysis within normal mapping protocols alongside electrical brain stimulation; this recommendation is made especially in those cases of extraoperative language mapping of young children capable of performing the task. With such an approach we can enhance our knowledge of brain structure and function as well as impart a direct benefit of patients in both the operating room and in the clinic.

# APPENDIX

The following is a list of questions of the auditory naming task described in this study:

What color is grass?
What animal has a long nose?
What fixes your hair?
What do babies drink from?
What color is an apple?
Where do you hang clothes?
What animal quacks?
What fish has sharp teeth?
What do you wear on your head?
What is a red fruit?
What cleans your hair?
What animal gives milk?
Where do frogs live?
What has wheels?
What do rabbits eat?
What do you wear to bed?
What bounces?
What do you write with?
What do you watch movies on?
Who fixes cars?
Where do you learn?
Who cleans your teeth?
What cleans your teeth?
What do you eat with?
Where do doctors work?
Where do teachers work?
What do we eat?
Where do you swim?
What opens locks?
What shines at night?
What Animal Says Ribbit?
What do You Throw?
What is the opposite of stop?
What is the opposite of up?
What tells the time?
What do you cut food with?
What do you wear when it's cold?
What do you use when it rains?
What color is the sun?
What do you dig with?
Where do you borrow books?
Where do fish live?
What shape has four sides?
What do we drink?
What animal lays eggs?
What color is a banana?
What cuts paper?
What gives light?
What tells the date?
What color is the sky?
What animal swims?
What cuts the grass?
Where do you get money?
What do you cook on?
What animal barks?
What do you hear with?
What is a sweet food?
What pounds nails?
What do you dry off with?
What color is a basketball?
What do you drink from?
Where do you buy food?
What do we read?
Where does a plane land?
What keeps you warm?
What lives in a zoo?
What cuts wood?
Where do pigs live?
What do firemen drive?
What flies in the sky?
What wakes you up?
What animal roars?
What plays music?
What keeps food cold?
What is very cold?
What do you wear on your feet?
What do you sit on?
What do you sleep on?
What do you see with?
What comes after April?
Who gives traffic tickets?
What comes after Thursday?
What do dogs eat?
What floats on the water?
What shape has three sides?

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## ABSTRACT

## MULTI-MODALITY ASSESSMENT OF LANGUAGE FUNCTION

by

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**May 2015**

**Advisor:** Dr. Eishi Asano

**Major:** Translational Neuroscience

**Minor:** Biomedical Engineering

**Degree:** Doctor of Philosophy

The work presented as part of this dissertation represents a multi-modality study of language structure and function. The primary functional modality employed is task-related electrocorticography (ECoG). This is complemented by discussion and evaluation of previously published functional magnetic resonance imaging (fMRI) data. Language-related structure is explored using diffusion-weighted magnetic resonance imaging in conjunction with ECoG data. The scientific questions pursued are broad and include reevaluation of previously proposed theories.

We start by taking the first steps in validating our naming-related ECoG approach by comparing our results from a small cohort of patients to the clinical gold-standard technique of electrical brain stimulation. This evaluation begins to address a clinical problem involving the insensitivity of electrical brain stimulation in language mapping of young children. Thus, our patients across all studies are a mixture of children, adolescents, and adults. Combining data presented within this thesis, data from other members of our team, and published data from teams at other institutions, evidence suggests that language-related ECoG mapping is a powerful language mapping tool

when it is employed with an appropriate task. The task employed here is a now well-studied auditory descriptive naming task.

Language-related ECoG is then utilized to dissect language function mechanistically employing contrast tasks alongside the descriptive naming task. Working memory and language functions of the frontal lobe are dissected and conclusions are drawn to shed light on their degree of overlap and interaction during ongoing language processing. Evidence of secondary auditory processing and language comprehension gained from other modalities is reevaluated. In particular, reverse speech and signal-correlated noise are employed and evaluated as control tasks for non-language-specific auditory function. A discrepancy between language-related ECoG and language-related fMRI is discovered in regards to the use of reverse speech as such a control task. It is found that signal correlated noise may be more reliable in identifying non-language auditory functions of the temporal lobe.

Age-old questions of language-related connectivity are explored by combining diffusion-weighted magnetic resonance imaging tractography with language-related ECoG findings to evaluate terminations of the arcuate fasciculus. Results support recent evidence suggesting that the precentral gyrus is an important termination of this language-related white matter pathway. New models modifying century-old, entrenched models are evaluated in light of these findings and proposals for follow-up work that may create further clarity are provided.

Finally, the thesis rounds out with a study exploring the effects of focal interictal epileptiform activity upon ongoing language processes; contributing beyond the neuroscience of language to the epilepsy literature, in honor of the patients providing

the data for these studies. Our data demonstrates that such localized pathological activity can have clinically imperceptible effects upon language functions, suggesting one possible mechanism toward cognitive deficits frequently reported in such patients.

## AUTOBIOGRAPHICAL STATEMENT

A guiding motivation in my career development, both toward and away from medicine, has been my personal experience with epilepsy, diagnosed at age 7 and weaned off of anticonvulsant medication at age 22. My original career ideal was to work with children experiencing epilepsy. However, my detour into the field of electrical engineering originated with the personal fear that epilepsy would somehow prevent me from undergoing the grueling life of a physician-in-training; an alternative route by which I could hope to contribute to the treatment of epilepsy and other neurological disorders was through development of biomedical devices. After years of learning my own personal limitations and how I could meet the challenges of a demanding career as well as having the good fortune to successfully discontinue epilepsy medication, I am happy to find myself contributing to research related to pediatric epilepsy surgery. I am grateful to be receiving the training I need to become a contributing, independent physician-scientist.

My overarching career goal is to contribute to the health and well-being of people living with epilepsy and other neurological disorders through both advancement of related research and direct clinical treatment. Epilepsy is a disorder for which a great deal must be understood about the brain in order to make significant progress in research. As part of the epilepsy-surgery-related research described here, I am learning rich detail about language, working memory, and other cognitive processes. I believe I have found the career path that will lead me to my goal. I find myself at the interface between science and the clinic; the place where dual MD/PhD professionals are meant to operate.

I have been fortunate to maintain a program of study in engineering, as represented by my minor in Biomedical Engineering. My research project here is highly technical. In the fields of Neurology and Psychiatry, I believe that all researchers should have some level of technical training in order to understand and effectively utilize the highly complex tools that we must use to ethically study the human brain. Also, I hope to become involved in the development of biomedical devices. I have some experience working with the Vagus Nerve Stimulator in a technical capacity. Such devices have been proven effective in some patients, but we have little to no understand as to how the clinical effect is achieved. Much research in these areas is necessary that can feed the technical development of newer, better devices.

Here, I would also like to mention my passion for global health. I have been involved with several medical teams in Latin American and have taken a particular interest in the problems encountered in Haiti. During the graduate work described here, I have also been working on a project to develop an electronic medical records system designed specifically for high volume, transient clinics; we call the system 'EasyEMR'. This multidisciplinary project involves colleagues all across campus and has already been deployed to Haiti. I hope my career path allows and helps me to continue such work.

I describe myself as a passionate person. I have a passion for helping others, for learning new things, and for travelling. My ultimate goal is to create a career in which I can satisfied all of my passions and contribute to the world in a meaningful way. I hope to find myself in an even more interesting position than I imagined when I was a child: a physician-scientist finding new ways to help patients with epilepsy as well as other conditions, here and around the world.