Harnessing electrocorticographic signals for neuroscience and neurosurgery

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HARNESSING ELECTROCORTICOGRAPHIC SIGNALS
FOR NEUROSCIENCE AND NEUROSURGERY

by

Adriana de Pesters

A Dissertation
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Daily human activities, such as speaking, driving or listening to music, are produced by activations of neurons in the brain. Where, when and how these activations occur has been the subject of intense debate for the last decades. Traditional techniques to image the human brain, such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), only provide limited information regarding where and when these activations take place. For that reason, critical information is currently missing regarding how neurons from different parts of the brain interact and coordinate their activity to implement behavior. This information is critical to understand human behavior and to develop new medical diagnostic and treatment options for neurological disorders that compromise behavior such as epilepsy or brain tumors.

Recently, electrocorticography (ECoG) has been shown to provide an unprecedented opportunity to image the subtle dynamics of the human brain in action. ECoG is a technique traditionally used in the treatment of epileptic patients, and consists of recording brain signals from arrays of electrodes placed directly on the surface of the brain. The high quality of signals recorded with ECoG allows neuroscientists to investigate the temporally and spatially precise activation of groups of neurons in the human brain.

In this dissertation, we take advantage of the possibilities offered by ECoG imaging to derive
novel understanding of the precise temporal and spatial coordination of neuronal activity during behavior. We demonstrate that different parts of the brain dynamically interact and coordinate their activity to implement behavior. Furthermore, we translate our findings into two novel clinical applications that build on existing neurological procedures to treat patients suffering from epilepsy and brain tumors. The proposed applications improve the speed and safety of existing procedures and expand the number and type of patients that can benefit from them.

Together, our results advance our understanding of the mechanisms implementing the coordination of the different brain regions necessary to produce behavior, and open new avenues for the development of safer clinical tools to treat those neurological disorders that compromise behavior.
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And finally my family for their unconditional support and love.
List of Publications

This dissertation is based on the following papers:


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¹joint first author
Outside this dissertation, the author has contributed to the following work:


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Daily human activities, such as speaking, driving or listening to music, are produced by the activity of neurons in the brain. Where, when and how this activity occurs has been the subject of intense debate for the last decades. Answering these questions is critical for understanding human behavior and for developing diagnostic and treatment options for neurological disorders that compromise behavior, such as epilepsy or brain tumors.

Each of the neurons that compose the brain makes connections with thousands of adjacent or distant neurons. From these connections and the molecular and cellular properties intrinsic to each neuron arise dynamic interactions between groups of neurons. Thus, understanding how neuronal activity implements behavior requires understanding of the principles that orchestrate those interactions.

Traditional techniques to image the human brain, such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), provide important information regarding the location or timing of neuronal activity in the brain. Unfortunately, those techniques cannot provide simultaneous information regarding timing and location. Indeed, fMRI accurately identifies the groups of neurons implementing a given behavior, but cannot describe the precise changes of activity of those neurons over short time scales. On the other hand, EEG can accurately track
those changes of activity, but only when averaged across large groups of neurons. Consequently, our knowledge of the precise spatial and temporal interactions that occur between groups of neurons in the human brain during behavior remains critically incomplete.

Electrocorticography (ECoG) is an imaging technique that recently received strong attention from the neuroscientific community. ECoG consists of placing small electrodes directly on the surface of the brain to record neuronal activity from different areas of the cortex. It has been commonly used in the medical treatment of patients suffering from epilepsy for close to eight decades. Because the electrodes are in very close proximity to the brain, they record the activity of well-defined groups of neurons with excellent spatial and temporal resolution. Thus, ECoG is an excellent candidate for capturing the precise interactions that occur between groups of neurons during behavior. In addition, ECoG is in a good position to serve as catalyst for research that translates neuroscientific understanding into clinical solutions.

In this dissertation, we take advantage of the possibilities offered by ECoG imaging to derive novel understanding of the mechanisms orchestrating the precise temporal and spatial interactions between groups of neurons during behavior. Furthermore, we translate our findings into two novel clinical applications that build on existing neurological procedures to treat patients suffering from epilepsy and brain tumors.

The dissertation is structured as follows: In Chapter 1, we provide an introduction to the general concepts used throughout this dissertation. We describe ECoG, the type of information that can be extracted from ECoG signals, and how this information can be used to advance our neuroscientific understanding of the mechanisms underlying human behavior and to develop novel clinical applications. In Chapter 2, we characterize the temporal and spatial dynamics of neuronal activity during different types of behavior and we provide experimental evidence for a general mechanism that modulates neuronal activity according to task demands. In Chapter 3,
we further the study of this mechanism by investigating the relationship between the different brain structures that implement this mechanism. In Chapters 4 and 5, we extend the existing clinical application of ECoG to the treatment of patients suffering from epilepsy or brain tumors. Specifically, we propose two novel techniques that improve the speed and safety of existing treatment procedures and expand the number and type of patients that can benefit from them. Finally, in Chapter 6, we provide our conclusions and a discussion of potential future directions.
1.1 An Introduction to Electrocorticography

In the following sections, we will provide a brief history of electrocorticography (ECoG) in humans and describe how ECoG evolved from a purely clinical technique to the modern neuroimaging technique that it has now become. We will follow with a description of the practical aspects of ECoG recordings, e.g., what type of patients are chronically or acutely implanted with ECoG grids, and how these patients can benefit research endeavors. Next, we will give a short overview of the physiological mechanisms underlying ECoG signals. Finally, we will discuss how ECoG compares to other neuroimaging techniques and identify the types of clinical and research questions that can take maximal benefit from ECoG.

1.1.1 A brief history of human electrocorticographic recordings

ECoG is an invasive technique. It requires opening the skull, removing tissues protecting the brain and placing electrodes directly on the surface of the cortex. For these reasons, human electrocorticography has long seen its usage restricted to the clinical field. It is only recently (i.e., in the last 5-10 years) that ECoG outgrew its clinical origins to acquire its current status of a unique neuroimaging technique for research.

The story of modern human electrocorticographic recordings can be traced back to the 1920’s in Germany. The First World War had brought its share of wounded soldiers, many of them suffering from epilepsy caused by brain trauma and lesions. How to safely remove those cerebral lesions without causing further damage was at the center of the work of Otfrid Foerster, a German neurosurgeon, and Wilder Penfield, his young American assistant. Around the same time, Hans Berger, a German psychiatrist, was showing for the first time that it was possible to record electrical signals arising from the brain (i.e., the electroencephalogram or EEG). It only took
a few years before several scientists, including the Canadian Herbert Jasper, demonstrated the utility of EEG signals recorded from epileptic patients for identifying the location of interictal activity (i.e., the pathological cortical activity observed in-between seizures). Thus, it was quite natural that Penfield, who had become a renown Canadian neurosurgeon and had founded the Montreal Neurological Institute, invited Jasper to run a laboratory of neurophysiology dedicated to the development of EEG and intracortical EEG (i.e., ECoG) for epilepsy surgery. In 1941, their collaboration resulted in a book chapter entitled ‘Epilepsy and Cerebral Localization’, the first of its kind to extensively describe the use of EEG and ECoG for the diagnosis and surgical treatment of epilepsy. Together, Penfield and Jasper developed a procedure to safely remove epileptic tissue without damaging surrounding healthy brain tissue, a procedure that would become famously known as the ‘Montreal Procedure’. This procedure involved recording cortical activity using ECoG, using these recordings to identify cortical tissue provoking the seizure, and probing the surrounding cortex while the patient was fully awake and under local anesthesia to map healthy cortical tissue that should not be removed. The Montreal Procedure proved to be highly successful, and ECoG and EEG mapping techniques soon spread to hospitals around the world.

At that time, electrocorticography was performed exclusively during surgery. It is in France in the 1950’s that Talairach and Bancaud developed the first chronically implanted ECoG electrodes. These implants, which could be left in place for several days, were useful because they were allowing the recording not only in-between seizures but also during seizures. In addition, the probing of surrounding brain tissue could now take place outside the operating room, which meant less time pressure for the clinician and more comfort and safety for the patient. Despite those advantages, it is only in the late 1980’s that the development of new biocompatible materials improving the safety and efficacy of ECoG grids led to the wider use of chronic implants for the
treatment of epilepsy.

The increased usage of chronic implants also favored neuroscientific investigation using ECoG. In the early 2000’s, the important finding that certain features ECoG signals could robustly track the precise temporal and spatial modulations of cortical activity (Crone et al., 2001, 1998a) progressively caught the attention of neuroscientists and engineers alike. Until then, most neuroscientific studies in humans were based on non-invasive imaging techniques such as EEG and functional magnetic resonance imaging (fMRI), which suffer from poor spatial and temporal resolution, respectively. In this milieu, ECoG provided an unprecedented opportunity to observe the subtle dynamics of the human brain in action.

1.1.2 Recording ECoG signals

In current clinical practice, ECoG grids are often implanted chronically, i.e., for several days, or acutely, i.e., for the duration of the surgery. Chronic and acute implantation are usually performed in different patient populations and with different clinical objectives. In the next section, we will describe the clinical and scientific implications of these two different types of implantation.

1.1.2.1 Chronic recording of ECoG signals

Traditionally, chronic implantation of ECoG grids is mostly performed in epileptic patients suffering from intractable epilepsy, i.e., epilepsy that does not respond to drugs. Epilepsy can result from a dysfunctional rearrangement of cortical tissues following a head trauma, a stroke, the growing of a brain tumor, or a dysplasia (i.e., abnormal cellular changes). This dysfunctional rearrangement of cortical tissues entrains abnormalities in cortical activity that can develop into seizures. When epileptic patients do not respond to medication, one of the solutions is to remove
the part of the brain that generates seizures, i.e., the epileptogenic focus. Neurologists can identify the exact location of the epileptogenic focus by recording cortical activity from different parts of the brain and detecting the abnormalities resulting from epileptic activity. Cortical activity is usually first recorded using scalp-recorded EEG, followed by a more refined ECoG acquisition using grids implanted in proximity of the hypothesized epileptogenic focus.

Epileptic patients usually come to the hospital for a first surgery during which part of their skull is removed (a procedure called a craniotomy). One or several grids and/or strips of electrodes of various sizes are placed directly on the surface of the brain, below the dura (i.e., the outermost of the meninges layers). Usually, grids only make contact with cortical gyri, i.e., they do not record activity from internal cortical convolutions (the sulci). The grids are typically composed of electrodes of diameter in the submillimeter to millimeter scale, embedded in a flexible transparent biocompatible material. Depending on the manufacturer, the distance between electrodes can vary from the centimeter to the millimeter scale. We will compare, in Chapter 4, the usage of low-density and high-density ECoG grids for clinical purposes. The electrical signal from each electrode is transmitted to a recording unit via wires that come out of the patient’s head via a small burr hole.

Cortical coverage using ECoG grids is dictated by the patient’s clinical needs and often includes a large portion of the temporal lobe and some of the frontal and parietal lobes, with usually little occipital coverage. From a research point of view, these limitations in coverage narrow down the type of sensory modalities and the number of research questions that can be investigated. Because of the large coverage of the temporal lobe (which contains many important auditory areas), most of the experimental tasks generally include some auditory component.

Aside from determining the location of the epileptogenic focus, it is important to define a safety margin for resection. The epileptogenic focus can be in close proximity with cortical
areas important for the quality of life of the patient (e.g., epileptic activity can arise from the inferior frontal cortex, which contains neuronal populations crucial for speaking). Therefore, it is important to identify the locations of these cortical areas as well. Here, ECoG electrodes serve a second role: not only can ECoG electrodes be used to record brain signals, but they can also be used to stimulate underlying cortex by passing a small amount of current through them. Stimulating the cortex under the electrode usually results in observable behavioral effects that are directly related to the cortical area being stimulated. For example, stimulating hand motor cortex will produce a brief movement of the hand, while stimulating the cortical areas involved in speech production will transiently impair the speaking abilities of the patient. During a typical stimulation session, the neurologist stimulates each electrode one after the other. Behavioral effects of the stimulation can be either observed by the neurologist or reported by the patient.

The patient usually stays in the epilepsy monitoring unit at the hospital for one to two weeks. During this time, the clinicians analyze ictal and interictal activity and locate the epileptogenic cortical regions. Patient’s brain signals are thus recorded 24 hours a day by the hospital recording devices. The stimulation procedure is usually performed as soon as the clinicians have identified the epileptogenic focus with a high level of confidence.

Research sessions take place whenever the patient is willing and able to participate. The time and duration of research sessions depend on many factors, such as the patient’s current epileptic activity, medication, pain level, overall postsurgical condition, personal and social needs, etc. We use BCI2000 software (Schalk et al., 2004a; Schalk and Mellinger, 2010b) to simultaneously present experimental stimuli and synchronously record brain signals and patient behavior (e.g., button press, eye tracking).

Once the clinicians have identified the epileptogenic focus and defined a safety margin for resection (based on the results of the stimulation), the patient undergoes a second surgery, during
which the ECoG grids and/or strips are removed and the epileptogenic focus resected.

1.1.2.2 Acute recording of ECoG signals

ECoG grids can also be implanted acutely, typically in patients with brain tumors. These patients usually undergo one surgery during which an ECoG grid can be placed over the cortical area that contains the tumor. The location of the tumor itself can be identified using magnetic resonance imaging (MRI) or computerized tomography (CT). The purpose of the ECoG electrodes is mainly to stimulate the cortex surrounding the tumor in order to identify functional healthy tissue and define safety margins for resection. Because the patient has to actively participate in the mapping procedure, anesthesia is partially reversed prior to stimulation and the patient is woken up. Because of the limited amount of time during which the patient can generally tolerate to be awake and other factors that will be developed in more detail in Section 1.3.2.3, there is an active field of research dedicated to the improvement of the speed, efficiency and safety of this procedure. We will discuss our contribution to this field of research in Chapters 4 and 5.

1.1.3 Physiological basis of ECoG signals

In this section, we will describe the general physiological processes underlying ECoG signals.

What we call cerebral activity is the combination of a wide range of mechanisms that include the redistribution of electrical charges inside and outside neurons, increase of blood flow, movement of molecules (e.g., neurotransmitters) from one neuron to another, and changes in gene expression (e.g., related to plasticity). Monitoring any of those mechanisms can provide important information about the state of the brain at a given time. ECoG measures one of those mechanisms, i.e., the voltage changes associated with currents generated by the redistribution of electrical charges. Specifically, ECoG electrodes detect the average variation of potential in
the extracellular field across a large number of neurons (approximately $10^5$ neurons per cm$^2$ of electrode).

Although all cells (neurons and glia) that act on the distribution of extracellular charges can in theory contribute to the variations of potentials recorded at the electrode, not all of them contribute the same amount. It is usually understood that excitatory post-synaptic currents in the pyramidal neurons of the cortex contribute the largest to the extracellular potential recorded with ECoG. Pyramidal cells are the most common type of excitatory neurons in the cortex and other brain structures such as the hippocampus. When a pyramidal cell receives an excitatory input at its dendrite, the glutamate released by the pre-synaptic neuron binds to glutamate receptors (AMPA and NMDA receptors) on the post-synaptic synapse. The subsequent opening of these receptors allows positive ions (e.g., Na$^+$ and Ca$^{++}$) to enter the cell. This transfer of positive ions from the extracellular to the intracellular space creates an extracellular ‘sink’ (i.e., the extracellular space loses some positive charge). This increase of positive intracellular ions is instantaneously counterbalanced by a loss of positive ions (or entrance of negative ions) somewhere else on the neuron, typically its soma. This pair of equal and opposite currents entering the cell at its dendrite and exiting it at its soma forms a dipole along the somatodendritic axis of the cell. This dipole is the basis of the signal that we record with ECoG. The contribution of each dipole decays with the square of the distance separating it to the recording point.

A single dipole cannot be detected using an ECoG electrode (the current produced by such a dipole is on the order of the picoampere), but neither can be a large number of dipoles if they do not possess some fundamental spatial and temporal properties. First, dipoles must be spatially arranged such that their activity does not cancel each other, as would happen with randomly arranged dipoles. This is one of the reason why cortical pyramidal cells, which are typically arranged parallel to each other in the cortex, emit a signal that can be readily detected.
with ECoG. Second, because the human cortex is folded, two cortical folds facing each other within a sulcus can result in dipoles that cancel each other out. In addition, because ECoG electrodes are usually placed on the superficial cortical surface (as opposed to within the sulci), cortical gyri contribute the most to the recorded signal. Finally, the timing of changes of the postsynaptic potential is also very important: a synchronized input to a population of pyramidal cells will generate a strongly synchronized postsynaptic response, leading to a strong effect on the recorded signal.

Action potentials themselves contribute only weakly to the recorded signal. This is because they consist of very rapid changes of cellular potentials that are filtered out by the low-pass filtering properties of neuronal dendrites (Lindén et al., 2010; Pettersen and Einevoll, 2008) and of the extracellular field (Bédard et al., 2004, 2006) on their way to the recording electrode. Therefore, by definition, what is being recorded in the ECoG signal is not the spiking output of a given population, but the effects of its synaptic input as described above. Nonetheless, pyramidal cells within a particular population largely interconnect and excite each other, which means that a large part of the observed synaptic input is due to local firing (Miller, 2010).

Finally, several other physiological phenomena can also affect the ECoG signal to a lesser degree, such as gap junctions that physically connect neurons, glia-generated currents, ephaptic interactions (i.e., possible feedback mechanisms exercised by the extracellular field on neuronal activity) and inhibitory post-synaptic potentials (in particular when they occur in depolarized firing neurons).
1.1.4 Strengths and limitations of ECoG as an imaging technique for neuroscientific research

The increasing use of ECoG for neuroscientific research is relatively recent. It is thus important to understand how it is positioned amongst other neuroimaging techniques. ECoG possesses great strengths but also has important limitations. In the next section, we will present these strengths and limitations and discuss their impact on neuroscientific investigation using ECoG.

1.1.4.1 Strengths of ECoG

The greatest strength of ECoG is to combine advantages of different non-invasive imaging techniques, namely, the excellent temporal resolution of EEG and MEG (i.e., magnetoencephalography) and the excellent spatial resolution of fMRI. While EEG and MEG have comparably high temporal resolution, they are limited by their poor spatial resolution. On the other hand, fMRI has excellent spatial resolution, but its poor temporal resolution (seconds to minutes) does not allow the investigation of temporally fast (sub-second) cortical events.

Second, in contrast to single-unit recordings, ECoG samples the brain quasi-uniformly from a large number of cortical regions.

Third, because ECoG electrodes make direct contact with the cortex, they are able to detect signals that cannot be readily detected with EEG or MEG. As we will see in Section 1.2.2, these subtle changes provide invaluable information regarding cortical activity.

Finally, on the practical side, ECoG electrodes are not in contact with the skin. This renders ECoG recordings highly robust to artifacts commonly encountered with EEG and MEG such as muscular and ocular movements.

For all these reasons, ECoG occupies a privileged position to investigate temporal and spatial dynamics of precise neuronal populations sampled over distinct cortical areas. As we will see
in the next chapters, accessing these cortical dynamics is critical from both scientific and clinical points-of-view.

1.1.4.2 Limitations of ECoG

Despite its strengths, ECoG suffers from important limitations that affect ECoG-based neuroscientific research at different levels. It is thus important to address and discuss these limitations. The first limitation concerns the limited extent of spatial coverage available with ECoG compared to EEG, MEG, or fMRI. Although several cortical lobes are usually covered by ECoG grids and strips, it is never the case that the entirety of the cortex is covered. Larger craniotomies result in increased risk of post-surgical complications such as infections, and the size of the craniotomy is therefore always kept to a minimum. Strips and grids can partly be slid below the skull, but the presence of bridging veins ultimately restricts the extent of ECoG coverage. Limited coverage restricts the type of neural systems that can be investigated. Limited coverage can also complicate results interpretation of scientific analyses. In some cases, it can be difficult to determine whether the absence of neural changes in a particular subject may result from a lack of coverage.

Second, in contrast to fMRI or depth electrodes, ECoG is unable to directly detect the activity of sub-cortical structures or from cortical sulci. Although some components of the ECoG signals, such as alpha oscillations (as we will discuss later) might be considered as a proxy for signals from subcortical structures such as the thalamus, simultaneous direct recordings from these structures (e.g., using depth electrodes) will eventually be necessary to complete our understanding of cerebral dynamics.

Third, although ECoG’s spatial resolution is high compared to EEG or MEG, it is lower than that of high-resolution fMRI or micro-electrodes recordings (sub-millimeter resolution). Higher spatial resolution is desirable, because it permits a more thorough investigation of cortical dy-
namics, a better delineation of important cortical areas for clinical mapping purposes, and an extension of scientific questions that can be investigated.

Finally, the suboptimal recording environment (i.e., the hospital room or an operating room), variable physical and mental conditions of the patient, and time limitations, limit the complexity of the experimental design.
1.2  Using ECoG to Investigate Cortical Activity and Excitability

In the previous section, we provided introductory information regarding the technique of electrocorticography. In the following section, we will discuss how signals recorded with ECoG can be decomposed into different components that provide specific information about the functional state of the neuronal population below the electrode. These components provide important information regarding brain function and will be used throughout the dissertation.

1.2.1 Introduction to the ECoG power spectrum

The ECoG signal reflects the composite of different physiological processes within the population of neurons below the electrode. Untangling these different processes requires decomposing the signal into their constituent components to analyze each part independently. One possible way to decompose the signal is to use Fourier decomposition, which states that any signal can be approximated by a sum of basic sine waves or oscillations. Each oscillation has a different frequency and amplitude. The amplitude of each oscillation can change over time depending on the shape of the ongoing recorded ECoG signal. Based on this decomposition, we can identify individual oscillations or groups of oscillations that change in their amplitude together during specific brain processes. We can then monitor the changes of amplitude of those specific oscillations as a proxy for the cerebral processes taking place during behavior and perception.

Importantly, different types of cortical processes affect the amplitude of frequencies differently. Typically, we can distinguish between two main types of cortical processes in terms of their effect on the spectrum: the ones that affect specific frequencies (those are called oscillatory processes), and the ones that affect all frequencies at once (those are non-oscillatory). Oscillatory processes are due to events that repeat over fixed amounts of time. For example, an event re-
peating every 100 ms will give rise to a 10 Hz component (i.e., 10 events per second) of a large amplitude in the spectrum. Non-oscillatory processes reflect events that occur randomly, i.e. without being temporally related to each other. The spectrum of such a distribution of uncorrelated events is a flat spectrum, i.e., a spectrum with equal amplitude at a broad range of frequencies, also called broadband. Importantly, in the case of ECoG, as well as MEG and EEG, the spectrum of broadband processes is not flat, but typically displays a 1/frequency (1/f) shape, i.e., higher frequencies are attenuated compared to lower frequencies. While the physiological mechanism underlying this 1/f shape is still debated, it is generally assumed to involve the low-pass filtering properties of neuronal dendrites (Lindén et al., 2010; Pettersen and Einevoll, 2008) and of the extracellular field (Bédard et al., 2004, 2006).

The amplitude of oscillatory components can be related to behavior. For example, it is generally assumed that the amplitude of 10 Hz oscillations observed over a particular cortical area decreases in preparation for behavior, e.g., in the motor cortex in preparation for a motor movement. On the other hand, broadband changes at a particular cortical area have been invariably reported to increase when the area was active. Because oscillatory and non-oscillatory components reflect different types of events (i.e., either repeated over fixed or random periods of time, respectively) and because they correlate differently with behavior (e.g., increase or decrease in amplitude), there is a vast amount of research trying to define what causes these mechanisms, how they relate to behavior, and how they relate to each other.

In the next sections, we will describe the physiological processes underlying broadband and oscillatory changes observed in the ECoG power spectrum and their relation to cortical processing.
1.2.2 Broadband changes of the ECoG power spectrum

Broadband changes of the ECoG power spectrum have been extensively studied over the last ten years and have vastly contributed to the success of ECoG as a neuroimaging technique. Their amplitude has been shown to be tightly correlated with the cortical activity of task-related neuronal populations. This has been shown for a large variety of tasks. For example, their amplitude increases in motor areas during motor movements (Crone et al., 1998b; Kubanek et al., 2009; Miller et al., 2007a), in areas processing speech during speech perception (Canolty et al., 2007; Crone et al., 2001), in auditory cortex during music perception (Potes et al., 2012) and auditory attention (Dijkstra et al., 2015; Golumbic et al., 2013; Mesgarani and Chang, 2012), in sensorimotor, prefrontal and visual areas during visual spatial attention (Gunduz et al., 2011, 2012), and in speech production areas during overt speech (Edwards et al., 2009) or imagined speech (Pei et al., 2011a).

As mentioned previously, broadband changes do not reflect repetitive events, but transient events uncorrelated with each other. It has thus been hypothesized that increases in broadband amplitude are due to synchronized excitatory inputs to pyramidal cells causing large changes of postsynaptic potentials. Manning et al. (2009) demonstrated using local field potentials (LFP) recordings that the amplitude of broadband changes increases with the averaged firing rate of close-by single neurons. While action potentials themselves do not contribute strongly to the ECoG signal (as was discussed in Section 1.1.3), it is reasonable to assume that the firing neurons that were recorded excited local neighboring neurons, thus inducing changes of postsynaptic potentials reflected in the LFP. When the number of action potentials fired increases, the number of postsynaptic events increases as well, which translates into a broadband increase of the recorded signal spectrum. Therefore, amplitude variations of broadband ECoG spectrum can
be considered an excellent proxy for the average firing rate of neuronal populations below the electrode. These variations have both a high temporal resolution (they track changes of the order of $\sim 10$ ms) and high spatial resolution (they exclusively track the activity of neurons directly below the electrode). Modulation of the amplitude of broadband changes are thus a precious tool to investigate temporal and spatial cortical dynamics.

Broadband changes of the ECoG spectrum are considered very challenging, if impossible, to observe using non-invasive imaging techniques such as EEG. On the other hand, these changes are easily detected in single trials of ECoG data. This difference is explained by a combination of two phenomena. First, oscillatory mechanisms often take place in the lower part of the EEG and ECoG power spectrum, i.e., below 60 Hz. These oscillations can superimpose on top of broadband changes and obscure them. Second, because of the $1/f$ shape of the spectrum, the amplitude of larger frequencies is fainter and more challenging to detect at the electrode. If the amplitude of the signal is smaller than the noise floor of the recording system (i.e., the amount of noise inherent to any recording system), the signal will be impossible to segregate from noise. For example, EEG can typically not detect frequencies higher than 60 Hz. Therefore, most of the variations of amplitude in the EEG power spectrum reflect amplitude modulations of oscillatory mechanisms below 60 Hz. In contrast, because ECoG electrodes are placed directly on the surface of the brain, they can detect signals that are much weaker than the ones detectable with non-invasive techniques (recall that the intensity of the dipole formed at a pyramidal cell decays with the square of the distance). These signals include high frequencies that are not ‘contaminated’ with the oscillatory components of the lower part of the power spectrum.

Finally, it is important to differentiate between broadband changes that are observed in the high frequencies (i.e., $> 60$ Hz) of the ECoG spectrum, and actual oscillations that occur between 40 and 60 Hz, called gamma oscillations. Many studies do not differentiate between the two,
although they reflect two completely different mechanisms (i.e., non-oscillatory or oscillatory mechanisms). Broadband changes are usually called ‘high gamma’ or ‘broadband gamma’ in the literature. We will frequently use the term broadband gamma throughout this dissertation.

1.2.3 Oscillatory components of the ECoG power spectrum

Oscillatory components of the ECoG power spectrum are caused by rhythmic changes of the extracellular potential recorded by the electrode. The presence and frequency of these changes is determined by the network properties of the neuronal population below the electrode, i.e., how are neurons connected to each other, and intrinsic properties of those neurons, e.g., the presence of particular ion channels in the membrane, the type of neurotransmitter being used, etc.

A typical network of neurons involves excitatory neurons, e.g., pyramidal cells in the cortex, and inhibitory cells, e.g., most types of interneurons. Excitatory neurons evoke a depolarization of their target cells, e.g., via the opening of postsynaptic glutamate receptors such as AMPA receptors. This depolarization increases the excitability of the target neuron, i.e., it facilitates the activity (or firing) of the target neuron. On the other hand, inhibitory neurons hyperpolarize their target neuron, usually via the opening of postsynaptic GABA receptors. This decreases the excitability of the target neuron, rendering the firing of an action potential more difficult. One of the basic network structures that gives rise to rhythmic cortical events is mutual interaction between those excitatory and inhibitory neurons. Consider a population of excitatory neurons interconnected with each other and with inhibitory interneurons. Firing excitatory neurons drive other excitatory neurons in a positive feedback loop. At the same time, they excite inhibitory interneurons. When the excitation of inhibitory interneurons reaches a critical point, inhibitory interneurons fire and hyperpolarize excitatory neurons, leading to a decreased excitatory drive. Without this excitatory drive, inhibition decreases and the next cycle begins anew.
Interestingly, inhibition is not necessarily generated by inhibitory neurons. Negative feedback can originate from the firing neuron itself. For example, membrane depolarization during firing triggers the opening of voltage-gated and calcium-gated channels letting potassium exit the cell, leading to decreased excitability. In this case, a neuron subject to a constant excitatory drive will fire rhythmically.

These events give rise to rhythmic changes of the extracellular potential. These changes can be observed at the level of the recording electrode when a large number of neurons are subject to the same rhythmic activity. Importantly, populations of neurons tend to synchronize when they share similar cellular properties. For example, many neurons display resonance properties, i.e., they respond more strongly to inputs at a specific frequency. The optimal (or resonance) frequency depends on the properties and constituents (e.g., specific ion channels) of the neuronal membrane. Additional properties also affect the ability for populations to oscillate and synchronize their activity. For example, gap junctions, i.e., channels that directly connect the cytoplasm of neurons, can synchronize two neurons by enabling the fast diffusion of ions from one to the other and the equalization of their membrane potentials.

Finally, the connectivity between different cerebral structures can modulate these oscillations. For example, as we will discuss in Section 1.3.1.2, the thalamus can rhythmically drive inhibition of cortical pyramidal cells by recruiting cortical inhibitory interneurons.

Therefore, oscillating neuronal populations reflect rhythmic inhibition generated either locally or by an external source. Oscillatory dynamics are important because they create alternating windows of low and high excitability. In other words, the postsynaptic response of a neuronal population to a given input depends on the timing of the input in relation to the ongoing oscillation. The response to the input will be lower during the inhibitory cycle of the oscillation and higher during the excitatory cycle of the oscillation. Because oscillations impact the processing of
cortical inputs, they have been hypothesized to actively modulate perception, behavior, and the underlying cortical flow of information throughout neuronal populations. We will discuss these hypotheses in the next section.
1.3 Harnessing ECoG Signals for Neuroscience and Neurosurgery

In the previous section, we described how oscillatory and non-oscillatory components of the ECoG signals represent the state of excitability and activity of the neuronal population below the electrode. In the following section, we will address how we can use this understanding to approach neuroscientific and neurosurgical challenges. While neuroscientific and neurosurgical objectives can be distinct, advances in one field can benefit the other. This stands particularly true for ECoG research, which is the fruit of a formidable collaborative effort between clinicians, engineers and scientists. While the role of ECoG in epilepsy surgery is well-established, its use can be complemented by novel clinical applications resulting from translational ECoG research.

In Section 1.3.1, we will discuss the contribution of a specific type of cortical oscillations called ‘alpha oscillations’ to the regulation of cortical information in the brain. This research aims at understanding the relationship between cortical activity and excitability during different types of behavior and the mechanisms that drive this relationship. Next, in Section 1.3.2, we will discuss how this neuroscientific understanding can be translated into novel clinical applications that facilitate and improve the safety of brain surgery. Specifically, we will first explain why mapping the cortex is a critical aspect of brain surgery. We will then describe state-of-the-art procedures to map the cortex and their limitations. Finally, we will discuss the advantages of cortical mapping using ECoG recordings and current associated challenges that remain to be addressed.

1.3.1 Harnessing ECoG signals for neuroscience

Human behavior can be divided between bottom-up (sensory-driven) behavior (e.g., being presented with an external auditory stimulus), and top-down (goal-directed) behavior (e.g., producing a voluntary motor movement or selectively attending to a particular stimulus). Top-down
behavior requires the active recruitment of specific neuronal populations in task-related cortical areas. The ability to flexibly recruit these populations despite a relatively static anatomy remains puzzling. Recent studies suggested that a specific subtype of cortical oscillations called ‘alpha oscillations’ could implement this recruitment by modulating cortical excitability according to task demands (Jensen and Mazaheri, 2010; Klimesch et al., 2007; Schalk, 2015). These oscillations, centered around a 10 Hz frequency, are hypothesized to reflect rhythmic inhibition arising from interactions between interneurons and excitatory cells in the cortex as well as subcortical structures. While the relationship between alpha oscillations and behavior has been observed since the 1920’s (Berger, 1929), their relation to cortical activity remains poorly defined. Moreover, it is currently unknown whether higher-level cortical areas important for flexibility and control of behavior (e.g., prefrontal cortex) modulate alpha oscillations.

In Chapters 2 and 3, we will investigate these questions by characterizing the relationship between alpha oscillations and cortical activity in several types of tasks involving either bottom-up and top-down processing. Moreover, we will investigate whether activity in prefrontal cortex relates to the presence of alpha oscillations in task-related cortical areas. In the sections that follow, we will elaborate on the physiology and relation to behavior of alpha oscillations. We will then discuss the advantages of using ECoG to study the relationship between alpha oscillations and cortical activity.

1.3.1.1 Alpha oscillations and behavior

Alpha oscillations were the first oscillations to be formally observed and named in human EEG (Berger, 1929). Alpha oscillations are usually observed between 8 to 12 Hz. Although they might be called differently depending on their location (they are usually named ‘alpha’, ‘mu’, or ‘tau’ over the visual, somatosensory or auditory cortices, respectively), their relation to cortical
inhibition is similar.

Alpha oscillations reflect a rhythmic inhibition of cortical processing. This inhibition can be directly related to behavior. The first to notice this relationship was Hans Berger, who in 1929 described the large oscillations that were appearing on time traces from occipital EEG electrodes (i.e., electrodes over the visual cortex) when the subject was closing his/her eyes. The idea that the amplitude of alpha oscillations increases in cortical populations that are not currently active (e.g., the visual cortex of a subject closing his/her eyes and thus not actively processing any external visual information) has since been corroborated with findings from many studies. For example, alpha oscillations over auditory cortex reduce in magnitude when the subject listens to auditory stimuli (Crone et al., 2001; Lehtelä et al., 1997; Tiihonen et al., 1991), and show the same behavior over sensorimotor areas when the subject performs a motor task (Crone et al., 1998b; Pfurtscheller and Berghold, 1989). It was further found that decreases of alpha amplitude do not only reflect cortical engagement during a task, but also the sensitivity of the cortical area to upcoming stimuli, i.e., its excitability. For example, reduced alpha power over occipital cortex enhances the perception of subtle visual stimuli (Lange et al., 2013; Romei et al., 2008) while reduced alpha power over auditory cortex is linked to increased occurrences of auditory illusions (Müller et al., 2013).

Not only does the magnitude of alpha oscillations relate to behavior and perception, but so does their phase, i.e., the specific state (peak/trough) of the oscillatory cycle. We described in the previous section how cortical oscillations reflect alternating windows of low and high excitability. The perception of a stimulus (in particular when the stimulus is close to perceptual threshold, i.e., can barely be perceived) has been shown to depend on the phase of ongoing alpha oscillations. For example, faint visual stimuli may not be perceived if they reach the visual cortex during a window of low excitability (Busch et al., 2009; Mathewson et al., 2009).
1.3.1.2 Physiological basis of alpha oscillations

Alpha oscillations observed at the level of the cortex can arise from two distinct mechanisms: corticocortical interactions (i.e., interactions between cortical layers) and thalamocortical interactions (i.e., interactions between specific layers of the cortex and the thalamus).

Corticocortical oscillations in the alpha range are generated by interactions between excitatory pyramidal cells and inhibitory interneurons. Specifically, pyramidal cells from cortical layer 5 excite interneurons that inhibit pyramidal cells of layers 2 and 3, which themselves excite neurons in layer 5 (Bollimunta et al., 2008). This inhibitory-excitatory feedback loop is similar to the one described in Section 1.2.3, and results in oscillations around 10 Hz.

Alpha oscillations can also be generated by thalamocortical interactions. The thalamus is a subcortical structure often described as an active relay between sensory information and the cortex. It projects excitatory connections to the layer 4 of the cortex. These projections innervate both inhibitory interneurons and excitatory neurons. Importantly, inhibitory interneurons have been shown to respond more strongly to thalamocortical excitation than excitatory neurons (Cruikshank et al., 2007). Therefore, thalamocortical input to the cortex results in a strong indirect inhibitory drive.

The thalamic input to the cortex is itself strongly modulated by different local thalamic populations of inhibitory and excitatory neurons and by excitatory drive from the cortical layer 6. When subject to excitatory drive from the cortex, groups of thalamic excitatory neurons fire with a 10 Hz frequency. This rhythmic firing arises from a mechanism similar to the one described in Section 1.2.3, i.e., the opening of potassium channels following firing. Gap junctions between those neurons result in the synchronization of their firing. This synchronized group of excitatory neurons innervate inhibitory interneurons which themselves make synapses onto thalamocorti-
cal cells. As a result, the thalamocortical input to the cortex is modulated at 10 Hz (Lőrincz et al., 2009).

While both corticocortical and thalamocortical interactions can generate 10 Hz oscillations, it remains unclear whether they both contribute equally to the alpha oscillations present in the ECoG power spectrum. It has been hypothesized that the two mechanisms contribute differently to the generation of alpha oscillations depending on the cortical area. For example, it has been observed that alpha oscillations in V1 in the visual cortex are mostly generated by thalamocortical interactions, while corticocortical interactions contribute more strongly to their generation in V2 and V4 (Bollimunta et al., 2011).

1.3.1.3 Modulation of alpha oscillations during top-down behavior

Top-down behavior involves the specific recruitment of populations in motor areas (e.g., in preparation for the execution of a motor movement) or in sensory areas (e.g., during selective attention to a particular stimulus). The recruitment of these populations is determined by the interactions between motor or sensory areas and higher-order cortical and subcortical areas important for goal-directed behavior (e.g., prefrontal cortex; Miller and Cohen 2001). Several recent theories suggested that modulations of cortical excitability could mediate these interactions by setting a cortical landscape facilitating intended behavior. Specifically, it has been postulated that the power (Jensen and Mazaheri, 2010) or instantaneous amplitude (Schalk, 2015) of alpha oscillations could mediate the recruitment of specific populations by determining cortical areas of high excitability (i.e., low power or instantaneous alpha) or low excitability (i.e., high power or instantaneous amplitude). These theories are supported by the strong relationship between alpha oscillatory activity and behavior (as discussed in Section 1.3.1.1) as well as the anatomical connectivity between prefrontal cortex and alpha-generating structures (e.g., the thalamus;
Cruikshank et al. 2012; Delevich et al. 2015; Zikopoulos and Barbas 2007). Furthermore, disrupting prefrontal activity during top-down behavior has been shown to perturb alpha oscillatory activity in task-related areas and decrease behavioral performance (Capotosto et al., 2009; Zanto et al., 2011).

Several questions remain currently unanswered: 1. What are the precise temporal and spatial relationships between alpha oscillations and cortical activity in task-related and task-unrelated areas? 2. How do these relationships differ during top-down behavior and bottom-up processing? 3. Are modulations of cortical excitability in task-related areas related to cortical activity in prefrontal cortex during top-down behavior?

We will answer these questions in Chapters 2 and 3. Specifically, we will use ECoG to study modulations of activity and excitability of specific neuronal populations. Importantly, the excellent spatial and temporal resolutions of ECoG recordings will allow us to investigate the precise spatiotemporal dynamics underlying interactions between distinct neuronal populations. In addition, the extensive coverage of ECoG will allow us to monitor these interactions not only within one cortical area (e.g., within the auditory or motor cortex) but across distinct cortical areas (e.g., between the auditory and prefrontal cortices).
1.3.2 Harnessing ECoG signals for neurosurgery

In the previous section, we introduced the neuroscientific problem that will be addressed using ECoG in this dissertation. In the next section, we will discuss the clinical applications that can benefit from ECoG recordings combined with our understanding of their dynamics. Specifically, we will describe how the same techniques that are used to characterize cortical activity for neuroscientific research can be applied to the clinical context. We will discuss how we can use these techniques to facilitate and improve the safety of resective brain surgery.

1.3.2.1 The importance of functional mapping prior to resective neurosurgery

Resective neurosurgery consists in removing pathological tissue from the brain, e.g., a tumor or an epileptogenic focus. One of the biggest challenges in resective neurosurgery is to selectively remove pathological tissue while preserving healthy functional cortex (Berger et al., 1989; Berger and Rostomily, 1997). In particular, eloquent cortex, i.e., cortex involved in speech, vision, somatosensation or motor movements, is considered critical to the patient’s postsurgical quality of life. Unfortunately, pathological tissue can be located in close proximity of eloquent cortical tissue. Hence, identifying the location of healthy eloquent cortex is a critical step during resective brain surgery.

Identifying eloquent cortex can be complicated by several factors. First, its location is highly variable from individual to individual (Ojemann et al., 1989a; Ojemann, 1979). Therefore, a resection solely based on the visual inspection of anatomical landmarks poses a significant risk. Second, brain tumors or recurrent seizures can lead to the functional reorganization of the cortex around pathological tissues (Sani et al., 2012; Vates et al., 2002; Wunderlich et al., 1998). Finally, in some cases, pathological tissue can retain functionality (Schiffbauer et al., 2001; Skirboll et al., 1996).
The critical need for tools and techniques that facilitate the identification, or mapping, of eloquent cortex during resective neurosurgery is well recognized. Studies have shown that functional mapping during brain surgery decreased the rate of permanent neurological deficits by more than half while significantly increasing the extent of resection (De Witt Hamer et al., 2012; Duffau et al., 2005; Sacko et al., 2011). The current gold-standard for mapping the brain is electrocorticostimulation (ECS), i.e., stimulation of the cortex to identify behavioral changes induced by the activation or inhibition of the stimulated cortical area. Surprisingly, ECS protocols have been practically unchanged since their development in the 1930’s, and ECS is still used in all major epilepsy centers around the world. Unfortunately, as we will further explain below, ECS suffers from several limitations that urge the need for novel functional mapping tools. In the following sections, we will elaborate on ECS and its current limitations. We will then address the potential role of ECoG recordings for functional mapping. This discussion lead to our two improvements of ECoG-based mapping techniques that are described in Chapters 4 and 5.

1.3.2.2 The current gold standard for clinical cortical mapping: electrocorticostimulation

ECS involves stimulating cortical tissues located in proximity to pathological tissue using a weak electrical current. The current depolarizes the neuronal population below the electrode and produces a behavioral response depending on the stimulated cortical area. Typically, stimulating a motor or sensory area triggers a motor response or a somatosensation, respectively, while stimulating a language area inhibits language production or comprehension.

During a typical ECS mapping session, the neurologist applies a 20 to 50 Hz electrical current of 1-15 mA to a pair of electrodes while the patient is being closely monitored. The neurologist gradually increases the current by steps of 2 mA until a behavioral response is observed or until the maximum current of 15 mA is reached, whichever comes first. When the stimulation of a
cortical location does not produce a behavioral response (i.e., it does not result in somatosensation, motor movements or language production and comprehension), the location is marked as negative. Negative locations are deemed safe for resection.

During language mapping, the patient is asked to perform a set of standardized tasks. These tasks assess his/her language production and comprehension during stimulation. These tasks involve answering some basic questions, naming pictures, counting, completing sentences, or generating verbs associated with a particular noun. These tasks require the patient to be in a position to understand and follow instructions.

ECS presents the advantage of providing a direct qualitative assessment of the potential neurological deficits resulting from the resection of a particular cortical location. Moreover, until the recent development of novel techniques relying on passive ECoG recordings, ECS was the only technique able to identify language production and comprehension areas intraoperatively, i.e., within the operating room.

1.3.2.3 Limitations of electrocorticostimulation

Even though ECS is seen as gold standard for clinical cortical mapping, it suffers from several noteworthy limitations. First, the high frequency of the current used during stimulation (i.e., 50 Hz) occasionally produces after-discharges, i.e. epileptogenic activity that can result in a seizure. Intraoperative seizures are particularly dangerous for the patient. They have been reported to occur in 24 % of intraoperative ECS mapping cases (Sani et al., 2012). Intraoperative seizures can result in tongue biting, obstruction of the airways, regurgitation or aspiration of gastric contents and hypoxemia (i.e., low concentration of oxygen in the blood). In addition, the involuntary movements of the patient during a seizure can result in scalp or cerebral injuries from the intracranial instrumentation or from devices used to maintain the head in a fixed position (Wilson
and Artru, 2004). In general, seizures can let the patient in a state of somnolence or confusion that can persist for several hours. This jeopardizes the ability to perform exhaustive cortical mapping and thus to preserve eloquent tissue from resection.

Second, ECS is subject to false positives and negatives. When the stimulation current is high, current can spread to adjacent areas by volume conduction or through functional connections between neuronal populations. This can lead to false positives (Blume et al., 2004). On the other hand, it may sometimes be necessary to abort stimulation of a particular location (e.g., because of the presence of after-discharges or discomfort for the patient). This can lead to false negatives (Simon, 2009).

Third, the exhaustive mapping of all cortical areas of interest requires an extensive amount of time. All locations need to be stimulated at incremental levels of current intensity and during different tasks (Duffau et al., 2002). A typical extraoperative (i.e., outside of the operating room) cortical mapping session with ECS lasts several hours. In the operating room, time restrictions can prevent the neurologist to perform the exhaustive mapping of all cortical areas of interest, which leads to higher risks of postsurgical neurological deficits.

1.3.2.4 Towards cortical mapping using passive ECoG recordings

ECS limitations urge the need for safer and faster methods to perform functional brain mapping. Current functional imaging techniques such as fMRI, positron emission tomography (PET) or MEG are not sensitive and specific enough to serve as alternatives (Giussani et al., 2010; Roux et al., 2003). Recently, the utility of ECoG recordings for functional mapping has been investigated. As discussed in Section 1.2.2, broadband changes of the ECoG power spectrum contain robust spatial and temporal information regarding neuronal activity below the electrode. While these changes can be used to characterize modulations of cortical activity for neuroscientific re-
search purposes, they can also be used in the clinical context. Specifically, quantifying broadband changes in response to a specific task (e.g., a motor or language task) can be used to identify those cortical locations whose activity increased during the task. In other words, this technique can identify the cortical areas functionally active during the task. This technique has already been shown to produce robust results in the clinical setting for various types of tasks. For example, it is possible to determine language or motor areas by identifying those electrodes which broadband gamma power increased while the patient was required to speak or move (Brunner et al., 2009; Roland et al., 2010). In Chapter 4, we will extend these results by investigating the practicality and efficiency of intraoperative functional language mapping using a novel type of high-density ECoG grid offering unprecedented spatial resolution. In addition, we will examine the relationship between mapping results obtained with high-density ECoG and those obtained extraoperatively using a conventional ECoG grid, ECS and fMRI.

Importantly, all current procedures to identify language cortical areas require the patient to speak and be able to follow task instructions. Unfortunately, active patient participation can be challenging for certain patient populations (e.g., pediatric populations that might not easily understand or follow instructions) or during certain situations (e.g., during awake craniotomies). Therefore, it would be valuable to develop novel language mapping techniques that remove or reduce the need for active patient participation. In Chapter 5, we will take advantage of ECoG’s high spatial and temporal resolutions and extensive coverage to propose a novel technique that safely and rapidly identifies language cortical areas without any patient participation. Furthermore, we will describe the results of application of this technique in three ECoG patients.
2.1 Summary of Problem and Approach

Performing different tasks, such as generating motor movements or processing sensory input, requires the recruitment of specific networks of neuronal populations. Previous studies suggested that power variations in the alpha band (8–12 Hz) may implement such recruitment of task-specific populations by increasing cortical excitability in task-related areas while inhibiting cortical activity in task-unrelated areas (Klimesch et al., 2007; Jensen and Mazaheri, 2010).

Currently, the precise temporal and spatial relationships between the modulatory function implemented by alpha oscillations and cortical activity remains undefined. Furthermore, while several studies suggested that alpha power indexes task-related populations across large and spatially separated cortical areas, it is largely unclear whether alpha power also differentially indexes smaller networks of task-related neuronal populations.

In this study, we will address these questions by investigating the temporal and spatial relationships of electrocorticographic power modulations in the alpha band and in the broadband
gamma range (70–170 Hz) during tasks involving top-down (e.g., the production of a voluntary motor movement) and bottom-up (e.g., passively listening to an auditory stimulus) processing in five human subjects and one macaque monkey.
2.2 Introduction

Performing different tasks, such as generating motor movements or processing sensory information, requires the recruitment of specific networks of neuronal populations dispersed throughout distinct cortical areas. How the brain implements the recruitment of these networks is still largely unclear, but there is increasing evidence that oscillatory activity plays an important role in this process. For example, several studies involving different sensorimotor modalities have reported a decrease in the power of low-frequency oscillations in the 8–12 Hz range (alpha band) in task-related areas (Crone et al., 2001; Pfurtscheller and Neuper, 1992; Potes et al., 2014). This phenomenon is frequently coupled with an increase in alpha power in areas unrelated to the task (Fu et al., 2001; Pfurtscheller and Berghold, 1989; Pfurtscheller and Neuper, 1992). These findings suggest that modulations in alpha power may index the excitability of different cortical areas, and, by extension, the spatial representation of selected functional networks (Jensen and Mazaheri, 2010; Klimesch et al., 2007; Schalk, 2015).

If oscillatory activity indeed provides a general mechanism for the selection of cortical networks through modulation of cortical excitability, we can make three specific predictions. First, increases in cortical activity in task-related areas should be accompanied by a decrease in alpha power irrespective of the task or the involved cortical areas, and alpha power should increase in all other regions.

Second, in top-down preparation for a motor output, increases in cortical excitability as measured by a decrease of alpha power should occur prior to increases in cortical activity. On the contrary, in a bottom-up response to a sensory stimulus, cortical excitability modulations may also be affected by the stimulus, and should thus trail stimulus-induced cortical activity. While the suppression in the alpha band has previously been reported to precede motor movements...
(Pfurtscheller and Berghold, 1989; Pfurtscheller and Neuper, 1992) and to follow auditory stimulation (Crone et al., 2001), such results remained to be demonstrated using single-trial analyses.

Third, we should observe task-selective alpha modulations not only on large spatial scales, e.g., across motor and auditory regions, but also on smaller scales, e.g., within auditory regions. Such small-scale modulations of oscillatory activity are a prerequisite if they were to play a central role in regulating information flow within the brain. While there is solid evidence supporting the idea that alpha power may constitute a selection mechanism across large, spatially separated areas (Foxe et al., 1998; Pfurtscheller, 1992; Pfurtscheller and Neuper, 1994; Thut et al., 2006), evidence that it may also support selection of small and interwoven networks is scarce (Harvey et al., 2013). At present, the general consensus is still that modulations of alpha power are spatially widespread and only poorly informative of detailed delineations of the functional networks underlying the performance of different tasks (Crone et al., 2001, 2006; Miller et al., 2009a; Pfurtscheller et al., 2003).

To test these predictions and to better understand the dynamics between modulatory alpha band oscillations and cortical activity, we recorded electrocorticographic signals (ECoG) during auditory and motor tasks in five human subjects and one macaque monkey. The high spatial and temporal resolution of these signals allowed us to study these dynamics not only across functional networks, i.e., auditory versus motor systems, but also within one functional network, i.e., the auditory system. In particular, we evaluated the spatial and temporal patterns of alpha power in response to different types of stimuli, over time, and in specific locations of auditory cortex, and related them to modulations of cortical activity as indexed by broadband gamma (70–170 Hz; Manning et al. 2009; Miller et al. 2009b; Ray and Maunsell 2011).

In agreement with the three predictions outlined above, we observed large modulations of alpha power across tasks: alpha power decreased in task-related areas and increased in a major-
ity of task-unrelated areas. These results were common to the human subjects and the macaque monkey. Because alpha power has been linked to cortical excitability, these changes likely subserve the preferential recruitment of those functional networks necessary to perform a particular task. Furthermore, we found that alpha power suppression lagged cortical activity in auditory areas during the auditory task, but preceded it in the motor areas during the motor task. Finally, decreases in alpha power within auditory areas indexed regions where cortical activity increased the most in response to specific auditory stimuli. Similarly, increases in alpha power indexed regions where cortical activity increased the least. Taken together, our results add further evidence to a central role of oscillatory activity in regulating cortical excitability, and thus in regulating information flow within the brain. They also suggest that this modulating mechanism might operate even across small cortical populations.

### 2.3 Methods

#### 2.3.1 Subjects

Five human subjects at Albany Medical Center (Albany, New York) and one macaque monkey at Radboud University (Nijmegen, Netherlands) participated in this study. The five human subjects (A–E) were patients with intractable epilepsy who underwent temporary placement of subdural electrode arrays to localize seizure foci prior to surgical resection. They included two women (A and B) and three men (C, D and E). The subjects’ clinical profiles is summarized in Table 2.1. Language lateralization (LL) was established preoperatively using the Wada test (Wada and Rasmussen, 1960). Human subjects gave informed consent for the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command. All animal procedures were
Table 2.1: Clinical profiles of the human subjects that participated in the study. All of the subjects had normal cognitive capacity and were functionally independent. Language lateralization (LL) was established using the Wada test.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Handedness</th>
<th>LL</th>
<th>Seizure Focus</th>
<th>Grid Locations</th>
<th># of Elec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29</td>
<td>F</td>
<td>R</td>
<td>L</td>
<td>Left temporal</td>
<td>Left fronto-parietal</td>
<td>64</td>
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<td></td>
<td>Left temporal</td>
<td>23</td>
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<td>Left temporal pole</td>
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<td></td>
<td>Left occipital</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>36</td>
<td>F</td>
<td>R</td>
<td>L</td>
<td>Right temporal</td>
<td>Right fronto-parietal</td>
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<td></td>
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<td></td>
<td>Right temporal</td>
<td>35</td>
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<tr>
<td>C</td>
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approved by the ethics committee of Radboud University, Nijmegen, Netherlands.

The subjects were implanted with electrode grids that were approved for human use (Ad-Tech Medical Corp., Racine, WI; and PMT Corp., Chanhassen, MN; for human subjects), or polyimide-based grids (Rubehn et al., 2009, for the macaque) over one hemisphere of the brain. Electrodes for the humans consisted of platinum-iridium discs (4 mm in diameter, 2.3 mm exposed), embedded in silicon and spaced 6–10 mm apart; for the macaque, electrodes were 1 mm in diameter and spaced 2, 2.5 or 3 mm apart. The total numbers of implanted electrodes were 58–134 for the humans and 252 for the macaque. In the humans, the grids were implanted for about 1 week and their location varied across subjects. They were placed over the left hemisphere for subjects A, C, D, E and the macaque, and covered frontal, parietal and temporal cortices. Following the placement of the subdural grid, each human subject had postoperative anterior–posterior and lateral radiographs, as well as computer tomography (CT) scans to verify grid location.
2.3.2 Data collection

We recorded ECoG signals from the five human subjects at the bedside using the general-purpose BCI2000 software (Schalk et al., 2004b; Schalk and Mellinger, 2010a) connected to eight 16-channel g.USBamp biosignal acquisition devices (g.tec, Graz, Austria). Clinical monitoring occurred simultaneously with the use of a connector that split the cables coming from the patient into one set that was connected to the clinical monitoring system and another set that was connected to the amplifiers. This ensured that clinical data collection was not compromised at any time. The signals were amplified, digitized at 1,200 Hz and stored by BCI2000. We used electrode contacts distant from epileptic foci and areas of interest for reference and ground. After visual inspection, we removed from all subsequent analyses those channels that did not contain clear ECoG signals (e.g., ground channels, channels with broken connections, presence of environmental artifacts, or interictal activity). We also removed occipital channels to avoid any confound due to the visual presentation of instructions during the tasks. This left 56–121 channels for further analyses. In addition to recording brain activity, we also simultaneously recorded the subjects’ behavior using a push button.

We recorded and amplified ECoG signals from the macaque using eight 32-channel headstages (Plexon Headstage 32 V-G20). We low-pass filtered these signals at 8 kHz, digitized them at 32 kHz (Neuralynx Digital Lynx 256 channel system) and resampled them at 1,200 Hz. 229 channels remained for further analysis after visual inspection for the presence of artifacts.

2.3.3 Anatomical mapping

We created subject-specific 3D cortical brain models for subjects A, C, D and E using high-resolution pre-operative magnetic resonance imaging (MRI) scans and Curry software (Neuroscan Inc., El Paso, TX). MRI scans were not available for subject B. Instead, for visualization
purposes, we used the 3D cortical template by the Montreal Neurological Institute (MNI)\(^1\). To identify the stereotactic coordinates of each grid electrode, we co-registered the MRI scans with post-operative computer tomography (CT) images. Finally, we projected each patient’s electrode locations onto the corresponding 3D brain model and rendered activation maps using the NeuralAct software package (Kubanek and Schalk, 2014).

For the macaque, the assignment of electrodes to cortical areas was based on high-resolution intra-operative photographs taken before and after grid placement, and used primarily sulcal landmarks.

2.3.4 Tasks and stimuli

During the auditory task, the human subjects and the macaque passively listened to natural auditory stimuli while otherwise resting. The stimuli consisted of 19 natural sounds that belonged to one of six different categories: speech (female and male voices (3 stimuli)), music (classical and jazz (4)), nature (forest, thunderstorm, water and waves (4)), animals (frogs, birds and dog (5)), engines (jet airplane and train (2)), or white noise (1). Each stimulus had a duration of 10 seconds. Stimuli were digitized at 44.1 kHz in waveform audio file format, and energy-matched.

We presented the stimuli in 10 blocks. Each block contained a randomly interleaved sequence of the 19 stimuli. We used binaural in-ear earphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from environmental noise) for the human subjects and a loudspeaker for the macaque. The sound volume was adjusted to a comfortable level for each subject.

At the end of each stimulus, we verified the human subject’s attention to the stimulus by engagement in a motor task in which s/he had to decide to which category the presented stimulus belonged. Specifically, two seconds after the end of the auditory stimulus presentation, we pre-

\(^1\)http://www.bic.mni.mcgill.ca
sented on a screen the names of two of the stimulus categories (e.g., ‘speech’, ‘music’). The names were presented simultaneously and next to each other. One of the names was the category to which the last stimulus belonged; the other one was randomly chosen from the other categories. Subjects were asked to assign the last stimulus to one of the two categories by pressing one of two possible response keys (e.g., left button for the choice on the left or right button for the choice on the right). Subjects used the hand contralateral to the grid implantation for the button press. The stimulus presentation resumed after a 2-second interval. Results of the behavioral data indicated that the human subjects were attending to the auditory stimuli. They correctly categorized the stimuli with an average accuracy of 97% (range: 92–99%; accuracy due to chance: 50%).

2.3.5 Feature extraction

To extract spectral power in the alpha and broadband gamma bands, we first high-pass filtered the signals at 0.1 Hz to remove drift. We then re-referenced the signals to a common average reference (CAR) montage for the human subjects and a bipolar montage for the macaque. We band-pass filtered the signals in the two frequency bands of interest, i.e., 8–12 Hz (alpha) and 70–170 Hz (broadband gamma) using Butterworth filters of the same order for the two bands. Next, for each subject, location, and stimulus, we removed evoked components in the alpha band (Fujioka and Ross, 2008; Klimesch et al., 2007) by subtracting the amplitude of alpha averaged across trials from the individual trials, according to the inter–trial variance method proposed by Kalcher and Pfurtscheller in 1995. We then extracted amplitude envelopes by computing the absolute value of the analytical band-passed signals, followed by a low-pass Butterworth filter at 4 Hz and down-sampling to 120 Hz. Finally, we normalized the amplitude envelopes to a baseline period, i.e., a 300 ms period just prior to the onset of the auditory stimulus. We chose

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2 Data for the macaque were collected across several different data acquisition systems, which invalidates the calculation of a spatial average across all channels.
this baseline period as the longest period of time that did not contain significant changes of broadband gamma or alpha power between averaged trials after visual inspection. We used the same baseline for all analyses throughout the study. For the remainder of the manuscript, we will refer to the signals that we obtained with these procedures as alpha and broadband gamma power, respectively.

To extract the sound intensity of the auditory stimuli, we first computed the square root of the squared amplitude of each stimulus. Similar to the neural signals, we then low-pass filtered the resulting signal at 4 Hz and down-sampled it at 120 Hz.

2.3.6 Data analyses

2.3.6.1 Spatial analysis

We first determined which cortical locations were responsive to the auditory or motor tasks, i.e., which locations exhibited higher broadband gamma power during the task period when compared to the baseline time period. For the auditory task, we defined the task period as the first 500 ms of auditory stimulus presentation. For the motor task, we defined the task period as the period from -250 ms to +250 ms relative to the button press. For each location and each task, we separately concatenated the task and baseline samples across all trials. We then calculated the coefficient of determination (Spearman’s $r^2$ value) between the baseline and task samples to determine the fraction of the total signal variance that was related to the task. We determined the statistical significance of these $r^2$ values using a permutation test in which we randomly re-assigned the label (task or baseline) to each time period and calculated the corresponding random $r^2$ value. (Note that we did not shuffle the samples within each time period, so the auto-correlation of the signal was preserved.) We repeated the randomization step 1000 times, generating a distribution of random $r^2$ values. We considered an observed $r^2$ value
to be significant at the 99th percentile of that distribution ($p < 0.01$, Bonferroni-corrected for the total number of electrodes in each subject). Our permutation test resulted in a set of reactive locations that defined task-related cortical areas, i.e., areas active during the auditory or motor task. Finally, we calculated the size of the observed effect at each location by computing the z-score obtained after normalizing the observed $r^2$ value against the mean and standard deviation of the random $r^2$ values distribution. The same process was applied to both the human and the macaque data\(^1\).

To quantify the spatial changes of alpha power in response to the auditory and motor tasks, we first determined whether the distribution of alpha power onset responses at each location was different from 0. For the locations that displayed a significant difference (two-sided t-test, $p < 0.05$, Bonferroni corrected for the number of locations) we determined whether the difference was positive or negative using a one-sided t-test ($p < 0.05$). This resulted in 3 sets of locations that displayed either an increase, a decrease, or no change of alpha power, respectively. We then compared the distributions of percentages of locations displaying an alpha power increase or decrease for each task using a two-sided t-test ($p < 0.05$).

\(2.3.6.2\) Temporal analyses

We first determined the temporal relationship between alpha and broadband gamma power, for each task period and across all the task-related locations previously defined. More specifically, we asked which of the two signals (i.e., alpha and broadband gamma) preceded the other in their modulations. To answer this question, we determined the delay between the positive peak of broadband gamma power and the negative peak of alpha power in single trials. We first low-

\(^{1}\)Since the macaque did not use his hand to verify the auditory stimulus, we defined motor cortical locations using separately collected data involving controlled hand motor movements. These hand movements were highly variable in duration and movement speed. Thus, they did not allow us to calculate event-related motor responses in the macaque. In addition, in the macaque, we only considered those locations that were posterior to the central sulcus during the auditory task, or anterior to the central sulcus during the motor task.
pass filtered the power in the alpha and broadband gamma bands at 2 Hz (MATLAB `filtfilt` command for zero phase-lag filtering). Next, for each frequency band, we averaged the power across those locations that were reactive during a particular task (i.e., auditory or motor). For each trial, we then determined the time of the maximum amplitude in the broadband gamma signal, and minimum amplitude in the alpha signal. In this analysis, we used the 200 to 800 ms period after auditory stimulus onset in the auditory reactive locations, and the -300 to 300 ms period relative to the button press in the motor reactive locations. This resulted in one peak time per trial, task and each of the two frequency bands. From the 190 trials, we obtained a distribution for each task and frequency band. After removing outliers (<5th or >95th percentiles), we applied a two-sided paired t-test to determine which of the two bands (i.e., alpha or broadband gamma) preceded the other.

To further establish the temporal relationship between alpha and broadband gamma power, we investigated whether the times of the peaks of the responses were related to each other. To do this, we computed the Spearman’s correlation coefficients between the times of the negative and positive peaks of alpha and broadband gamma power, respectively.

### 2.3.6.3 Correlation analyses

We investigated how the moment-by-moment variations in alpha power, sound intensity and broadband gamma power relate to each other. Specifically, we quantified these relationships by computing the Spearman’s correlation coefficient between alpha power and sound intensity, and between alpha power and broadband gamma power. In this context, it is important to recognize that each location will respond to the auditory stimulation with a different delay. To account for this delay, we temporally aligned the time course of alpha power with those of sound intensity and broadband gamma power. To do this, for each location, we first concatenated the signal
time courses across all stimuli after averaging across repetitions. We then shifted the alpha time
course by the delay (between 0 and 300 ms) that minimized the cross-correlation between alpha
power and sound intensity/broadband gamma power. We then computed the Spearman’s corre-
lation coefficient $r$ between alpha power and the sound intensity/broadband gamma power time
courses for each location. To assess the statistical significance of the obtained observed corre-
lation coefficient, we performed a permutation test in which we circularly shifted the reversed time
course of alpha power by a random value and calculated the corresponding Spearman’s corre-
lation coefficient between the obtained time courses. We repeated this randomization step 500
times, generating a distribution of random $r$ values. We considered an observed $r$ value to be sig-
nificant at the 95th percentile of that distribution ($p < 0.05$, Bonferroni-corrected for the number
of auditory locations in each subject). Finally, for each subject, we computed the median delay
and $r^2$ across locations displaying a significant correlation value, along with the percentages of
those locations.

2.4 Results

2.4.1 Spatial distribution of broadband gamma activations

The locations that were reactive during the auditory and motor tasks for each subject are shown in
Fig. 2.1. In line with previous research, in the human subjects, we found these locations primarily
close to superior temporal gyrus (STG) or other perisylvian regions during the auditory task
(Crone et al., 2001; Edwards et al., 2009), and close to premotor, motor and somatosensory cortices
during the motor task (Crone et al., 1998b; Miller et al., 2007a). Thus, these results confirm that
task-related increases in broadband gamma power can robustly localize functional cortical areas
(Brunner et al., 2009; Crone et al., 2011; Miller et al., 2014). In the macaque monkey, these
locations were largely concentrated around STG during the auditory task and around primary motor cortex (F1), dorsal premotor area (F2) and ventral premotor area (F4) during the motor task.

Figure 2.1: Increases in broadband gamma power index functional cortical locations. For each of the human subjects (A–E) and the macaque monkey (F), colored circles represent locations that were reactive during the auditory task (blue circles) or motor task (red circles). The size of the circle corresponds to the size of the response (see reference circles at the bottom of the figure). Small black circles denote non-reactive locations. They do not include artifactual and occipital electrodes that were removed from the analysis. AS, arcuate sulcus; CS, central sulcus; IPS, intraparietal sulcus; LuS, lunate sulcus; STS, superior temporal sulcus.

2.4.2 Differential amplitude relationship of broadband gamma and alpha modulations across large-scale cortical systems

To approach the main questions posed in our study, we established the relationship of the amplitude of broadband gamma and alpha responses to the auditory and motor tasks, i.e., across two different large-scale cortical systems. According to our first prediction, we expected to locate decreased alpha power in task-related regions (identified by increased broadband gamma), and increased alpha power in task-unrelated regions. Our results confirm this prediction.
Fig. 2.2 summarizes the average power in alpha and broadband gamma across all task-related locations during auditory or motor tasks, respectively (auditory task: 200 to 800 ms following auditory stimulus onset; motor task: -300 to 300 ms relative to the button press). These results show that in the auditory locations, the broadband gamma power increase during the auditory task was accompanied by a decrease in alpha power (two-sided t-test; see Fig. 2.2 for significance values). Such induced depression of alpha power over the auditory cortex is consistent with previous studies reporting a decrease of the so-called ‘tau’ rhythm centered around 10 Hz during the presentation of auditory stimuli (Krause et al., 1994; Lehtelä et al., 1997; Tiihonen et al., 1991). The same relationship was conserved in the motor locations during the motor task, where broadband gamma power increased and alpha power decreased (two-sided t-test; $p < 0.001$ for the humans). This finding is also consistent with the well-established event-related suppression of the mu rhythm (8–12 Hz) during motor movements (Pfurtscheller and Berghold, 1989).

These results also demonstrate that the reduction in alpha power in task-related areas was paralleled by an increase in alpha power in the task-related area of the opposite task (two-sided t-test; see Fig. 2.2 for significance values). For example, during the auditory task, alpha power was increased in motor locations both in the human subjects (left panel) as well as the macaque (center panel).

Finally, we were interested whether this observed increase in alpha power would extend to cortical areas that were not involved in any of the two tasks investigated here. To provide a qualitative assessment, for each of the two tasks, we projected all the electrodes of the five human subjects or the macaque onto a three-dimensional template brain and rendered the color-coded alpha power during task onset at each location. The results are shown in Fig. 2.3A-B. Results indicate that alpha power decreased in the corresponding reactive locations and increased over the majority of the cortical areas not involved in any of the tasks. Notably, we observed large
Figure 2.2: **Alpha power is suppressed in task-related locations and increased in non-related locations.** The bar plots show the amplitude of the responses, averaged across all task-related locations (i.e., auditory or motor areas), during the auditory task in humans (left panel), macaque (middle panel), and motor task in humans (right panel) for broadband gamma (blue) and alpha (red) bands. Error bars denote the standard error. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Increases in alpha power over the prefrontal and the inferior temporal cortices. In addition, the decrease in alpha power was spatially more restricted than the increase in alpha power (two-sided t-test, $p < 0.05$ for both tasks): 56% of locations exhibited an increase in alpha power for the human subjects and 53% for the macaque during the auditory task; and 60% for the human subjects during the motor task (see Fig. 2.3C). These results show that the increase in alpha power occurs in a majority of the locations.

### 2.4.3 Temporal relationship of broadband gamma and alpha modulations

We next determined whether the task-related decrease in alpha power preceded or followed the increase of cortical activity in the task-related locations. According to our second prediction, the task-related decrease in alpha power should lag the increase of cortical activity in the auditory
Figure 2.3: **A localized decrease in alpha power in the task-related locations is accompanied by an increase in the majority of the remaining locations.** A, B) The topographies show color-coded alpha power averaged during the auditory task for all human subjects (200–800 ms; top left panel) and the macaque (200–800 ms; bottom left panel) and motor task (-300–300 ms; top right panel). Colored circles represent locations that were reactive during the auditory task (blue circles) or the motor task (red circles). AS, arcuate sulcus; CS, central sulcus; IPS, intraparietal sulcus; LuS, lunate sulcus; STS, superior temporal sulcus. C) The bar plots show the percentage of all locations for which alpha activity decreased (blue), increased (red) or did not change (green), for the human subjects during the auditory (left) and motor (middle) tasks, and for the macaque during the auditory task (right). Error bars represent the standard error.

locations during the auditory task, but precede it in the motor locations during the motor task. This would be in line with previous studies that suggested that suppression in the alpha band follows auditory stimulation (Crone et al., 2001), while it precedes motor movements (Pfurtscheller and Berghold, 1989; Pfurtscheller and Neuper, 1992).

To qualitatively verify the temporal relationship between alpha power and cortical activity, we averaged the time traces of the power over all auditory or motor locations. The results for all subjects are shown in Fig. 2.4. They indicate that, during the auditory task, broadband gamma power showed a clear onset response peaking at 230 ms, consistent with the times reported in
other studies (161–250 ms range for Crone et al. 2001 and Edwards et al. 2009). This increase was followed by a decrease in the alpha band with a negative peak at 450 ms. This delay of about 200 ms between the broadband gamma and alpha power responses is consistent with the results observed in previous work (Edwards et al., 2009; Potes et al., 2014). During the motor task, a depression of alpha power peaked at 220 ms before the button press, during which the broadband gamma power reached its maximum. In sum, alpha power lagged broadband gamma power in auditory regions during the auditory task but preceded it in motor locations during the motor task.

Figure 2.4: Alpha power suppression lags broadband gamma power in auditory areas during the auditory task, but precedes it in the motor areas during the motor task. The time courses depict the averaged responses in auditory locations during the auditory task in humans (left panel), macaque (middle panel) and in motor locations during the motor task in humans (right panel) for broadband gamma (blue) and alpha (red) bands. Semi-transparent shading represents the standard error. The vertical dashed lines indicate the timing of the positive peaks of the broadband gamma band (blue) and the negative peaks of alpha band (red) for each task.

We confirmed this temporal relationships of the peaks of these two signals in individual trials using quantitative statistical analyses (auditory task: two-sided paired t-test; $p < 0.001$
for the human subjects and the macaque; motor task: two-sided paired t-test; $p < 0.001$ for the human subjects). Furthermore, single-trial analyses established that the times of the negative and positive peaks of alpha and broadband gamma power, respectively, were significantly correlated for both auditory and motor tasks ($r = 0.23$ for the auditory task in the human subjects and $r = 0.49$ for the macaque; $r = 0.19$ for the motor task in the human subjects; $p < 0.001$ for each condition). These findings, consistent across all human subjects and the macaque, support our hypothesis that the central nervous system can regulate cortical excitability during top-down preparation for motor output and during bottom-up responses to an auditory stimulus. In both cases, alpha power modulations index these changes of cortical excitability.

2.4.4 Differential alpha modulations within the auditory system

Finally, if indeed oscillatory activity reflects a general mechanism that gates information flow throughout the cortex, similar task-related patterns of decrease and increase in alpha power should also be present within the small scale of a single cortical system (e.g., the auditory system).

Initial investigations suggested that this was the case. Specifically, while alpha power dropped consistently across the whole auditory system across all different types of auditory stimuli, alpha modulations in individual locations varied substantially across different types of stimuli. Fig. 2.5 gives exemplary time course of alpha and broadband gamma power over the whole duration of the stimulus for two exemplary locations and four different exemplary stimuli in subject A.

We first investigated how the moment-by-moment variations in alpha power, sound intensity and broadband gamma power related to each other. The results of our correlation analyses showed that alpha power was significantly negatively correlated with broadband gamma power in $69 \pm 7$ % of the auditory locations (mean $r^2 = 0.13$, $p < 0.05$, Bonferroni-corrected for the number of auditory locations in each subject), and was lagging it by a median of 160 ms. In
Figure 2.5: The same auditory location can exhibit drastically different modulations of alpha and broadband gamma power according to the type of auditory stimulus presented. For two different auditory locations in subject A (left and right panels, respectively), the average time courses in response to four different auditory stimuli are shown for alpha and broadband gamma power (red and blue, respectively). Semi-transparent areas represent the standard error.

contrast, alpha power was significantly negatively correlated with sound intensity in only 2% of the auditory locations (mean $r^2 = 0.04, p < 0.05$, Bonferroni-corrected for the number of auditory locations in each subject), and lagged it by 170 ms. Because alpha power variations clearly trail broadband gamma power variations, our results suggest that during auditory stimulation, cortical excitability in the auditory locations is predominantly affected by variations in cortical activity rather than variations in stimulus intensity.

To further quantify these modulations of broadband gamma and alpha power, we first sought to determine whether the alpha power decrease in response to each sound affected all locations within the auditory system or was instead limited to a subset of auditory locations. Hence, we computed the percentage of locations that displayed any type of change (i.e., increase or decrease) of alpha power during the auditory stimulation when compared to baseline. To do this, we first concatenated the whole alpha power time courses for stimuli of each category. We then computed
the significance of a two-sided t-test on the obtained distributions ($p < 0.05$ Bonferroni corrected for the number of locations). We averaged across subjects the percentages of locations displaying a significant change of alpha power. This revealed that $91 \pm 4\%$ of auditory locations displayed a significant change of alpha power in response to auditory stimulation.

We then investigated how these changes varied with categories. When broken down across the 6 different sound categories, we observed that $68 \pm 15\%$ locations responded with a decrease of alpha power to speech stimuli, $58 \pm 12\%$ to music stimuli, $48 \pm 31\%$ to animal sounds, $35 \pm 25\%$ to engine sounds, $25 \pm 23\%$ to nature stimuli and $21 \pm 22\%$ to the white noise stimulus (one-sided t-test, $p < 0.05$ Bonferroni corrected for the number of locations and sound categories).

Next, we identified the locations within the auditory system that responded the most or the least to each particular auditory stimulus. To do this, we averaged the broadband gamma power of each stimulus across trials and time, which yielded one value for each auditory location, subject and stimulus. In each subject and for each stimulus, we identified those locations whose broadband gamma power was within the top and bottom 25% of these distributions (i.e., the most and least reactive auditory locations, respectively). In summary, this procedure identified the sets of locations that responded the most or the least to a particular stimulus. These reactive locations were largely different across stimuli; on average, only 30% of the most reactive locations were common across a pair of stimuli. Finally, we averaged the broadband gamma and alpha power across the most or least reactive locations and across all stimuli and human subjects. Results for human subjects are shown in Fig. 2.6. Notably, the alpha power decreased in the most reactive locations (two-sided t-test; $p < 0.001$), and was increased in the least reactive locations (two-sided t-test; $p < 0.05$), mirroring the increase versus decrease of alpha power previously observed across the auditory and motor systems. In the macaque, alpha power was higher than baseline in both the least and most reactive locations, which may be attributed to the lack of sustained attention.
to the auditory stimulus.

Finally, we determined whether these dynamics were also present on a single-stimulus basis. To do this, we determined, for each stimulus, whether the alpha power in the least reactive locations was indeed larger than the alpha power in the most reactive locations: we averaged alpha power across trials, time and the least or most reactive locations for each stimulus and subject. This resulted in two distributions (i.e., one for the most reactive locations and one for the least reactive locations), where each data point represented the alpha power for one stimulus and one subject. A paired t-test between these two distributions revealed that alpha power in the least reactive locations was indeed robustly larger than in the most reactive locations on a single-stimulus basis (paired t-test, \( p < 0.001 \)).

Figure 2.6: Within the auditory system, patterns of alpha power suppression in reactive locations and increase in non-reactive locations parallel the modulations of alpha power across systems. The bar plots show the amplitude of the responses in broadband gamma (blue) and alpha (red) power, averaged across the most or least reactive locations of the human subjects. Error bars denote the standard error. *: \( p < 0.05 \); ***: \( p < 0.001 \).
2.5 Discussion

2.5.1 Summary of results

In this study, we investigated the spatial and temporal dynamics of alpha and broadband gamma power modulation across two distinct systems (auditory and motor) in both humans and one non-human primate and within the human auditory system. Our results confirm results from previous studies that showed increased broadband gamma power and decreased alpha power in task-related areas (Crone et al., 2001; Edwards et al., 2009; Miller et al., 2007a; Potes et al., 2014). More importantly, our results demonstrated increased alpha power in task-unrelated areas, both across but also within large-scale cortical systems. In addition, the decrease in alpha power in the motor locations preceded gamma increases during the motor movement, but followed it in the auditory locations during the auditory task.

In sum, the results shown in this paper further highlight the critical role of oscillatory modulations in facilitating or inhibiting task-related processing, even within interwoven and spatially restricted networks.

2.5.2 Cortical activity, cortical excitability and the selection of functional networks

Throughout the study, we used modulations of broadband gamma power as a measure of cortical activity. In contrast to the alpha band (8–12 Hz) and the canonical gamma band (30–60 Hz, Engel et al. 2001; Fries 2005), broadband gamma has been shown not to be an oscillatory phenomenon (Miller et al., 2009b). Several studies have demonstrated that modulations in broadband gamma power strongly correlate with the asynchronous firing of neuronal populations in humans (Manning et al., 2009) and non-human primates (Ray and Maunsell, 2011; Whittingstall and Logothetis, 2009). As such, broadband gamma is a direct and robust measure of cortical activity levels that
is related to the average firing rate of populations of neurons directly underneath the recording electrode. It should be noted that the frequency range that we considered in our study (70–170 Hz) is a sufficient approximation of the wider broadband signal reported by Miller et al. (Miller, 2010; Miller et al., 2014), which is not theoretically limited by any cutoff frequencies except for the ones imposed by the noise-floor of the recording device and the sampling rate of the recording (Miller et al., 2009b).

Over the last decade and increasingly during the last few years, several ECoG studies have demonstrated that broadband gamma power specifically increases in task-related locations. Such results have been obtained during a large variety of tasks, such as auditory perception (Canolty et al., 2007; Crone et al., 2001; Edwards et al., 2009; Potes et al., 2012), motor movements (Crone et al., 1998b; Miller et al., 2007a), visual spatial attention (Gunduz et al., 2011, 2012), auditory attention (Dijkstra et al., 2015; Golumbic et al., 2013; Mesgarani and Chang, 2012) or imagined speech (Pei et al., 2011a,b). Here, we used the broadband gamma response to locate areas that responded to the auditory and motor tasks. Our set of selected locations in the humans and the macaque monkey were in line with expectations based on prior studies investigating auditory processing (Crone et al. 2001; Edwards et al. 2009, for results in humans; Hackett et al. 1998; Rauschecker et al. 1995, for results in the macaque) and motor movements (Crone et al. 1998b; Miller et al. 2007a, for results in humans; Rizzolatti et al. 1998, for results in the macaque). Moreover, the locations in the humans co-localized with the hemodynamic responses observed during fMRI studies investigating complex sound processing (Mukamel et al., 2005) and hand movement (Lotze et al., 1999). Within the auditory network, we found that the responses in broadband gamma power during the auditory task were strongly specific to the type of auditory stimulus presented. Such specificity is in agreement with the compartmentalized representation of the auditory cortex derived from single-neuron studies in non-human primates (Rauschecker
et al., 1995; Wang et al., 2005) and ECoG and fMRI studies in humans (Crone et al., 2001; Leaver and Rauschecker, 2010; Staeren et al., 2009). Taken together, these results support the view that increased broadband gamma power can accurately be used as an index of increased cortical activity and of task-related functional cortical networks.

In contrast, we found that the power in the alpha band consistently decreased over those same task-related areas and increased in task-unrelated areas, both across and within cortical systems. It is generally well accepted that alpha power decreases with increased cortical activity, as demonstrated by its negative correlation with broadband gamma power (Crone et al., 2001; Miller et al., 2009a; Potes et al., 2014) and the blood-oxygen-level dependent (BOLD) response (Mukamel et al., 2005). The mechanisms supporting these apparent interrelationships between alpha and broadband gamma power are still unclear (but see Podvalny et al. 2015; Voytek and Knight 2015; Voytek et al. 2015b). At the same time, alpha power decreases are clearly not simply a direct reflection of cortical activity since alpha power decreases can be observed in the absence of cortical activity and in preparation for an upcoming stimulus (Mazaheri et al., 2014; Romei et al., 2010). Hence, decreased oscillatory power is more likely an index of increased cortical excitability (i.e., an increased probability of cortical excitation) rather than a direct reflection of actual cortical excitation (Klimesch et al., 2007; Rajagovindan and Ding, 2011; Romei et al., 2008; Sauseng et al., 2009).

Conversely, an increase in alpha power is associated with a decrease of cortical excitability (Romei et al., 2008; Sauseng et al., 2009). Long considered a simple passive idling state (Adrian and Matthews, 1934; Pfurtscheller et al., 1996), alpha oscillations have more recently been shown to modulate cortical activity in a time-specific manner, with lower broadband gamma power (Osipova et al., 2008; Voytek et al., 2010) or lower firing rates (Haegens et al., 2011) coinciding with the peaks of the alpha wave. Moreover, studies have demonstrated that increases in alpha
power are not simply caused by a return to baseline from previously active cortical areas (Fu et al., 2001; Kelly et al., 2006). Therefore, increased alpha power has been considered to reflect an active inhibition phenomenon involved in the gating of cortical information (Jensen and Mazaheri, 2010; Klimesch et al., 2007).

Finally, the high spatial resolution of alpha power modulations that we observed within the auditory system in our study opposes the common notion that alpha oscillations are spatially widespread (Crone et al., 2001, 2006; Miller et al., 2009a; Pfurtscheller et al., 2003). Interestingly, most auditory studies investigating broadband gamma and alpha modulations employ short stimuli (Crone et al., 2001; Edwards et al., 2005, 2009), while the stimuli employed in the current study were 10 seconds long. It is possible that the stimulus specificity of alpha power modulations during sustained auditory stimulation changes over time, as has been demonstrated in previous studies (Picton et al., 1978a,b).

2.5.3 Current experimental limitations

As is the case with practically all human ECoG studies, the location of the electrode grids implanted in the five human subjects was dictated solely by clinical requirements. Thus, electrode coverage was variable across subjects, and limited to a single hemisphere. Furthermore, the clinical and cognitive state of the subjects is usually variable, both across but also within subjects over time, and can be influenced by their post-operative treatment plan and associated factors such as medication regimen or quality of sleep. At the same time, our behavioral validation indicated that all patients were able to meet the demands of the task and attend to the auditory stimuli. In addition, our results were consistent with the findings from other imaging modalities. Finally, definitively establishing the generalization of our results to macaques would require data collection in more macaque subjects.
2.6 Conclusion

The results of our study showed that alpha power is decreased in task-related areas and increased in task unrelated areas, both across but also within large-scale cortical systems. We also showed that alpha power decreases lag gamma power increases in the auditory system during the bottom-up response to a sensory stimulus, but precede gamma power increases in the motor system during the top-down preparation for a motor output. We conclude that our results further strengthen the view that oscillatory activity shapes task-related cortical networks by differentially biasing cortical excitability. Our results further suggest that this mechanism might operate not only across but also within large-scale functional networks, and may be conserved across species. Future research could determine the generality of this mechanism, establish the causal role of oscillatory activity in this process, and delineate both the origin of oscillatory activity as well as its guiding parameters.
2.7 Interim Summary

In Chapter 2, we investigated the temporal and spatial relationship between cortical excitability (as measured by the power of alpha oscillations) and cortical activity (as measured by the power of broadband changes of the ECoG spectrum) during an auditory task involving bottom-up processing and a motor task involving top-down processing. We showed that, in line with previous research, broadband gamma power accurately tracks task-related behavior and alpha power decreases in task-related areas. Importantly, alpha power suppression lagged cortical activity in the auditory cortex during the auditory task, but preceded it in motor cortex during the motor task. This suppression of alpha power in task-related areas was accompanied by a general increase in all other areas not related to the task. In addition, we showed for the first time that these differential modulations of alpha power could be observed not only across widely distributed systems (e.g., motor vs. auditory cortex), but also within such system (e.g., auditory cortex). Specifically, alpha power was suppressed in the locations within the auditory cortex that most robustly responded to particular sound stimuli. Our results provided experimental evidence for a mechanism that preferentially recruits task-related neuronal populations by increasing cortical excitability in task-related cortical areas and decreasing cortical excitability in task-unrelated areas.
3.1 Summary of Problem and Approach

In the previous study, we showed that cortical activity in task-related areas during top-down behavior was preceded by a decrease of alpha power, i.e., an increase of excitability. However, the mechanisms underlying this modulation of alpha power in preparation for the task are not yet fully elucidated. It is generally well accepted that top-down behavior results from interactions between task-related areas, i.e., sensory and motor areas, and higher-order cortical and subcortical areas important for goal-directed behavior such as the prefrontal cortex (Corbetta and Shulman, 2002; Gazzaley et al., 2007; Miller and Cohen, 2001; Rossi et al., 2009). In addition, several studies demonstrated that oscillatory activity in the alpha band in preparation for a task during top-down behavior was perturbed by disruption of prefrontal activity (Capotosto et al., 2009; Zanto et al., 2011). Therefore, here, we hypothesized that prefrontal cortex may exert
modulatory influences on cortical excitability in task-related areas during top-down behavior.

To investigate the relationship between task-related cortical excitability and prefrontal cortical activity, we recorded ECoG in human subjects while they performed a cocktail party task, i.e., a task requiring the subject to selectively attend to one particular speaker while ignoring another. The cocktail party task allowed us to investigate bottom-up (i.e., the processing of auditory information) and top-down (i.e., selective attention to one particular auditory stream) interactions between sensory and prefrontal areas. We hypothesized that prefrontal cortex receives task-relevant information from auditory cortical areas, and may use this information to exert modulatory influences on cortical excitability in those same areas.
3.2 Introduction

Humans are exceptionally skilled at segregating between simultaneous streams of speech and selectively attending to one of them (“cocktail party effect”; Cherry 1953). In auditory cortex and other peri-Sylvian areas (i.e., cortical areas surrounding the fissure that separates the temporal lobe from the frontal and parietal lobes), the attended stream of speech is strikingly over-represented in comparison with ignored simultaneous streams (Dijkstra et al., 2015; Ding and Simon, 2012; Golumbic et al., 2013; Kerlin et al., 2010; Mesgarani and Chang, 2012). Different mechanisms have been suggested to explain this neurophysiological selectivity, such as rhythmic modulation of cortical excitability in auditory cortex and higher-order cortical areas by low-frequency oscillations (Golumbic et al., 2013; Horton et al., 2013; Kerlin et al., 2010; Lakatos et al., 2013), or rapid changes of short-term plasticity in primary (Fritz et al., 2003) or non-primary auditory cortices (Ahveninen et al., 2011). However, the specific mechanism of the brain’s ability to shape the neurophysiological representation of the attended speaker is still unclear.

Several lines of evidence point to an important role of the prefrontal cortex (PFC). Indeed, the PFC plays a crucial role in several of the cognitive processes deployed during a cocktail party task, such as top-down modulation of auditory attention (Benedict et al., 1998; Bidet-Caulet et al., 2015; Chao and Knight, 1997), abstract rules switching (Asaad et al., 2000; Johnston et al., 2007; Milner, 1963; Muhammad et al., 2006) and encoding (Badre and D’Esposito, 2007; Badre et al., 2009; Christoff et al., 2009; Wallis et al., 2001), representation of task-relevant stimuli (Rainer et al., 1998), and working memory (D’Esposito et al., 2000; Funahashi et al., 1989, 1993; Jonides et al., 1993; McCarthy et al., 1996; Miller et al., 1996). Unsurprisingly, the PFC is usually active during auditory selective attention tasks (Bushara et al., 1999; Golumbic et al., 2013; Hashimoto et al., 2000; Jäncke and Shah, 2002; Lipschutz et al., 2002; Thomsen et al., 2004). In addition,
recent studies demonstrated how the PFC can modulate activity in task-relevant areas using phase-amplitude coupling (Voytek et al., 2015a) or phase-coherence in the alpha band (≈8–12 Hz; Buschman and Miller 2007; Fritz et al. 2010; Zanto et al. 2011). While this abundance of evidence points to an important role of the PFC in a cocktail party task, little is known regarding the potential implementation of its exact mode of action.

In this study, we hypothesized that interplays between bottom-up sensory representations in early auditory areas and top-down influences by the PFC might subserve the cocktail party effect. Specifically, we hypothesized that feedforward interactions between the auditory and prefrontal cortices might encode task-relevant information, while the PFC may provide feedback by modulating cortical excitability in auditory areas.

To test these hypotheses, we applied connectivity analyses to electrocorticographic (ECoG) signals recorded from nine human subjects during a cocktail party task. Taking advantage of the excellent spatial and temporal resolutions of the ECoG technique, we demonstrated that the PFC receives information specific to the attended auditory stream from auditory and peri-Sylvian cortical areas. Our results also suggest that the PFC modulates the power of ECoG activity in the alpha band in auditory areas, thereby putatively selectively controlling cortical excitability (Haegens et al., 2011; Jensen and Mazaheri, 2010; Klimesch et al., 2007) and setting a favorable cortical landscape for optimal processing of the attended auditory stream.

### 3.3 Methods

#### 3.3.1 Subjects

Nine patients (4 men: A, D, E, F; 5 women: B, C, G, H, I) with intractable epilepsy participated in this study (Albany Medical Center, Albany, New York). They were implanted with subdural
electrode grids to localize epileptogenic foci as part of their treatment. All patients had extensive coverage over the frontal and temporal lobes. The number and placement of the grids is depicted in Fig. 3.2. A Wada test was used preoperatively to determine language lateralization (Wada and Rasmussen 1960). All patients gave informed consent prior to the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command.

3.3.2 Data collection

We recorded ECoG signals from the nine patients at the bedside using BCI2000 software (Schalk et al., 2004b; Schalk and Mellinger, 2010a) and eight 16-channel g.USBamp biosignal acquisition devices (g.tec, Graz, Austria). Implanted subdural grids were approved for human use (Ad-Tech Medical Corp., Racine, WI; and PMT Corp., Chanhassen, MN) and consisted of platinum-iridium electrodes (4 mm diameter; 2.3 mm exposed) that were embedded in silicone and spaced 6–10 mm from each other. The acquired signals were amplified and digitized using a sampling frequency of 1200 Hz. Reference and ground were either subdural electrodes distant from the epileptogenic foci or skull electrodes.

3.3.3 Anatomical mapping

We created 3D cortical brain models for each patient using preoperative magnetic resonance imagining (MRI) scans, Curry software (Neuroscan Inc., El Paso, TX) or Freesurfer (http://surfer.nmr.mgh.harvard.edu). We determined the electrodes’ stereotactic coordinates by co-registering the MRI scans with post-operative computer tomography (CT) images using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) and custom MATLAB scripts (The MathWorks Inc., Natick, MA). Each electrode was assigned to its respective Brodmann area using the Ta-
lairach Daemon (Lancaster et al., 1997, 2000) and projected onto a three-dimensional brain model using custom NeuralAct software (Kubanek and Schalk, 2014).

3.3.4 Task and stimuli

We developed a simulated cocktail party situation during which the subject had to attend to one of two simultaneous streams of speech (Fig. 3.1). The two streams consisted of the original inauguration addresses from John F. Kennedy and Barack Obama broken into 10 energy-matched segments of 15–25 seconds. The sound intensity of the auditory stimuli for the two speakers were not correlated with each other (Spearman’s coefficient = -0.02, p > 0.1). The streams were mixed into a binaural presentation through in-ear monitoring earphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from environmental noise) such that one speaker was represented with a 1:5 ratio in one ear compared to the other speaker and a 5:1 ratio in the other ear. Each trial consisted of a cueing period (4 seconds), followed by the stimulus (15–25 seconds) and the inter-stimulus period (5 seconds). The cue instructed the subject which speaker and ear to attend using a 2–second long auditory beep in the corresponding ear and a visual cue that indicated the identity of the speaker and his aural location (e.g., ‘JFK in RIGHT ear’) on a screen located in front of the subject. The visual cue remained on the screen throughout the trial. Each of the 10 segments was repeated four times so that each of the four combinations of aural location and identity of the attended speaker was produced once. The combinations were not randomized, i.e., a specific stream of JFK’s speech was always presented with the same stream of Obama’s speech. The 40 resulting trials were divided into 5 ~ 2.5 min duration blocks of 8 trials each.
Figure 3.1: **Experimental setup.** We recorded ECoG activity while subjects performed a task simulating a cocktail party. The subjects were asked to attend to one of two simultaneous streams of speech. The two streams consisted of the original inauguration addresses from John F. Kennedy and Barack Obama mixed into a binaural presentation. Adapted from 'Identifying the Attended Speaker Using Electrocorticographic (ECoG) Signals,' by K. V. Dijkstra et al., 2015, *Brain-Computer Interfaces*, 2.4, p. 164. Copyright 2015 by Taylor and Francis.

### 3.3.5 Processing of electrocorticographic and auditory signals

After visual inspection, we excluded from further analysis any channel contaminated with 60 Hz noise or interictal activity. This left a total of 41–126 channels per subject. To investigate modulations of cortical excitability and activity, we extracted the amplitude envelope in the alpha and broadband gamma bands, respectively. To do so, we first removed drift in the ECoG signals by subjecting them to a high-pass filter at 0.5 Hz. We then re-referenced the results to a common average reference (CAR) montage computed independently for every group of 16 channels (Liu et al., 2015). We then band-pass filtered the signals between 8–12 Hz (alpha range) and 70–170 Hz (broadband gamma range) using the zero-phase lag filtfilt Matlab command (Mathworks, Natick, MA) and Butterworth filters of order 6 for the two bands. We obtained the amplitude envelope in these two bands by computing the absolute value of the analytical signals. Finally,
we low-pass filtered the signals with a Butterworth filter at 4 Hz and down-sampled them at 120 Hz.

Similarly, we extracted the sound intensity of the speech stimuli by first submitting them to a Butterworth band-pass filter between 80–6000 Hz. We then computed the absolute value of their Hilbert transform before applying a low-pass filter at 4 Hz and down-sampling at 120 Hz.

### 3.3.6 Selection of responsive locations

Previous literature has shown that different cortical regions respond differently to the attended and unattended speakers presented during this task. Specifically, primary auditory regions tend to respond similarly to both attended and unattended speakers (i.e., *non-selective* locations) while surrounding locations on the posterior superior temporal gyrus (STG) predominantly track the attended stream (i.e., *selective* locations; Dijkstra et al. 2015; Golumbic et al. 2013). To better understand the interactions between prefrontal cortex and auditory areas during the cocktail party task, we thus differentiated between those neuronal populations that responded selectively to the attended speaker and the ones that responded non-selectively to both attended and unattended speakers. To do that, we submitted cortical activity (as measured by the amplitude envelope in the broadband gamma range) at each location to an inter-trial coherence analysis (ITC; similar to Golumbic et al. 2013). ITC measures the consistency of cortical activity across trials at each location by computing the Spearman’s correlation between the broadband gamma time course of pairs of trials during which the same two auditory segments were presented, but during which either the same or a different speaker was attended.

Specifically, we first identified task-related locations, i.e., locations that responded to any auditory stimulus. We defined task-related locations as those that responded similarly (i.e., had high ITC) to two identical auditory stimuli during which the same speaker was attended. We
then defined non-selective and selective auditory locations as those task-related locations that were on the temporal lobe and that respectively responded similarly (i.e., had high ITC) or differently (i.e., had low ITC) to a particular pair of trials, depending on whether the attended speaker was similar or not between the two trials.

Statistical significance of the computed ITC values was assessed using a permutation test. For each of the permutation, we computed the ITC value corresponding to broadband gamma time courses that were reversed and circularly shifted by a random value. We repeated this step 5000 times, generating random distributions of ITC values. We considered an ITC value to be significant at the 95th percentile of the corresponding distribution after Bonferroni-correcting for the number of locations on the temporal lobe in each subject. Finally, the selectivity of a location was defined as the z-score obtained after normalizing the difference of its ITC values against the mean and standard deviation of the corresponding random distribution.

Prefrontal locations of interest were selected based on their Brodmann areas extracted from the Talairach Daemon (Lancaster et al., 1997, 2000). Regions of interest included ventrolateral prefrontal cortex (areas 44, 45 and 47), dorsolateral prefrontal cortex (areas 8, 9 and 46) and orbitofrontal cortex (areas 10 and 11).

3.3.7 Correlation analyses

To investigate the relationship between prefrontal and auditory cortical activity, we computed Spearman’s correlation coefficient between the broadband gamma amplitude time course of each prefrontal and selected auditory location. To investigate the relationship between cortical prefrontal activity and auditory excitability while accounting for potential effects of auditory broadband gamma amplitude (de Pesters et al., 2016; Potes et al., 2014), we computed partial Spearman’s correlation coefficient between the broadband gamma amplitude time course of each
prefrontal location and the alpha amplitude time course of each selected auditory location controlling for auditory broadband gamma amplitude at the same location.

Specifically, to proceed, we first temporally aligned the time courses of each pair of locations in order to account for potential time lags between the cortical activity or excitability of different locations. For each trial and pair of locations, we shifted the prefrontal and auditory broadband gamma or alpha time courses by the delay (between 0 and 500 ms) that maximized or minimized, respectively, their cross-correlation. Next, for each pair of locations, we concatenated all trials and computed the resulting Spearman’s or partial Spearman’s correlation between prefrontal broadband gamma amplitude and auditory broadband gamma or alpha amplitude, respectively.

Statistical significance of the computed correlation coefficients was assessed using a permutation test comparable to the one described in Section 3.3.6 with the difference that we performed Bonferroni correction for the total number of possible connections (i.e., the number of auditory locations times the number of prefrontal locations). The strength of each connection was defined as the z-score obtained after normalizing the observed correlation coefficient by the mean and standard deviation of its corresponding random distribution.

Finally, to investigate the relationship between auditory cortical activity and the sound intensity of the presented auditory stimulus, we computed Spearman’s correlation coefficient between the broadband gamma amplitude time course of each selected auditory location and the sound intensity of the attended or unattended speaker. Similar to above, we first temporally aligned the time courses of broadband gamma amplitude and sound intensity each pair of locations in order to account for potential time lags between the cortical activity or excitability of different locations. For each trial and pair of locations, we shifted the prefrontal and auditory broadband gamma or alpha time courses by the delay (between 0 and 500 ms) that maximized or minimized, respectively, their cross-correlation. Next, for each pair of locations, we concatenated all trials and
computed the resulting Spearman’s or partial Spearman’s correlation between prefrontal broadband gamma amplitude and auditory broadband gamma or alpha amplitude, respectively.

3.3.8 Temporal analyses

For each significant connection, we investigated the temporal relationship between time courses of prefrontal broadband gamma amplitude and auditory broadband gamma or alpha amplitude by determining which one preceded the other. To do this, we submitted the delays distributions computed in Section 3.3.7 to a 1-sided Wilcoxon signed-rank test ($p < 0.05$).

3.3.9 Specificity to the attended speaker

To determine whether the connectivity between the prefrontal and auditory cortices was more strongly encoding information related to the attended speaker compared to the unattended speaker, we compared the strength of connections for congruent and incongruent attentional modalities. Specifically, we computed the correlation between prefrontal activity while the subject attended to one speaker and auditory activity for trials when the subject attended to either the same (congruent condition) or the other (incongruent condition) speaker. To account for the fact that prefrontal and auditory time courses in the incongruent condition could not be derived from the same trial, we only correlated time courses from different trials in the congruent conditions. Hence, our analyses were not biased towards the congruent condition.

To proceed, we performed correlation analyses comparable to the ones in Section 3.3.7, which established the significance of Spearman’s correlation between the temporally aligned time courses of cortical activity at each pair of locations. This resulted in one z-score for each of the congruent and incongruent conditions values and for each of the pairs of locations resulting from the analyses in Section 3.3.7.
3.4 Results

3.4.1 Spatial distribution of selective and non-selective auditory locations

Fig. 3.2 depicts the locations that responded selectively to the attended speaker (i.e., selective locations; blue circles) and the locations that responded non-selectively to both attended and unattended speakers (i.e., non-selective locations; red circles) for each subject. We identified an average of 0–15 and 1–11 selective and non-selective locations per subject, respectively. The spatial distribution of selective and non-selective locations over the superior temporal gyrus, superior temporal sulcus and supramarginal gyrus was consistent with the literature on cortical processing of speech (Binder et al., 2000; Canolty et al., 2007; Price et al., 1992). No selective locations were found in subjects F–I. Possible reasons include limitations in coverage, the conservative nature of our selection algorithm or differences in behavioral performance. Thus, we removed subjects F–I from further analyses.
Figure 3.2: **Cortical locations of interest.** For each of the subjects (A–I), colored circles represent prefrontal locations (green circles), auditory locations that responded to both attended and unattended speakers (red circles) and auditory locations that responded selectively to the attended speaker (blue circles) during the cocktail party task. Small black dots denote all remaining locations.

### 3.4.2 Differential auditory cortical processing of the attended and unattended auditory streams

To characterize the functional differences between selective and non-selective locations, we investigated the relationship between auditory cortical responses at selective or non-selective locations and the attended or unattended auditory stimuli. To do that, we computed the correlation between the sound intensity of each speaker and cortical activity at each selective or non-selective auditory location. Based on previous literature, we expected activity at the selective locations,
but not at the non-selective ones, to be better correlated with the sound intensity of the attended
speaker than with the intensity of the unattended one (Dijkstra et al., 2015; Kubanek et al., 2013;
Mesgarani and Chang, 2012).

As expected, broadband gamma activity at selective locations was better correlated with the
sound intensity of the attended speaker than the sound intensity of the unattended one \( (p < 0.05; \)
2-sided Wilcoxon rank-sum test). To verify that our results were not due to a single subject effect,
we repeated the analysis using subsets of subjects with a single subject removed. Results were
maintained for all subsets of subjects. In contrast, correlation coefficients between broadband
gamma activity at non-selective locations and sound intensity of attended or unattended speakers
were not statistically different \( (p > 0.05 \) for all subsets of subjects; 2-sided Wilcoxon rank-sum
test). These results confirmed that selective (but not non-selective) locations were selectively
tracking the attended speaker.

### 3.4.3 Feedforward connectivity between prefrontal and auditory cortices

We then investigated the relationship between prefrontal and auditory cortical activity at the
selective and non-selective locations. Specifically, we hypothesized that attended auditory infor-
mation would be conveyed from selective auditory locations to prefrontal cortex. To test this
hypothesis, we first identified those pairs of auditory and prefrontal locations for which cortical
activity in the broadband gamma range was correlated. To do that, we computed Spearman’s
correlation between broadband gamma amplitude time courses of each possible pair of audi-
tory and prefrontal locations, and assessed the significance of the correlation coefficients using
permutation tests and Bonferroni-correction for the total number of possible pairs (see Section
3.3.7 for the details of the analysis). Pairs of locations for which broadband gamma activity was
significantly correlated are depicted for each subject in the top row of Fig. 3.3.
Figure 3.3: Connectivity between prefrontal and auditory areas. **Top row:** For each of the subjects displaying both selective and non-selective types of auditory locations (A–E), significant correlation between broadband gamma activity at prefrontal and auditory locations is depicted by an arrow between the two locations. **Bottom row:** Arrows depict significant correlation between the broadband gamma amplitude at a prefrontal location and the alpha activity at an auditory location. Black and yellow arrows denote connections for which auditory activity preceded or lagged prefrontal activity, respectively. Legend for the colored circles is similar to the one in Fig. 3.2.

We then determined whether cortical activity in prefrontal cortex preceded or followed cortical activity in auditory cortex. According to our hypothesis, prefrontal broadband gamma activity should lag auditory broadband gamma activity. To verify this, we computed the delay that maximized the Spearman’s cross-correlation between the broadband gamma amplitude time courses of each pair of locations. Quantitative results are displayed in Fig. 3.4. Indeed, we found that connections for which auditory broadband gamma amplitude preceded the frontal outnumbered and were stronger than connections with opposite directivity (2-sided Wilcoxon signed rank test, \( p < 0.05 \) for selective and non-selective locations). There was no significant difference between the number or strength of connections involving selective or non-selective locations (2-sided Wilcoxon signed rank test, \( p > 0.05 \) for both tests).
Figure 3.4: **Correlation between prefrontal and auditory broadband gamma activity.** The bar plots on the left display the number of pairs of locations for which prefrontal broadband gamma activity was significantly correlated with and lagged (blue) or preceded (red) auditory broadband gamma activity. Numbers were normalized by the number of selective and non-selective locations in each subject and averaged across subjects. The bar plots on the right display the strength (i.e., z-score) of these interactions, averaged across interactions and subjects. *: p< 0.05; Wilcoxon signed rank test.

Finally, we determined whether the connectivity between the auditory and prefrontal cortices was more strongly encoding information related to the attended speaker compared to the unattended one. We hypothesized that selective auditory cortical areas would primarily convey auditory information selective to the attended speaker to the prefrontal cortex. To verify this hypothesis, we computed the correlation between prefrontal activity when one speaker was attended and auditory activity when the same pair of stimuli was presented but when either the same or the other speaker was attended. We hypothesized that if information shared by auditory and prefrontal locations were to be nonspecific to the attended speaker, correlation coefficients when the same or different speaker was attended should not be statistically different. However, if this information were to be specific, correlation coefficients when the same speaker was attended should be larger than when different speakers were attended. We found the latter to be the case for selective auditory locations only, hence confirming that feedforward connectivity between
specific auditory cortical areas and the prefrontal cortex was specific to the attended speaker ($p < 0.05$ for selective locations, 2-sided Wilcoxon signed rank test; $p > 0.05$ for non-selective locations, 2-sided Wilcoxon signed rank test).

### 3.4.4 Feedback connectivity between prefrontal and auditory cortices

We then investigated whether prefrontal cortical activity may modulate auditory excitability, as measured by amplitude modulations in the alpha band (8–12 Hz; Haegens et al. 2011; Jensen and Mazaheri 2010; Klimesch et al. 2007). Specifically, we hypothesized that prefrontal cortical activity should be negatively correlated with and should precede modulations of auditory excitability. To test this hypothesis, we first determined the pairs of prefrontal and auditory locations for which respective broadband gamma and alpha amplitude were significantly negatively correlated. Qualitative results are depicted for each subject in the bottom row of Fig. 3.3.

To verify that prefrontal activity was indeed preceding auditory alpha amplitude modulations, consistent with a modulation of excitability in auditory cortex by prefrontal cortex, we compared the number and strength of connections for which prefrontal broadband gamma amplitude preceded or lagged auditory alpha amplitude. Quantitative results are displayed in Fig. 3.5. We found that pairs of locations for which prefrontal broadband gamma amplitude preceded auditory alpha amplitude outnumbered ($p < 0.05$ for selective and non-selective ones, 2-sided Wilcoxon signed rank test) and were stronger ($p < 0.05$ for selective and non-selective ones, 2-sided Wilcoxon signed rank test) than pairs of locations with the opposite directivity. There was no significant difference between the number or strength of connections involving selective or non-selective locations (2-sided Wilcoxon signed rank test, $p > 0.05$ for both tests).
Figure 3.5: Correlation between prefrontal broadband gamma activity and auditory alpha activity. The bar plots on the left display the number of pairs of locations for which prefrontal broadband gamma activity was significantly correlated with and lagged (blue) or preceded (red) auditory alpha activity. Numbers were normalized by the number of selective and non-selective locations in each subject and averaged across subjects. The bar plots on the right display the strength (i.e., z-score) of these interactions, averaged across interactions and subjects. *: p< 0.05; Wilcoxon signed rank test.

Finally, we investigated whether the feedforward and feedback networks between prefrontal and auditory cortices involved the same pairs of locations. Out of the 83 pairs of locations displaying either feedforward or feedback connectivity between prefrontal and auditory broadband gamma activity or between prefrontal broadband gamma and auditory alpha activity, only one of them supported both feedforward and feedback connectivity, suggesting the presence of different networks underlying each type of connectivity.

3.5 Discussion

The precise neuronal mechanisms underlying the ability to attend to one out of several voices are not yet completely understood. In this study, we showed that feedforward connections between specific regions of the auditory cortex and prefrontal cortex encoded information specific to the attended speaker during a cocktail party task. In addition, we found PFC cortical activity to be
correlated with and preceding auditory cortical excitability as measured by modulations of amplitude in the alpha band (8–12 Hz). These results hinted at an important top-down mechanism relying on the modulation of auditory cortical excitability by the PFC during the cocktail party task.

3.5.1 Feedforward connectivity between prefrontal and auditory cortices

The feedforward connectivity observed between the auditory and prefrontal cortices is supported by the extensive anatomical connectivity existing between those two areas (Croxson et al., 2005; Glasser and Rilling, 2008; Pandya et al., 1969; Petrides and Pandya, 1988; Romanski et al., 1999; Saur et al., 2008). Specifically, auditory regions processing speech, including the primary auditory cortex and superior temporal gyrus, are known to convey specific auditory information to the PFC (Plakke and Romanski, 2014). Consistent with these anatomical findings, our analyses determined that the PFC was targeted by connections from the superior temporal gyrus in addition to some more posterior peri-Sylvian areas. Interestingly, those connections arose from locations that were selectively tracking the attended speaker as well as locations that were non-selectively tracking both speakers. This suggests that the encoding of attended information in prefrontal cortex benefits from the extraction of both low-level (e.g., pitch, sound intensity), as well as more complex (e.g., lexical and semantic structures, prosody) features related to the attended speaker, in agreement with the cortical processing chain of speech (Belin et al., 2004; Rauschecker and Scott, 2009; Warren et al., 2006).

Functional connectivity between auditory and prefrontal cortices during the cocktail party task is also supported by functional magnetic resonance imaging (fMRI) studies reporting increased correlation of blood-oxygen-level dependent (BOLD) activity across frontal and task-related sensory areas during attention tasks (Büchel and Friston, 1997; Sakai and Passingham,
These findings are consistent with the view that synchrony in the temporal and spectral domains can subserve communication between distant cortical areas (Buschman and Miller, 2007; Fries, 2005; Gregoriou et al., 2009; Saalmann et al., 2012).

### 3.5.2 Role of the prefrontal cortex in top-down modulation of cortical excitability

The well-established role of the PFC in top-down attention (Miller and Cohen, 2001) was further supported in our study by the correlation between its activity and the modulations of alpha envelope amplitude in auditory cortex. Spatiotemporal variations in the alpha band have been strongly associated with cortical excitability and attention (Frey et al., 2014; Romei et al., 2008; Sauseng et al., 2009) and have been observed during PFC-driven top-down modulation (Buschman and Miller, 2007; Fritz et al., 2010; Zanto et al., 2011). To the best of our knowledge, it is the first time that their relationship with the PFC is reported in the context of the cocktail party task in humans. It is likely that their modulation by the PFC results in the bias of auditory cortical areas towards the relevant stimulus (Knight et al., 1989; Miller and Cohen, 2001; Morishima et al., 2009). Indeed, modulations in the alpha band can actively shape cortical activity, as they have been shown to modulate broadband gamma power (Osipova et al., 2008; Voytek et al., 2010) and neuronal firing rates (Haegens et al., 2011). For these reasons, they have been considered central to sensory gating (Jensen and Mazaheri, 2010; Klimesch et al., 2007; Schalk, 2015) and predictive coding theories (Bauer et al., 2014; Van Kerkoerle et al., 2014). In addition, recent intracortical studies have shown that modulations of alpha power are spatially more localized than was previously thought (de Pesters et al., 2016; Harvey et al., 2013), and could thus subserve the precise modulations of excitability involved in the cortical selection of the attended speaker during the cocktail party task. It remains to be shown whether the modulatory effects exerted by the PFC are direct or rather mediated by a third actor (e.g., subcortical structures such as the the
thalamus (Saalmann et al., 2012; Wimmer et al., 2015) or basal forebrain (Golmayo et al., 2003)).
3.6 Interim Summary

In Chapter 3, we investigated the role of a higher-level cortical area, the prefrontal cortex, in the modulation of alpha oscillations during the cocktail party task that requires selective top-down auditory attention. We found that feedforward connectivity between auditory and prefrontal cortices encoded selective information about the attended stimulus. In addition, prefrontal cortex activity was negatively correlated and was preceding cortical excitability in auditory cortex. Our results shed new light on the cortical dynamics underlying the interactions between bottom-up sensory-driven and top-down attentional modulations at play during the cocktail party task, and add new evidence to the relation between higher-order cortical areas such as prefrontal cortex and modulations of cortical excitability in task-related areas during top-down behavior.
4.1 Summary of Problem and Approach

In the two previous studies, we utilized the power of broadband gamma in ECoG recordings to robustly track the spatial and temporal modulations of cortical activity in neuronal populations beneath each recording electrode. In Chapters 4 and 5, we will investigate how broadband gamma activity can be used in the clinical context to improve current techniques to identify healthy functional cortical regions prior to resective surgery. More specifically, in Chapter 4, we will study the case of a patient suffering from seizures caused by a tumor in very close proximity to cortical regions involved in speech production (also called Broca’s area or expressive language cortex). In preparation of tumor resection, the patient underwent multiple functional language mapping procedures. In this case report, we will investigate the utility and practicality of intraoperative functional mapping of expressive language cortex using high-resolution...
ECoG. Furthermore, we will examine the relationship of results obtained with intraoperative high-resolution ECoG, extraoperative ECoG utilizing a conventional subdural grid, extraoperative electrical cortical stimulation (ECS) mapping, and functional magnetic resonance imaging (fMRI).
4.2 Introduction

Precise localization of eloquent cortex facilitates optimal surgical outcomes in patients with tumors, epileptogenic foci, or vascular abnormalities. Operative planning balances removal of pathologic tissue that portends specific symptomatic morbidity with preservation of the eloquent cortex necessary for maintaining an acceptable quality of life. Historically, functional mapping has been conducted primarily with electrical cortical stimulation (ECS) (Ojemann, 1991; Penfield and Boldrey, 1937), but also with functional magnetic resonance imaging (fMRI; Chakraborty and McEvoy 2008), extraoperative (chronic) electrocorticography (ECoG; Crone et al. 1998b; Leuthardt et al. 2007; Miller et al. 2007a), electroencephalography (EEG; Graimann et al. 2002; Lachaux et al. 2003), magnetoencephalography (MEG; Ganslandt et al. 1999), or positron emission tomography (PET; Bittar et al. 1999). Each of these techniques carries inherent limitations that impede widespread application in the approximately 111,000 patients that undergo brain surgery for removal of a brain tumor or epileptogenic focus each year (AANS, 2012).

Electrical cortical stimulation currently stands as the ‘gold standard’ for functional mapping. The technique is procedurally simple and has a relatively low cost. Its most notable limitation remains the extensive amount of time required to conduct the procedure. This issue becomes particularly apparent when ECS is performed under the time constraints of an awake craniotomy in the operating room. In addition, active stimulation of the brain with ECS can provoke after-discharges and seizures. Seizures can increase patient morbidity as well as the duration of mapping.

Functional MRI is another mapping technique that has garnered avid attention recently. Its primary advantage is its noninvasive nature and excellent spatial resolution. However, it only indirectly evaluates neuronal activity by measuring task-related blood oxygenation level depen-
dent (BOLD) changes (Holodny et al., 1999; Schreiber et al., 2000). Highly vascularized malignant tumors can alter cerebrovascular hemodynamics and BOLD patterns; hence, they may not accurately reflect eloquent cortical function (Kekhia et al., 2011; Tharin and Golby, 2007). Furthermore, clinical application of fMRI for real-time mapping is hindered by the extensive time and expertise required for the requisite post hoc analyses.

Passive functional mapping using ECoG is currently undergoing significant investigation. Recording the changes in cortical activity in response to specific language, motor, or cognitive tasks does not require application of electrical impulses to induce an effect, thereby eliminating the risk of seizures. Electrocorticography changes in the broadband gamma range (>60 Hz) are of particular relevance in this context of functional mapping (Crone et al., 1998b; Miller et al., 2014). Recent advances in neural signal acquisition (Schalk et al., 2004b; Wilson et al., 2010) and processing (Schalk et al., 2008) have provided the methodological basis for mapping of cortical activity in real time (Miller et al., 2007b). Despite these advances, ECoG-based mapping predominantly occurs in the epilepsy monitoring unit, remaining as an extraoperative endeavor. With few exceptions (Roland et al., 2010; Wu et al., 2010), the practicality and potential value of ECoG-based mapping in the operating room remains largely unexplored, particularly with investigation using high-resolution recordings. In this case report, we test the feasibility of intraoperative mapping using real-time ECoG.

In summary, accurate and practical functional mapping in the operating room still faces challenges in contemporary practice. Mapping based on ECoG promises rapidity, a high spatial specificity, and no increased morbidity. Combining data obtained from ECS, ECoG, and fMRI can provide complementary information that may be useful for surgical planning of complex cases. In the present case, we mapped expressive language function with ECoG using a high-density grid during an awake craniotomy. We confirmed the location of frontal language ar-
eas extraoperatively using fMRI, standard ECS mapping, and ECoG mapping. We integrated and visualized the results, producing highly detailed functional maps. These composite results suggested qualitative concordance of eloquent expressive language cortex across the different mapping modalities.

4.3 Case Report

4.3.1 Initial presentation

The patient was a 33-year-old male who presented after a motor vehicle accident while experiencing a first time seizure. The patient had a computerized tomography (CT) scan as part of his initial evaluation that suggested a hypodensity in the left frontal lobe. Magnetic resonance (MR) imaging revealed a nonenhancing left frontal mass (Fig. 4.1, left), and MR spectroscopy characteristics supported a low-to-medium grade tumor. Given the anatomic location of the tumor’s proximity to presumed Broca’s area, the patient underwent fMRI and diffusion tensor imaging (DTI). The fMRI confirmed the close relationship of the tumor to Broca’s area (within 3–5 mm) with verb generation and object naming tasks (p < 0.05, family-wise error correction; Fig. 4.1, right).

The patient did not have any further seizures after the initiation of levetiracetam, i.e., an anticonvulsant, and he remained neurologically intact without any focal deficits or aphasia. To comprehensively evaluate expressive language cortex for an optimal postoperative outcome, the patient elected to pursue a two-staged brain mapping procedure with the use of subdural grids and ECS. Prior to surgery, the patient had neuropsychological testing for baseline evaluation using the Wechsler Adult Intelligence Scale WAIS-IV (Wechsler, 2014). The patient gave informed consent for a protocol that was reviewed and approved by the institutional review board of
Albany Medical College as well as the US Army Medical Research and Materiel Command.

![Preoperative axial T2-weighted FLAIR MR image on 1.5 T magnet demonstrating a tumor in the anterior left frontal lobe. Preoperative fMRI on 3 T magnet indicating proximity of tumor to Broca’s area, within 3–5 mm on postprocessed images. Red and yellow areas depict increased BOLD activity.](image)

**Figure 4.1:**  **(Left)** Preoperative axial T2-weighted FLAIR MR image on 1.5 T magnet demonstrating a tumor in the anterior left frontal lobe. **(Right)** Preoperative fMRI on 3 T magnet indicating proximity of tumor to Broca’s area, within 3–5 mm on postprocessed images. Red and yellow areas depict increased BOLD activity.

### 4.3.2 Stage 1 operation

The patient underwent implantation of an $8 \times 8$ cm silicon subdural grid embedded with 64 platinum iridium electrodes of 4 mm diameter (2.3 mm exposed) and interelectrode distance of 1 cm [PMT, Chanhassen, MN] (Fig. 4.2, panels A and B). Contacts 1, 2, and 9 were removed for better contour along the cortical surface. Contact 57 was located most anteriorly, contact 64 most superiorly, and contact 8 most posteriorly (Fig. 4.3). A four-contact electrode strip was placed on the skull to provide a ground for the clinical monitoring system. The patient tolerated the first stage well and was connected to a Nihon Kohden Neurofax video-EEG monitoring system [Tokyo, Japan] that continuously recorded ECoG signals as well as accompanying clinical behavior. To ensure integrity of clinical data collection, passive splitter connectors simultaneously...
provided ECoG signals to eight optically isolated and synchronized 16-channel g.USBamp amplifier/digitizer units (g.tec, Graz, Austria) with signal sampling at 1200 Hz. Clinical review of ECoG signals identified frequent left frontal spikes and spike and wave discharges at contact 23.

Figure 4.2:  (A) Intraoperative photograph of left frontal lobe exposure with standard 64-contact subdural grid. (B) Example of subdural grid used during the case, courtesy of PMT Corporation. (C) Intraoperative photograph of high-density grid placed over eloquent cortex previously identified by the standard grid. (D) High-density 64-contact silicon grid used during the case.

4.3.3 Clinical mapping

4.3.3.1 Extraoperative ECoG mapping using a standard subdural grid

On postoperative day 2, the patient underwent extraoperative functional cortical mapping in the epilepsy monitoring unit (EMU) with ECoG and ECS procedures. For ECoG mapping, the broadband gamma signal at each contact location was measured and compared between rest and
task epochs to establish the statistical difference across these tasks (see Brunner et al. 2009 for detailed methodology). The patient first rested quietly for six minutes to establish a model of baseline ECoG activity. The patient then performed several repetitive motor and language tasks as instructed by visual cues: 1) solve Rubik’s cube, 2) shrug shoulders, 3) stick out tongue, 4) purse lips, 5) listen to a narrative, 6) generate verbs, and 7) imagine generating verbs. This ECoG paradigm identified electrode contacts 11 and 12 (Fig. 4.3) as expressive language nodes within a few minutes.

![Figure 4.3: Numbers represent electrode contacts of the standard subdural grid coverage. The tumor margins are displayed as light blue. Electrical stimulation of contacts 11 and 12 (dark blue) caused speech arrest in Broca’s area. Electrical stimulation of contacts 23 and 41 (red) caused an electrographic seizure; contacts 1, 2 and 9 (light gray) were removed for better contour along the cortical surface.](image)

4.3.3.2 Extraoperative ECS mapping

For the ECS procedure, we used a digital Grass S12X stimulator [Grass Technologies, Warwick, RI] to stimulate pairs of electrodes using a pulse duration of 0.3 ms, variable frequencies between 20 and 50 Hz, current ranging from 1 to 15 mA, and train durations of 5 s. Current at each pair of electrodes was increased until after-discharges or a functional response was elicited, or the max-
imum amount of current was reached at 15 mA. Stimulation of contacts 11 and 12 with 10 mA at 20 Hz rendered complete speech arrest. These nodes were confirmed on four separate occasions throughout the procedure. Oral motor function was also identified. An electrographic seizure was elicited with stimulation of contacts 23 and 41 during mapping; the patient was treated with 2 mg IV lorazepam, 1000 mg IV levetiracetam, and 500 mg fosphenytoin. Further mapping was delayed for approximately 90 min due to the stimulus-induced seizure and subsequent postictal period.

4.3.4 Stage 2 operation and intraoperative ECoG mapping using a high-density subdural grid

Five days after the initial subdural grid implantation, the patient returned to the operating room for the second stage. Once the previous craniotomy flap was reopened and the cortical surface was exposed with good hemostasis, the standard subdural grid was replaced with a high-density 64-contact silicon grid (PMT Corp., Chanhassen, MN), measuring 2.5 × 2.5 cm embedded with platinum iridium electrodes of 2 mm diameter (1 mm exposed) and with an interelectrode distance of 3 mm (Fig. 4.2, panels C and D). To further refine the boundary of expressive language function, this high-density grid covered only the language cortex previously identified by extraoperative ECoG and ECS mapping. The patient was reversed from anesthesia for awake passive mapping. Within minutes, intraoperative ECoG mapping using verb generation and word repetition identified the most significant ECoG changes at locations corresponding to contacts 11 and 12 of the original standard subdural grid. These locations were outlined for preservation. The patient tolerated the procedure very well and was induced back under anesthesia for the remainder of the surgery.
4.3.5 Postoperative course

The patient experienced an excellent recovery and had very mild issues of transient confusion. He had adjuvant chemoradiation therapy. Postoperative neuropsychological testing (at 1 year) demonstrated a 28% decline in verbal fluency and a slight decrement in recent memory/new learning (although still within high average range). Surveillance imaging over 28 months has yet to demonstrate recurrence.

4.3.6 Coregistration of mapping techniques

The main results presented in this case report are the mapping results from fMRI, ECS, and extra- and intraoperative ECoG. They are summarized in Fig. 4.4.

We created a three-dimensional patient-specific cortical surface brain model by submitting the preoperative high resolution MRI scans to Freesurfer (http://surfer.nmr.mgh.harvard.edu). We identified the stereotactic coordinates of the standard subdural grid using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) and custom MATLAB scripts (The MathWorks Inc., Natick, MA), which coregistered the MRI scans with the postoperative CT scans. The high-density subdural grid contacts were coregistered with those of the standard subdural grid using scalp fiducial markers, an intraoperative neuronavigation system (BrainLab AG, Feldkirchen, Germany) and novel custom software (Gupta et al., 2014). The electrode locations were then projected onto a three-dimensional brain model and custom NeuralAct (Kubanek and Schalk, 2014) software was used to render activation maps of corresponding ECoG activity.
Figure 4.4:  **(Top left)** Functional MRI showing increased BOLD activity (shown in yellow and orange) in Broca’s area, as well as auditory/receptive language area, precentral gyrus, supplementary motor/premotor cortex and prefrontal cortex. ECS (white circles) caused speech arrest in Broca’s area, adjacent to increased BOLD activity.  **(Top right)** Small black dots represent electrode contacts of the standard extraoperative subdural grid. Results from extraoperative ECoG-based functional mapping (shown in green) demonstrated increased activity in Broca’s area, precentral gyrus, supplementary motor/premotor cortex and postcentral gyrus.  **(Bottom)** Results from intraoperative ECoG-based mapping are shown in red. The diameter of each circle is proportional to the activity under the corresponding electrode contact. The largest circles identify locations that are qualitatively concordant with those from extraoperative ECoG-based and ECS mapping.

### 4.4 Discussion

This case report represents the first application of high-resolution ECoG-based mapping in the operating room and demonstrates one of the most comprehensive examples of multimodal functional mapping to date. We mapped expressive language function in a patient using four different modalities: ECS, extraoperative ECoG, intraoperative ECoG, and fMRI. Recent technological
advances enabled us to combine the results into an informative display that facilitated comparison across modalities. This comparison suggested qualitatively concordant functional language maps. In particular, ECS and extraoperative ECoG delineated identical critical language nodes using a standardized grid coordinate system. The same locations were confirmed with intraoperative high-resolution ECoG. Thus, our results highlight the value of passive ECoG-based mapping in the extraoperative as well as the intraoperative environment.

Electrical cortical stimulation currently represents the "gold standard" for functional cortical mapping even in the absence of standardization and validation by randomized controlled trials. Given the recent technological advances, ECoG-based mapping offers the potential for similar precision but with a greater safety profile, better patient tolerability, and faster data acquisition time. Several studies have compared the mapping results of ECoG with those of ECS, reporting sensitivities ranging from 0.43–1.0 and specificities of 0.72–0.94 for sensorimotor mapping (Brunner et al., 2009; Crone et al., 1998b; Leuthardt et al., 2007; Sinai et al., 2005; Vansteensel et al., 2013). However, evidence for concordance of ECoG with ECS for language mapping is relatively sparse. In their 2005 study of 13 patients, Sinai et al. reported a sensitivity of 38 % and specificity of 78 % for language mapping (Sinai et al., 2005). Miller et al. (Miller et al., 2011) applied extraoperative ECoG in 7 patients to elucidate cortical areas for expressive and receptive language. They reported a sensitivity of 89 % and specificity of 66 % for a noun-reading task and a sensitivity of 74 % and specificity of 48 % for a verb generation task when compared with ECS. A case report of a 13-year-old patient with intractable epilepsy yielded sensitivity of 75 % and 90 % when using the ‘next-neighbor’ hypothesis for ECoG compared with ECS mapping for language function (Korostenskaja et al., 2014). Case reports in the intraoperative environment (Roland et al., 2010; Wu et al., 2010) have provided qualitative concordance between ECoG and ECS data, suggesting that ECoG can facilitate more efficient ECS interrogation. Our case
reinforces the practical advantage of ECoG for language mapping.

Comparing the concordance of ECS and ECoG proves difficult given the fundamental differences in the approach of lesion-based mapping versus physiologic-based mapping. Electrical cortical stimulation "actively" disrupts cortical networks critical for a particular function and only identifies those subsets of task-related cortical networks whose lesion produces the most severe functional deficits, whereas ECoG "passively" highlights all cortical networks involved with a particular task (Su and Ojemann, 2013). Thus, ECoG can be expected to define a larger area for preservation and underestimate the margin for safe resection. In this context, it is worth noting that patients have been reported to have postoperative language deficits after resection of an ECoG(+)ECS(−) node (Cervenka et al., 2013; Genetti et al., 2015; Kojima et al., 2012; Korostenetskaja et al., 2014; Miller et al., 2011; Sinai et al., 2005). In a study of 77 patients, postoperative language deficits could be predicted by the number of ECoG(+) language nodes resected (Kojima et al., 2013). At present, most resections are based primarily on ECS results even though ECS has never been validated in randomized, clinical trials (Su and Ojemann, 2013).

Ultimately, the most important aspect is the relative clinical utility of each method. Establishing clinical utility requires standardized preoperative and postoperative assessments in a large number of patients. For ECoG, such larger assessments do not yet exist. With continued refinement and validation, ECoG may play an even larger role in presurgical functional mapping in the future. At the same time, without additional information, we currently do not suggest replacing exhaustive ECS mapping but rather argue that ECoG-based mapping provides useful and complementary information.

Electrical cortical stimulation and ECoG each have important limitations for clinical application. Both modalities currently require awake craniotomies or 2-stage procedures and depend entirely on patient comfort and compliance. 2-stage procedures carry significant financial bur-
den as well as stress associated with a prolonged hospitalization in an unfamiliar environment. The risk of infection increases with implanted materials and duration of implantation. Patients assume all the surgical risks of a second operation. The physical mapping with ECS is time and labor intensive for the clinician and the patient. The appropriate stimulation energy must be determined and then applied to each single grid contact in an organized method. Electrical stimulation can cause pain from activation of dural nociceptive afferents and general cephalalgia (Su and Ojemann, 2013). Electrical cortical stimulation can produce after-discharges that may summate into seizures with subsequent postictal periods that can further delay mapping. Finally, ECS may produce inhibitory responses that cannot readily be observed and may have variable propagation of stimulation current due to individual anatomy and procedural differences (Brunner et al., 2009; Ojemann et al., 1989b). In our case, the patient did have a seizure that prolonged the mapping time by 1.5 h, increasing total mapping duration to 4.5 h. Passively recorded ECoG incurs less risk of cephalalgia, reduces the risk for iatrogenic seizures, and has dramatically shortened mapping time since it can evaluate cortical activity from all electrodes simultaneously.

As with ECS and ECoG, the concordance between ECS and fMRI varies, with reported sensitivity and specificity measurements for language mapping varying between 59–100 % and 53–97 %, respectively (Bizzi et al., 2008; FitzGerald et al., 1997; Giussani et al., 2010; Pouratian et al., 2002; Roux et al., 2003; Rutten et al., 2002a). Our case report demonstrated strong concordance between fMRI, ECoG, and ECS for the language sites identified on the pars opercularis but not as well for the language sites on the pars triangularis. Multiple issues can influence this mismatch on the pars triangularis. First, we used a conservative fMRI threshold, and only the most robust sites reached this threshold in the analysis. Second, blood flow artifacts can obscure the fMRI signal, making it more difficult to measure in certain regions compared with others (Kekhia
et al., 2011; Tharin and Golby, 2007). Lastly, previous fMRI studies often used a battery of language tasks to localize language areas (Rutten et al., 2002b), whereas we only evaluated verb generation and word repetition. A more comprehensive battery across modalities may provide better-matched results.

To our knowledge, this is the first instance of using a high-density subdural grid in the intraoperative environment for language mapping. With its superior spatial resolution, we were able to create a highly refined boundary between the tumor and expressive language cortex. These results are encouraging, but important questions are not yet resolved. How does this improved spatial resolution translate into improved patient outcomes? What is the optimal electrode diameter size and interelectrode distance for best spatial resolution that will provide nonredundant recordings (Freeman et al., 2000; Leuthardt et al., 2009; Wang et al., 2009)? At what point will the spatial resolution of high-density subdural grids exceed the operative resolution of neurosurgery with available techniques?

Even with mapping of Broca’s area and the specific language nodes, our patient still suffered a 28 % decline in verbal fluency at one year. Can we attribute this decline in verbal fluency as a postoperative deficit (as seen in 3–13 % of patients with brain tumor who undergo surgery Reulen et al. 1997; Sacko et al. 2011; Schiffbauer et al. 2002) or to that of radiation necrosis potentiated by chemotherapy (that afflicts 2.5–5 % of patients Shaw et al. 2002)? Our patient had undergone formal neuropsychiatric evaluation. Functional limitations or clinical observations (as used in some other studies) would likely have missed these subtle changes.

Functional language mapping during an awake craniotomy remains a challenge. Here, we demonstrate that functional mapping with high-resolution electrocorticography can readily be performed in the intraoperative environment and that its results appear qualitatively concordant with ECS. At this juncture, there is no universal standard of care for functional language map-
ping. Taking into account the unique strengths and limitations of each modality, no one technique is clearly superior to the others. The rate of investigation into various modalities for functional brain mapping is at its zenith, with the impetus to improve clinical outcomes for patients with epilepsy, tumors, or vascular malformations.
4.5 **Interim Summary**

In Chapter 4, we investigated the utility and practicality of passive intraoperative functional mapping of expressive language cortex using high-resolution ECoG. Our results demonstrated that intraoperative mapping using high-resolution ECoG is feasible and, within minutes, produces results that are qualitatively concordant to those achieved by extraoperative mapping modalities. They also suggested that functional language mapping of expressive language areas with ECoG may prove useful in many intraoperative conditions given its time efficiency and safety. Finally, they demonstrated that integration of results from multiple functional mapping techniques, both intraoperative and extraoperative, may serve to improve the confidence in or precision of functional localization of healthy functional cortex.
5.1 Summary of Problem and Approach

In Chapter 4, we investigated the utility and practicality of passive intraoperative functional mapping of expressive language cortex using high-resolution electrocorticography. In the study that is summarized in this chapter, we will introduce a novel technique to identify cortical areas involved in speech production without requiring the patient to speak. Currently, all established protocols to perform such mapping require substantial time and patient participation during tasks such as verb generation or similar tasks. These issues can make language mapping impractical in certain clinical circumstances (e.g., during awake craniotomies) or with certain populations (e.g., pediatric patients). Thus, it is important to develop new techniques that reduce mapping time and the requirement for active patient participation.

Here, we hypothesized that activity in auditory cortex would also briefly engage anatomically...
connected areas in inferior frontal cortex (i.e., Broca’s area) involved in speech production. We took advantage of the high temporal and spatial resolution of ECoG recordings to investigate the presence of brief changes of cortical activity in speech production areas during passive listening of auditory speech sounds. We further investigated whether we could use these brief changes of cortical activity to identify cortical areas involved in speech production without actually requiring the patient to speak.
5.2 Introduction

Language is crucial for meaningful interaction and communication. Key language abilities, such as perception and production, are governed by multiple regions in the brain. These abilities can quickly become jeopardized in people with brain tumors, epilepsy, or other structural abnormalities. Many of these patients require resection of pathological tissue near eloquent language areas to prolong or improve quality of life. Inevitably, such resection carries inherent risks to language function. Thus, functional language mapping for precise localization of eloquent language areas is necessary for achieving optimal surgical outcomes in such patients.

Functional language mapping for perioperative planning in individual patients is of utmost importance given the high variability in structural anatomy and function across individuals (Ojemann et al., 1989a). Most typically, language mapping is achieved using electrical cortical stimulation (ECS) mapping. While ECS is widely considered the gold standard (Ojemann et al., 1989a; Su and Ojemann, 2013), it does have noteworthy limitations. First, a thorough ECS interrogation is very time-consuming. Second, ECS increases the risk of after-discharges or seizures that result from "active" stimulation of the cortex using electrical impulses. Finally, ECS can be difficult to accomplish in the subset of pediatric patients and patients with psychiatric and cognitive comorbidities. These issues have prompted recent and increasingly encouraging investigations suggesting that "passive" methodologies, such as electrocorticography (ECoG) or functional magnetic resonance imaging (fMRI), may prove useful for functional mapping and may have distinct advantages in efficiency, morbidity, or the range of patients that can benefit from it (Håberg et al., 2004; Kamada et al., 2014, 2007; Korostenskaja et al., 2014; Mahvash et al., 2014; Miller et al., 2011; Roland et al., 2010; Tie et al., 2014; Vlieger et al., 2004).

Unfortunately, traditional mapping of expressive language function with any of these existing
techniques carries the additional requirement that patients actually speak, i.e., fully participate in specific tasks such as verb generation, object naming, or counting. This requirement currently precludes the use of these techniques in many patients, such as those with aphasia or cognitive deficits or very young patients.

Together, these limitations and requirements preclude or greatly impede functional mapping of expressive language areas in certain clinical circumstances (such as during awake craniotomies) or with certain populations (such as pediatric patients). Hence, it is desirable to have access to a technique that does not electrically stimulate the brain and that eliminates or reduces the requirement for patient participation. Such a technique may eventually reduce ECS mapping time by guiding the clinician with a preliminary map of eloquent expressive language cortex. This would not only diminish the risks of patient morbidity, discomfort, and iatrogenic seizures but would also increase the number of patients who could be eligible for functional mapping of expressive language areas.

Identification of eloquent expressive language cortex without requiring the patient to speak is supported by several findings. Previous fMRI studies reported activations of the left (Mazoyer et al., 1993; Nakai et al., 1999) and bilateral (Abrams et al., 2012; Binder et al., 1997; Suarez et al., 2014; Wilson et al., 2004) inferior frontal gyri while subjects listened to speech stimuli but did not perform any overt speaking task. In addition, Suarez et al. demonstrated using fMRI that a passive listening task recruited similar cortical areas as a verb generation task in a cohort of 15 pediatric patients (Suarez et al., 2014). However, fMRI is still expensive and requires substantial expertise that is not available in all centers, and its reliability in the context of functional mapping is still uncertain (Giussani et al., 2010; Roux et al., 2003). Thus, to date, fMRI-based mapping has not achieved widespread acceptance.

Electrocorticographic recordings also provide opportunities for functional mapping in the
context of mapping of motor (Brunner et al., 2009; Leuthardt et al., 2007; Miller et al., 2014; Roland et al., 2010; Su and Ojemann, 2013) or language (Miller et al., 2011; Roland et al., 2010) function, in pediatric patients (Korostenskaja et al., 2014), and in the operating room (Kamada et al., 2014; Roland et al., 2010). Together, these studies demonstrated that ECoG-based mapping can be achieved in real time (i.e., while signals are being recorded), does not require expertise in signal analysis, and can produce clinically useful results that can readily be compared with ECS results in a few minutes. However, evidence for its utility in identifying expressive language without subject participation was lacking. Indeed, only two previous neuroscientific ECoG studies reported activations in the inferior frontal cortex during a passive listening task (Edwards et al., 2009; Sinai et al., 2005), but they did not determine whether these activations could be identified using a common analysis approach, establish the concordance between locations resulting from ECoG- and ECS-based mapping, or discuss the feasibility of such passive mapping ECoG protocol in the context of presurgical or intraoperative mapping. The present report provides initial evidence on this topic from three subjects.

5.3 Methods

5.3.1 Patients

Three subjects (A–C) participated in this study. All three subjects were patients at Albany Medical Center (Albany, New York). Subject A was diagnosed with a low-grade glioma in the left frontal lobe after presenting with new-onset seizures. Subjects B and C suffered from intractable epilepsy. All subjects underwent temporary placement of subdural electrode grids to localize seizure foci and eloquent cortex prior to surgical resection. The subjects’ clinical profiles are summarized in Table 5.1. The electrode grids were approved for human use (Ad-Tech Medical
Corp., Racine, WI and PMT Corp., Chanhassen, MN) and covered different areas within frontal, temporal, and parietal lobes of the left hemisphere. Most importantly, all three subjects had coverage of frontal lobe language areas, and two of the three (subjects B and C) also had coverage of temporal lobe language areas. Electrodes consisted of platinum-iridium discs (4 mm in diameter, 2.3–3 mm exposed), were embedded in silicone, and were spaced 6–10 mm apart. The total number of implanted electrodes was 61, 98, and 134 in subjects A–C, respectively. Following subdural grid implantation, each subject had postoperative anterior-posterior and lateral radiographs, as well as computer tomography (CT) scans to verify grid location. Preoperative language lateralization (LL) had been assessed previously with fMRI in subject A and with WADA testing (Wada and Rasmussen, 1960) in subjects B and C. Based on these evaluations, language was lateralized to the left hemisphere in all three subjects. All subjects signed informed consent to participate in the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command.

5.3.2 Data collection

Once subjects recovered postoperatively, we recorded ECoG signals at the bedside using general-purpose BCI2000 software (Schalk, 2010; Schalk et al., 2004b), which controlled eight 16-channel g.USBamp biosignal acquisition devices (g.tec, Graz, Austria). To ensure integrity of clinical data collection, a connector split the electrode cables into two separate sets. One set was connected to the clinical monitoring system, and another set was connected to the g.USBamp acquisition devices. The ECoG signals were amplified, digitized at 1200 Hz, and stored by BCI2000. We used electrode contacts distant from epileptogenic foci and areas of interest for reference and ground.
Table 5.1: Clinical profiles of the 3 patients. ‘LL’ reflects language lateralization.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Handedness</th>
<th>LL</th>
<th>Seizure Focus</th>
<th>Grid Locations</th>
<th># of Elec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34</td>
<td>M</td>
<td>R</td>
<td>L</td>
<td>Left frontal</td>
<td>Left frontal</td>
<td>61</td>
</tr>
<tr>
<td>B</td>
<td>28</td>
<td>M</td>
<td>R</td>
<td>L</td>
<td>Left temporal</td>
<td>Left frontal</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left temporal</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left parietal</td>
<td>16</td>
</tr>
<tr>
<td>C</td>
<td>25</td>
<td>F</td>
<td>R</td>
<td>L</td>
<td>Left temporal</td>
<td>Left frontal</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left temporal</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left parietal</td>
<td>4</td>
</tr>
</tbody>
</table>

5.3.3 Anatomical mapping

We created 3D cortical brain models for each subject by submitting preoperative high-resolution magnetic resonance imaging (MRI) scans to Freesurfer software (http://surfer.nmr.mgh.harvard.edu). We coregistered MRI scans with postoperative CT images using SPM software (http://www.fil.ion.ucl.ac.uk/spm) and identified the stereotactic coordinates of each grid electrode using custom MATLAB scripts (The MathWorks Inc., Natick, MA). Finally, we visualized the cortical surface of each subject and ECoG grid locations using NeuralAct software (Kubanek and Schalk, 2014).

5.3.4 Task and stimuli

In our study, we asked the subjects to listen to four short stories narrated by a male voice (stimulus duration: 17.15–35.70 s; interstimulus interval (ISI) of 10 s) which were part of the Boston Aphasia Battery (Goodglass and Kaplan, 1983). The stimuli were digitized at 44.1 kHz in waveform audio file format and binaurally presented to each subject using in-ear monitoring earphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from environmental noise). The sound volume was adjusted to a comfortable level for each subject. The subjects did not perform any overt task (such as repeating words and generating verbs in response to the words they heard).
5.3.5 Feature extraction

We identified ECoG activations by detecting task-related changes in the broadband gamma (70–170 Hz) band. To identify those locations that responded to auditory stimulation, we first removed channels that did not contain clear ECoG signals (e.g., ground/reference channels, channels with broken connections, or channels corrupted by environmental artifacts or interictal activity). Of a total of 61, 98, and 134 channels, this left 59, 79, and 132 channels for subjects A–C, respectively, which we submitted to subsequent analyses. In these analyses, we high-pass filtered the signals at 0.1 Hz to remove drifts and re-referenced the signals to a common average reference (CAR) montage. We band-pass filtered the results in the broadband gamma band using a Butterworth filter of order 16. We then obtained the power of these signals by computing the absolute value of the analytical signal, followed by a low-pass filter at 4 Hz and down-sampling to 120 Hz. Finally, we normalized the resulting broadband gamma power estimates by subtracting from them the signal mean calculated from a baseline period (–6 to –0.5 s prior to the onset of the auditory stimulus) and by dividing them by the standard deviation of the signal during the baseline period.

5.3.6 ECoG-based mapping of expressive language cortex

We determined those locations whose ECoG broadband gamma activity following onset of the auditory stimulus (i.e., the response period) was different from that during the baseline period. Several studies have shown that, in receptive auditory areas, broadband gamma activity reliably tracks the time course of the envelope of the intensity of the auditory stimulus (Potes et al., 2014, 2012) or speech stimulus (Kubanek et al., 2013). A few isolated reports documented discrete and brief broadband gamma activations in inferior frontal cortex after the onset of an auditory speech stimulus (Edwards et al., 2009; Sinai et al., 2005) that occurred after the activations in receptive
auditory areas (Sinai et al., 2005). Based on these reports, we defined the response period as 250–750 ms following the onset of the auditory stimulus. Then, for each location, we determined the magnitude of the change in ECoG broadband gamma power that was related to auditory stimulation by calculating the coefficient of determination (Spearman’s $r^2$ value). Finally, we determined the statistical significance of each $r^2$ value, i.e., the probability that ECoG broadband gamma samples differed in amplitude between the response and baseline periods, using a permutation test. In this test, we cut the ECoG broadband gamma power time courses into blocks of 500 ms (thereby preserving the autocorrelation of the signal), randomly permuted the resulting blocks, and finally calculated the corresponding random $r^2$ value. We repeated the permutation step 1000 times, thus generating a distribution of 1000 random $r^2$ values at each location. We considered $r^2$ values to be significant at the 95th percentile of that distribution ($p = 0.05$, Bonferroni-corrected for the total number of electrodes in each subject). The result of this procedure was a set of locations whose ECoG broadband gamma activity was significantly different between the baseline and the response periods and, hence, responded to the speech stimuli. Among the resulting locations, we identified those that were situated within inferior frontal cortex. This included all electrodes whose Talairach (Talairach and Tournoux, 1988) coordinate was within $x$ –28 to –55, $y$ –8 to +34, and $z$ 0 to 28, consistent with previous observations (Embick and Poeppel, 2006).

5.3.7 **ECS-based mapping of expressive language cortex**

Standard electrocortical stimulation mapping of expressive speech was performed extraoperatively for clinical purposes. The subjects took part in two simple tasks commonly used for this purpose: a picture-naming task, during which subjects were asked to verbally name sequentially presented pictures of simple objects and a verb generation task, during which subjects had to
verbally generate verbs associated with simple nouns presented auditorily. Different electrode pairs were stimulated to establish whether a given pair induced a disruption of expressive language function, e.g., speech arrest or hesitation. Stimulation intensity typically started at 2 mA and was increased in incremental steps of 2 mA until the neurologist observed clinical effects or after-discharges or reached the 10 mA threshold.

5.4 Results

The main results of our study are presented in Fig. 5.1. This figure highlights those locations that were identified by our analyses of the ECoG signals corresponding to the presentation of the speech stimuli (filled circles) and locations that produced arrest of expressive language function using ECS mapping (yellow circles).

Locations identified by ECoG mapping included the expected locations (highlighted by gray-filled circles) in superior temporal gyrus and/or perisylvian areas (all subjects) as well as in premotor and/or supplementary motor areas (subjects A and C; Potes et al. 2012). Consistent with previous observations (Potes et al., 2012), our method also identified responsive locations on or close to superior precentral gyrus (Patient C). Most relevant in the context of the present study, our ECoG-based mapping identified locations (highlighted by blue-filled circles) in inferior frontal cortex (pars triangularis and/or pars opercularis) in all three subjects. Fig. 5.1C also presents exemplary time courses of ECoG broadband gamma activity in Patient C.

Electrical cortical stimulation mapping identified 1–2 locations in which stimulation produced expressive language arrest in each subject (yellow circles). These locations were also located in or around pars triangularis and pars opercularis. The ECS-positive sites overlapped with the sites identified using ECoG or were located no more than one contact away.
Figure 5.1: In this figure, panels A–C reflect results for the patients A–C, respectively. The electrode locations for each patient are overlaid in black, while white, blue, and yellow circles correspond to locations described in the legend above. Panel C also includes four graphs presenting ECoG activity over exemplary sites from −500 ms to 1500 ms after stimulus onset. Shaded areas reflect the standard error of the mean, the vertical dashed lines show stimulus onset, the horizontal dashed lines show baseline activity, and the horizontal dotted red lines show a 3 z-score threshold above which ECoG activity is significantly different from baseline. The exact timing at which ECoG activity passes this threshold is further denoted by an arrow under each time plot.

5.5 Discussion

In our study of three patients with chronically implanted subdural electrode grids, we provide initial evidence that it is possible to use passively recorded ECoG in response to presentation of speech stimuli to identify not only locations in the receptive language network that are located primarily in the temporal lobe but also locations within the expressive language network in the inferior frontal cortex.
With further refinement of the protocol and validation in more subjects, the passive mapping approach described here could lead to a mapping method that may have important clinical implications. The ability to map expressive language cortex with greatly reduced needs for patient participation expands the utility of functional language mapping. Specifically, it enables functional mapping of expressive language in patients who are unable to cooperate productively such as pediatric populations or patients suffering from aphasia or psychiatric and cognitive comorbidities. We envision passive language mapping using ECoG to either complement existing ECS or fMRI mapping protocols or provide an alternative when other expressive language mapping techniques are inadequate. ECoG passive mapping may also have distinct advantages in the time-limited settings of the intraoperative environment. A preliminary map of eloquent expressive language cortex could inform ECS mapping, likely resulting in reduced ECS mapping time and thereby diminishing the risks of patient morbidity, discomfort, and ECS-induced seizures. This would prove extremely useful in an intraoperative decision-making situation.

5.5.1 Additional evidence from other studies supports the mapping of expressive language function without requiring the patient to speak

A critical question raised by the present study is to what extent the encouraging results presented here generalize to a larger number of patients. For two reasons, we are optimistic that the results in a larger number of patients will echo the initial results reported here. First, several groups have reported activation of the inferior frontal gyrus in response to presentation of passive speech stimuli (Abrams et al., 2012; Binder et al., 1997; Lehericy et al., 2000; Mazoyer et al., 1993; Nakai et al., 1999; Suarez et al., 2014). Mazoyer et al. first demonstrated activation of the left inferior frontal gyrus on positron emission tomography (PET) scans in 16 subjects while listening to lists of words and stories (Mazoyer et al., 1993). Several fMRI (Abrams et al., 2012; Binder
et al., 1997; Lehericy et al., 2000; Nakai et al., 1999; Suarez et al., 2014) and ECoG (Edwards et al., 2009; Sinai et al., 2005) studies have replicated these results using similar tasks. Second, recent evidence indicates that ECoG-based mapping can identify locations in expressive language areas when sites in receptive language areas are stimulated using electrical stimulation (i.e., corticocortical evoked potentials or CCEPs; Matsumoto et al. 2004; Saito et al. 2014; Tamura et al. 2016; Yamao et al. 2014). For example, Matsumoto et al. (Matsumoto et al., 2004) described the technique of delivering a single pulse electrical stimulation in the inferior frontal language area and recording a cortical evoked potential in the temporal-parietal area, establishing structural neuronal connectivity between the two functional regions. In a smaller subset of patients, they were able to elicit CCEPs in the inferior frontal and basal temporal regions with stimulation of the temporo-parietal language area. This bidirectional connectivity is likely mediated at least in part by the arcuate fasciculus, although the anatomical distribution of the arcuate fasciculus may be more complex than historically assumed (Bernal and Altman, 2010; Brown et al., 2014; Catani et al., 2005; Tate et al., 2014). More generally, the language network connectivity model appears to be much more complex than initially believed, with an interplay of numerous cortical regions and white matter tracts (Catani, 2007; Catani and De Schotten, 2008; Catani et al., 2005; Hickok and Poeppel, 2007).

5.5.2 Study limitations

While our initial results are encouraging, different circumstances could temper the significant positive implications of expressive language mapping using passive stimuli. When applied in intraoperative scenarios, different surgical realities (such as intermittent irrigation on the subdural grid, cable adjustment, variable clinical or cognitive status of the patient) may lead to lower signal-to-noise ratio and a resultant decrease in ability to detect task-related ECoG changes. The
duration of mapping may be increased if the grid requires repositioning with reinitiation of
tasks. Furthermore, it is possible that passive engagement of expressive language function may
not elucidate the whole expressive language network. Finally, the current study is only reporting
results for 3 subjects. Further investigation in a larger number of patients is required to assess
the potential benefit of our findings to resective neurosurgical planning. Furthermore, while our
method successfully identified expressive language sites in a patient diagnosed with a left frontal
tumor in close proximity to Broca’s area (subject A), it is not possible to predict how our method
would generalize to patient populations with different types of distorting pathologies. It would
also be valuable to determine if our method can identify eloquent expressive language cortex in
patients with aphasia.

5.6 Conclusions

In this paper, we report initial results of an approach to functional mapping of expressive lan-
guage function that could greatly reduce the need for subject participation. With further refine-
ment and validation, the approach described here may lead to a simple, easy-to-use protocol that
would simultaneously identify receptive and expressive language areas for surgical planning.
This protocol would be widely applicable in a significantly greater number of patients. Finally,
because our approach does not require the patient to speak, it opens up the possibility for apply-
ing it to patients under general anesthesia. Thus, this approach has the potential to completely
revolutionize functional language mapping in neurosurgery; the initial results presented here
clearly encourage further investigation.
5.7 Interim Summary

In Chapter 5, we investigated the possibility to use ECoG passive mapping to identify expressive language areas without requiring the patient to speak. Our results provided encouraging preliminary evidence that this is indeed possible. We found that merely listening to auditory speech stimuli briefly engaged distinct locations in inferior frontal cortex in addition to traditional receptive speech areas located in the superior temporal gyrus and/or peri-Sylvian areas. The sites in inferior frontal cortex that we identified with our procedure were either on or immediately adjacent to locations identified using electrical cortical stimulation (ECS) mapping.

This protocol could provide the clinician with a map of expressive language cortex within a few minutes. Thus, it may be useful as an adjunct to ECS interrogation or as an alternative to mapping using functional magnetic resonance imaging (fMRI). With further development and validation in more subjects, the approach presented here could help in identifying expressive language areas in situations where patients cannot speak in response to task instructions.
Conclusions and Future Directions

In this dissertation, we used electrocorticographic recordings to advance our understanding of the precise temporal and spatial coordination of neuronal activity implementing behavior. In addition, we translated our findings into two novel clinical applications that improve the safety of brain surgery. In this final Chapter, we will summarize the findings resulting from our neuroscientific studies (Chapters 2 and 3) and clinical studies (Chapters 4 and 5). For each section, we will also discuss potential future directions that may be explored.

6.1 Neuroscientific Studies: Conclusions and Future Directions

6.1.1 Conclusions

Human perception and behavior result from timely activity in specific populations of neurons. The excitability of these neuronal populations is believed to play an important role in the regulation and facilitation of this activity. ECoG recordings provide a unique opportunity to observe the relationship between cortical activity, excitability, behavior, and perception. In Chapters 2 and 3, we investigated the temporal and spatial relationships between cortical excitability and activity (respectively measured by the power of oscillations around 10 Hz and broadband changes
of the ECoG spectrum) during several behavioral tasks. In particular, we were interested in understanding how those relationships between cortical activity and excitability differed between bottom-up and top-down processes. We showed that in task-related cortical areas, increases of cortical excitability preceded increases of cortical activity during top-down processes, but lagged it during bottom-up processing. This increase of excitability in task-related areas was accompanied by a general decrease of excitability in areas not related to the task. Finally, we investigated the mechanisms underlying the modulations of cortical excitability during top-down behavior. We hypothesized that the prefrontal cortex, an important region for top-down processing of cortical information, would be involved in the modulation of alpha oscillations during an auditory task requiring selective attention. First, we found that prefrontal activity was correlated with auditory activity encoding selective information about the attended stimulus. Second, we found that prefrontal activity was correlated with and preceded cortical excitability in auditory cortex.

Together, our results contribute to our understanding of the mechanisms underlying the selection of the specific neuronal populations required for task execution. They provide additional evidence for the role of alpha oscillations in cortical information processing. Specifically, they suggest that rhythmic inhibition (as measured by the power of alpha oscillations) is decreased in task-related areas in preparation for the task. This decrease of inhibition presumably facilitates cortical activity in those areas. In addition, our results refined our understanding of the relationship between higher-order cortical areas, such as prefrontal cortex, and task-related areas during top-down behavior. Our results suggest that modulations of cortical excitability in preparation for a task may be driven by the prefrontal cortex. These results add evidence for the role of cortical oscillations in mediating interactions between cortical areas important for behavioral control and task-related sensory or motor areas during top-down behavior (Buschman and Miller, 2007; Fritz et al., 2010; Voytek et al., 2015a; Zanto et al., 2011).
6.1.2 Future directions

Several aspects of the studies presented in Chapters 2 and 3 may be improved and extended.

First, it has recently become evident that oscillatory processes cannot be represented by pure sine waves and that current signal processing analyses based on Fourier decomposition, which decomposes the signal into sinusoids, are suboptimal to accurately capture the dynamics of oscillatory processes. (Cole and Voytek, 2017). Rather, oscillatory processes in the ECoG signal are better represented by non-sinusoidal patterns such as arch- or sawtooth-like patterns, the specific shape of which depends on their underlying cellular and molecular characteristics. It may thus be interesting to replicate and expand our analyses using signal processing techniques that take these differing shapes into account (such as Matching Pursuit).

In addition, it may be interesting to investigate whether subject’s performance during top-down behavior is related to different variables of interest. For example, it may be possible to investigate the relationship between a subject’s behavior during a cocktail party task (i.e., how well did the subject pay attention to the attended stream of speech) and variables such as feedforward and feedback connectivity between higher-order cortical areas and sensory/motor areas, or activity and excitability in task-related locations that are specific or non-specific to the attended stream.

We may also consider designing a variation of the cocktail party task presented in Chapter 3 that would allow us to further characterize the dynamics of cortical activity and excitability in the auditory cortex during selective auditory attention. For example, instead of focusing on one of two streams of speech, the subject may be asked to focus on one stream of speech versus one stream of music. Using high-resolution ECoG grids (such as the one used in Chapter 4) it may be possible to differentiate between those locations of auditory cortex responding exclusively
to speech or to music stimuli. We may observe differential modulations of cortical activity and excitability in these different populations preceding to and during stimulus presentation, while the subject focuses his/her attention on either music or speech. In addition, we may further refine our understanding of the top-down modulations of cortical excitability by prefrontal cortex by quantifying the connectivity between prefrontal cortex and those particular populations of neurons in auditory cortex responding to music or speech.

Finally, it may be interesting to characterize the modulations of cortical excitability and activity over time during the full time course of the 10 seconds long auditory stimuli of the study in Chapter 2. Firing rates of auditory neurons are known to adapt differently depending on their tuning to the presented stimulus (Wang et al., 2005). Therefore, the relationship between cortical activity and excitability may change over the duration of the stimulus, according to the preference of a location for a particular category of sound (i.e., speech, music, white noise, etc.). Characterizing those changes may further refine our understanding of the subtle cortical dynamics underlying human auditory perception.

### 6.2 Clinical Studies: Conclusions and Future Directions

#### 6.2.1 Conclusions

Preserving healthy functional tissue during resective brain surgery is critical to preserve the patient’s quality of life. Unfortunately, establishing a clear demarcation between healthy functional tissue and pathological tissue is not straightforward. The current gold-standard for identifying (i.e., mapping) healthy cortex consists of stimulating the cortex and observing the patient’s behavioral responses. This procedure is lengthy, presents health risks for the patient, and its outcome can be unpredictable. In addition, the procedure usually requires active participation
from the patient, which can be challenging to certain patient populations (e.g., children) or during certain circumstances (e.g., during intraoperative mapping during an awake craniotomy). In such cases, patients might not benefit from functional mapping at all, which increases the risk of postoperative cognitive deficits. Thus, it is necessary to develop novel techniques that are simpler, safer, faster, and more robust.

In Chapters 4 and 5, we described two techniques that combine our scientific understanding of ECoG signals with the inherent advantages of ECoG. In Chapter 4, we investigated the utility and practicality of a novel high-density ECoG micro-grid to identify cortex involved in speech production. We recorded signals intraoperatively while the patient was awake and performed a language task and we detected corresponding changes of broadband power changes in the ECoG spectrum. The results of our analysis were qualitatively concordant to those achieved by electrical stimulation of the cortex and by extraoperative mapping modalities such as fMRI and chronic ECoG. In addition, our results were produced within minutes. Therefore, our results indicated that functional language mapping of expressive language areas using ECoG may prove useful in intraoperative conditions given its time efficiency and safety. In Chapter 5, we investigated whether expressive language cortex could be identified without requiring any patient participation. We were able to observe transient increases of broadband gamma power in the inferior frontal cortex of three patients while they were solely listening to speech stimuli. The sites in the inferior frontal cortex that we identified with our procedure were either on or immediately adjacent to locations identified using electrical cortical stimulation mapping. Thus, these results provide preliminary evidence that it is possible to identify expressive language cortex without active patient participation. This would be highly beneficial to populations that cannot undergo awake craniotomies or who cannot easily follow instructions. It may also guide and speed up electrocortical stimulation procedures by providing clinicians with a preliminary map
of expressive language cortex.

6.2.2 Future directions

Our two clinical studies were based on a small sample size (1 and 3 subjects, respectively). To develop a protocol based on the procedure proposed in Chapter 5 requires recording, testing, and validation in a larger cohort of patients. The experimental design of the procedure proposed in Chapter 5 also needs to be refined. For example, it remains to be determined which types of auditory stimuli generate the strongest response in expressive language areas. It might also be possible to adjust the time window of interest in our analysis (i.e., the time window during which the power of broadband gamma is quantified) on an individual basis. Finally, it may be interesting to include the underlying oscillatory activity in our analysis. As we have discussed in Chapter 1, the probability for a neuronal population to respond to a given input may be rhythmically modulated. These modulations determine temporal windows during which the brain does or does not respond to a stimulus. In our case, passive transmission of action potentials from receptive to expressive language areas may be directly determined by the current excitability state of the receiving population (i.e., expressive language areas). Thus, we may investigate whether we can increase the sensitivity of our activity detection in expressive language areas by adjusting our window of analysis to the phase or amplitude of underlying oscillatory activity (e.g., in the alpha band) in those areas.

In the long-term, we foresee that functional mapping using passive ECoG recordings will affect the practice of resective neurosurgery in primarily three areas. First, if combined with electrocortical stimulation (ECS), it will make ECS procedures faster for the neurologist and safer for the patient by pre-identifying a number of cortical areas of interest and therefore narrowing down the number of electrodes requiring stimulation.
Second, the procedure proposed in Chapter 5 may benefit patients who cannot easily follow instructions during language tasks (e.g., young children), patients who cannot fully cooperate during awake craniotomies (e.g., because of pain, emotional distress, etc.), and patients who cannot undergo exhaustive ECS mapping (e.g., often, electrodes in close proximity to the epileptic focus are not stimulated because of the heightened risk of triggering a seizure during stimulation).

![Figure 6.1: This figure depicts the time courses of normalized cortical activity (i.e., power of broadband gamma) in one location involved in language comprehension on the right hemisphere of one patient, in response to speech stimuli (blue traces) and frequency-matched noise stimuli (red traces) while the patient is awake (left panel) or under general anesthesia (right panel).](image)

Third, functional mapping using ECoG without subject participation opens the door to the exciting perspective of mapping the cortex under general anesthesia. This would remove the need for awake craniotomies altogether, and would benefit a large number of additional patients who cannot undergo awake craniotomies (e.g., patients with cardio-pulmonary comorbidities, elevated depression scores, significantly lower IQs, or psychiatric disorders). In such patients, resective surgery is performed without functional brain mapping at the risk of causing severe postoperative cognitive deficits. Over the past three years, we have been actively investigating the possibility to map the cortex under general anesthesia. We recorded ECoG in more than 15 patients who listened to speech stimuli and frequency-matched noise stimuli while they were awake, and separately while they were unconscious under propofol anesthesia. Our preliminary
results show that listening to speech sounds activates the same auditory regions whether or not the person is awake or unconscious (see Fig. 6.1). Thus, it may be possible to identify cortical areas involved in speech processing without having to awaken the patient during the surgery.

Finally, the development of higher-density ECoG grids similar to the one utilized in the study from Chapter 4 opens up exciting neuroscientific and clinical opportunities. Their spatial resolution and coverage enables the study of the human cortex with unprecedented level of detail (see Fig. 6.2 for an example). Moreover, increased spatial resolution may improve our ability to decode imagined speech and motor movements in locked-in patients who rely on a brain-computer interface (BCI) to communicate or move.

![Normalized cortical activity](image)

Figure 6.2: The patient presented in the study from Chapter 4 was the first to be implanted with a high-density grid. The grid was only implanted for the duration of the functional mapping. We have since recorded ECoG data from a patient who was chronically implanted with a high-density grid four times larger than the one used in Chapter 4. The figure above depicts color-coded cortical activity (i.e., power of broadband gamma) while this subject listened to auditory stimuli. Note how areas of cortical activity precisely follow the shape of the superior temporal gyrus.
A List of Contributions

A.1 Chapter 1: Introduction

In this Chapter, we introduce background information relevant to this dissertation.

- I wrote the text.
- G. Schalk edited the text.

A.2 Chapter 2: Alpha Power Indexes Task-Related Networks on Large and Small Scales

In this study, we characterized the temporal and spatial relationships between cortical excitability and cortical activity during top-down (generation of a motor movement) and bottom-up (passively listening to an auditory stimulus) behavioral processes.

- For this study, I wrote custom MATLAB code to conduct all data analyses. I wrote the manuscript and responses to reviewer commentary and created the figures.
- W. G. Coon and G. Schalk edited the manuscript.
A.3 Chapter 3: Bottom-Up and Top-Down Interactions Between Prefrontal and Auditory Cortices During a Cocktail Party Task

In this study, we characterized the interactions between prefrontal cortex and task-related areas during top-down behavior. We also refined our current understanding of the mechanisms underlying selective auditory attention.

- For this study, I wrote custom MATLAB code to conduct all data analyses, wrote the manuscript and created the figures.
- P. Brunner designed the experiment and implemented it in BCI2000.
- P. Brunner, W. G. Coon, A. Gunduz and I recorded the data.
- G. Schalk edited the manuscript.

A.4 Chapter 4: Intraoperative Mapping of Expressive Language Cortex Using Passive Real-Time Electrocorticography

In this study, we demonstrated the feasibility of passive intraoperative functional mapping of expressive language cortex using high-resolution ECoG.
A. M. Taplin and I co-wrote the manuscript.

G. Schalk edited the manuscript.

I wrote responses to reviewer commentary, wrote custom MATLAB code, and created the figures.

P. Brunner and I designed the experiment and implemented it in BCI2000.

P. Brunner recorded the ECoG data.

D. Gupta and I performed the analysis of the ECoG data.

D. Hermes, P. Brunner and I performed the analysis of the fMRI data.

A.5 Chapter 5: Electrocorticographic Mapping of Expressive Language Function Without Requiring the Patient to Speak

In this study, we provided preliminary evidence that it may be possible to identify expressive language areas without requiring the patient to speak.

For this study, I wrote custom MATLAB code to conduct all data analyses, created the figures and wrote responses to reviewer commentary.

A. M. Taplin and I co-wrote the manuscript.

P. Brunner and I recorded the data.

G. Schalk edited the manuscript and wrote responses to reviewer commentary.
A.6 Chapter 6: Conclusions and Future Directions

In this Chapter, we exposed our conclusions of the four studies and discussed future directions.

► I wrote the text, analyzed the data using custom MATLAB scripts and created the figures.

► P. Brunner, W. Coon and I collected the data needed to produce the figures.

► G. Schalk edited the text.
## List of Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BCI</td>
<td>Brain-Computer Interface</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood Oxygenation Level Dependent</td>
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<tr>
<td>CAR</td>
<td>Common Average Reference</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>ECoG</td>
<td>Electrocorticography</td>
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<tr>
<td>ECS</td>
<td>Electrical Cortical Stimulation</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>LFP</td>
<td>Local Field Potential</td>
</tr>
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Identifying the attended speaker using electrocorticographic (ECoG) signals

K.V. Dijkstra, P. Brunner, A. Gunduz, et al

Brain-Computer Interfaces

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Alpha power indexes task-related networks on large and small scales: A multimodal ECoG study in humans and a non-human primate

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\section*{ABSTRACT}
Performing different tasks, such as generating motor movements or processing sensory input, requires the recruitment of specific networks of neuronal populations. Previous studies suggested that power variations in the alpha band (8–12 Hz) may implement such recruitment of task-specific populations by increasing cortical excitability in task-related areas while inhibiting population-level cortical activity in task-unrelated areas (Klimesch et al., 2007; Jensen and Mazaheri, 2010). However, the precise temporal and spatial relationships between the modulatory function implemented by alpha oscillations and population-level cortical activity remained undefined. Furthermore, while several studies suggested that alpha power indexes task-related populations across large and spatially separated cortical areas, it was largely unclear whether alpha power also differentially indexes smaller networks of task-related neuronal populations. Here we addressed these questions by investigating the temporal and spatial relationships of electrocorticographic (ECoG) power modulations in the alpha band and in the broadband gamma range (70–170 Hz, indexing population-level activity) during auditory and motor tasks in five human subjects and one macaque monkey. In line with previous research, our results confirm that broadband gamma power accurately tracks task-related behavior and that alpha power decreases in task-related areas. More importantly, they demonstrate that alpha power suppression lags population-level activity in auditory areas during the auditory task, but precedes it in motor areas during the motor task. This suppression of alpha power in task-related areas was accompanied by an increase in areas not related to the task. In addition, we show for the first time that these differential modulations of alpha power could be observed not only across widely distributed systems (e.g., motor vs. auditory system), but also within the auditory system. Specifically, alpha power was suppressed in the locations within the auditory system that most robustly responded to particular sound stimuli. Altogether, our results provide experimental evidence for a mechanism that preferentially recruits task-related neuronal populations by increasing cortical excitability in task-related cortical areas and decreasing cortical excitability in task-unrelated areas. This mechanism is implemented by variations in alpha power and is common to humans and the non-human primate under study. These results contribute to an increasingly refined understanding of the mechanisms underlying the selection of the specific neuronal populations required for task execution.

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\section*{Introduction}
Performing different tasks, such as generating motor movements or processing sensory information, requires the recruitment of specific networks of neuronal populations dispersed throughout distinct cortical areas. How the brain implements the recruitment of these networks is still largely unclear, but there is increasing evidence that oscillatory activity plays an important role in this process. For example, several
studies involving different sensorimotor modalities have reported a decrease in the power of low-frequency oscillations (event-related desynchronization (ERD)) in the 8–12 Hz range (alpha band) in task-related areas (Pfurtscheller and Neuper, 1992; Crane et al., 2001; Potes et al., 2014). This phenomenon is frequently coupled with an increase in alpha power (event-related synchronization (ERS)) in areas unrelated to the task (Pfurtscheller and Berghold, 1989; Pfurtscheller and Neuper, 1992; Fu et al., 2001). Separately, alpha oscillations with higher amplitudes modulate the firing of neuronal populations more strongly than oscillations with lower amplitudes (Haegens et al., 2011), which establishes a link between modulations of alpha power and cortical excitability. Taken together, these findings suggest that modulations in alpha power may index the degree of inhibition in different cortical areas, and, by extension, the spatial representation of selected functional networks (Klimesch et al., 2007). These observations have been consolidated into the gating-by-inhibition (GBI) hypothesis (Jensen and Mazaheri, 2010), and most recently synthesized with the communication-through-coherence (CTC) hypothesis (Fries, 2005) into the function-through-biased oscillations (FBO) hypothesis (Schalk, 2015). The view that emerges from this theoretical and experimental work is that the selection of functional networks is achieved by modulation of cortical excitability, and that cortical excitability is measured most directly by the instantaneous amplitude of oscillatory activity (that is influenced by oscillatory phase as well as oscillatory power) (Schalk, 2015).

If oscillatory activity indeed provides a general mechanism for the selection of cortical networks through modulation of cortical excitability, we can make three specific predictions. First, increases in population-level cortical activity in task-related areas should be accompanied by a decrease in alpha power irrespective of the task or the involved cortical areas, and alpha power should increase in all other regions. Second, in top-down preparation for a motor output, increases in cortical excitability should be coupled with a decrease in alpha power (Pfurtscheller and Berghold, 1989; Pfurtscheller and Neuper, 1992) and to follow auditory stimulation (Crone et al., 2001), such results remained to be demonstrated using single-trial analyses. Third, we should observe task-selective alpha modulations not only on large spatial scales, e.g., across motor and auditory regions, but also on smaller scales, e.g., within auditory regions. Such small-scale modulations of oscillatory activity are a prerequisite if they were to play a central role in regulating information flow within the brain. While there is solid evidence supporting the idea that alpha power may constitute a selection mechanism across large, spatially separated areas (Pfurtscheller, 1992; Pfurtscheller and Neuper, 1994; Foxe et al., 1998; Thut et al., 2006), evidence that it may also support selection of small and interwoven networks is scarce (Harvey et al., 2013). At present, the general consensus is still that modulations of alpha power are spatially widespread and only poorly informative of detailed delineations of the functional networks underlying the performance of different tasks (Crone et al., 2001; Pfurtscheller et al., 2003; Crane et al., 2006; Miller et al., 2009a).

To test these predictions and to better understand the dynamics between modulatory alpha band oscillations and population-level cortical activity, we recorded electrocorticographic signals (ECoG) during auditory and motor tasks in five human subjects and one macaque monkey. The high spatial and temporal resolution of these signals allowed us to study these dynamics not only across functional networks, i.e., auditory versus motor systems, but also within one functional network, i.e., the auditory system. In particular, we evaluated the spatial and temporal patterns of alpha power in response to different types of stimuli, over time, and in specific locations of auditory cortex, and related them to modulations of population-level activity as indexed by broadband gamma (70–170 Hz) (Manning et al., 2009; Miller et al., 2009b; Ray and Maunsell, 2011).

In agreement with the three predictions outlined above, we observed large modulations of alpha power across tasks: alpha power decreased in task-related areas and increased in a majority of task-unrelated areas. These results were common to the human subjects and the macaque monkey. Because alpha power has been linked to cortical excitability, these changes likely subserve the preferential recruitment of those functional networks necessary to perform a particular task. Furthermore, we found that alpha power suppression lagged population-level activity in auditory areas during the auditory task, but preceded it in the motor areas during the motor task. Finally, decreases in alpha power within auditory areas indexed regions where population-level activity increased the most in response to specific auditory stimuli. Similarly, increases in alpha power indexed regions where population-level activity increased the least. Taken together, our results add further evidence to a central role of oscillatory activity in regulating cortical excitability, and thus in regulating information flow within the brain. They also suggest that this modulating mechanism might operate even across small cortical populations.

Methods

Subjects

Five human subjects at Albany Medical Center (Albany, New York) and one macaque monkey at Radboud University (Nijmegen, Netherlands) participated in this study. The five human subjects (A–E) were patients with intractable epilepsy who underwent temporal placement of subdural electrode arrays to localize seizure foci prior to surgical resection. They included two women (A and B) and three men (C, D and E). The subjects’ clinical profiles are summarized in Table 1. Language lateralization (LL) was established preoperatively using the Wada test (Wada and Rasmussen, 1960). Human subjects gave informed consent for the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command. All animal procedures were approved by the ethics committee of Radboud University, Nijmegen, Netherlands.

The subjects were implanted with electrode grids that were approved for human use (Ad-Tech Medical Corp., Racine, WI; and PMT Corp., Chanhassen, MN; for human subjects), or polyimide-based grids ([Rubehn et al., 2009], for the macaque) over one hemisphere of the brain. Electrodes for the humans consisted of platinum-iridium disks (4 mm in diameter, 2.3 mm exposed), embedded in silicon and spaced 6–10 mm apart; for the macaque, electrodes were 1 mm in diameter and spaced 2-2.5 or 3 mm apart. The total numbers of implanted electrodes were 58–134 for the humans and 252 for the macaque. In the humans, the grids were implanted for about 1 week and their location varied across subjects. They were placed over the left hemisphere for subjects A, C, D, E and the macaque, and covered frontal, parietal and temporal cortices. Following the placement of the subdural grid, each human subject had postoperative anterior–posterior and lateral radiographs, as well as computer tomography (CT) scans to verify grid location.

Data collection

We recorded ECoG signals from the five human subjects at the bedside using the general-purpose BCI2000 software (Schalk et al., 2004; Schalk and Mellinger, 2010) connected to eight 16-channel g.LABamp biosignal acquisition devices (gtec, Graz, Austria). Clinical monitoring occurred simultaneously with the use of a connector that split the cables coming from the patient into one set that was connected to the clinical monitoring system and another set that was connected to the amplifiers. This ensured that clinical data collection was not compromised.
at any time. The signals were amplified, digitized at 1200 Hz and stored by BI2000. We used electrode contacts distant from epileptic foci and areas of interest for reference and ground. After visual inspection, we removed from all subsequent analyses those channels that did not contain clear EEG signals (e.g., ground/reference channels, channels with broken connections, presence of environmental artifacts, or interictal activity). We also removed occipital channels to avoid any confound due to the visual presentation of instructions during the tasks. This left 56–121 channels for further analyses. In addition to recording brain activity, we also simultaneously recorded the subjects’ behavior using a push button.

We recorded and amplified ECoG signals from the macaque using eight 32-channel headstages (Plexon Headstage 32 V-G20). We low-pass filtered these signals at 8 kHz, digitized them at 32 kHz (Neuralynx Digital Lynx 256 channel system) and resampled them at 1200 Hz. 229 channels remained for further analysis after visual inspection for the presence of artifacts.

Anatomical mapping

We created subject-specific 3D cortical brain models for subjects A, C, D and E using high-resolution pre-operative magnetic resonance imaging (MRI) scans and Curry software (Neuroscan Inc., El Paso, TX). MRI scans were not available for subject B. Instead, for visualization purposes, we used the 3D cortical template by the Montreal Neurological Institute (MNI). To identify the stereotactic coordinates of each grid electrode, we co-registered the MRI scans with post-operative computer tomography (CT) images. Finally, we projected each patient’s electrode locations onto the corresponding 3D brain model and rendered activation maps using the NeuralAct software package (Kubanek and Schalk, 2014).

For the macaque, the assignment of electrodes to cortical areas was based on high-resolution intra-operative photographs taken before and after grid placement, and used primarily sulcal landmarks.

Tasks and stimuli

During the auditory task, the human subjects and the macaque passively listened to natural auditory stimuli while otherwise resting. The stimuli consisted of 19 natural sounds that belonged to one of six different categories: speech (female and male voices (3 stimuli)), music (classical and jazz (4)), nature (forest, thunderstorm, water and waves (4)), animals (frogs, birds and dog (5)), engines (jet airplane and train (2)), or white noise (1). Each stimulus had a duration of 10 s. Stimuli were digitized at 44.1 kHz in waveform audio file format, and energy-matched. We presented the stimuli in 10 blocks. Each block contained a randomly interleaved sequence of the 19 stimuli. We used binaural in-ear headphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from environmental noise) for the human subjects and a loudspeaker for the macaque. The sound volume was adjusted to a comfortable level for each subject.

At the end of each stimulus, we verified the human subject’s attention to the stimulus by engagement in a motor task in which s/he had to decide to which category the presented stimulus belonged. Specifically, two seconds after the end of the auditory stimulus presentation, we presented on a screen the names of two of the stimulus categories (e.g., ‘speech’, ‘music’). The names were presented simultaneously and next to each other. One of the names was the category to which the last stimulus belonged; the other one was randomly chosen from the other categories. Subjects were asked to assign the last stimulus to one of the two categories by pressing one of two possible response keys (e.g., left button for the choice on the left or right button for the choice on the right). Subjects used the hand contralateral to the grid implantation for the button press. The stimulus presentation resumed after a 2-s interval. Results of the behavioral data indicated that the human subjects were attending to the auditory stimuli. They correctly categorized the stimuli with an average accuracy of 97% (range: 92–99%; accuracy due to chance: 50%).

Feature extraction

To extract spectral power in the alpha and broadband gamma bands, we first high-pass filtered the signals at 0.1 Hz to remove drift. We then re-referenced the signals to a common average reference (CAR) montage for the human subjects and a bipolar montage for the macaque. We band-pass filtered the signals in the two frequency bands of interest, i.e., 8–12 Hz (alpha) and 70–170 Hz (broadband gamma) using Butterworth filters of the same order for the two bands. Next, for each subject, location, and stimulus, we removed evoked components in the alpha band (Klimesch et al., 2007; Fujioka and Ross, 2008) by subtracting the amplitude of alpha averaged across trials from the individual trials, according to the inter-trial variance method proposed by Kalcher and Pfurtscheller in 1995. We then extracted amplitude envelopes by computing the absolute value of the Hilbert transform of the corresponding band-pass filtered signals, followed by a low-pass Butterworth filter at 4 Hz and down-sampling to 120 Hz. Finally, we normalized the amplitude envelopes to a baseline period, i.e., a

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1 http://www.hic.mni.mcgill.ca

2 Data for the macaque were collected across several different data acquisition sessions, which invalidate the calculation of a spatial average across all channels.
300 ms period just prior to the onset of the auditory stimulus. We chose this baseline period as the longest period of time that did not contain significant changes of broadband gamma or alpha power between averaged trials after visual inspection. We used the same baseline for all analyses throughout the study. For the remainder of the manuscript, we will refer to the signals that we obtained with these procedures as alpha and broadband gamma power, respectively.

To extract the sound intensity of the auditory stimuli, we first computed the square root of the squared amplitude of each stimulus. Similar to the neural signals, we then low-pass filtered the resulting signal at 4 Hz and down-sampled it at 120 Hz.

**Data analyses**

**Spatial analyses**

We first determined which cortical locations were responsive to the auditory or motor tasks, i.e., which locations exhibited higher broadband gamma power during the task period when compared to the baseline period. For the auditory task, we defined the task period as the first 500 ms of auditory stimulus presentation. For the motor task, we defined the task period as the period from −250 ms to +250 ms relative to the button press. For each location and each task, we separately concatenated the task and baseline samples across all trials. We then calculated the coefficient of determination (Spearman’s $r^2$ value) between the baseline and task samples to determine the fraction of the total signal variance that was related to the task. We determined the statistical significance of these $r^2$ values using a permutation test in which we randomly re-assigned the label (task or baseline) to each location. To answer this question, we determined whether the distribution of $r^2$ values was reactive during a particular task (i.e., auditory or motor). For each trial, we then determined the time of the maximum amplitude in the broadband gamma signal, and minimum amplitude in the alpha signal. In this analysis, we used the 200 to 800 ms period after auditory stimulus onset in the auditory reactive locations, and the −300 to 300 ms period relative to the button press in the motor reactive locations. This resulted in one peak time per trial, task and each of the two frequency bands. From the 190 trials, we obtained a distribution for each task and frequency band. After removing outliers ($<5\text{th}$ or $>95\text{th}$ percentiles), we applied a two-sided paired t-test to determine which of the two bands (i.e., alpha or broadband gamma) preceded the other.

To further establish the temporal relationship between alpha and broadband gamma power, we investigated whether the times of the peaks of the responses were related to each other. To do this, we computed the Spearman’s correlation coefficients between the times of the negative and positive peaks of alpha and broadband gamma power, respectively.

**Correlation analyses**

We investigated how the moment-by-moment variations in alpha power, sound intensity and broadband gamma power relate to each other. Specifically, we quantified these relationships by computing the Spearman’s correlation coefficient between alpha power and sound intensity, and between alpha power and broadband gamma power. In this context, it is important to recognize that each location will respond to the auditory stimulation with a different delay. To account for this delay, we temporally aligned the time course of alpha power with the onset of sound intensity and broadband gamma power. We then computed the Spearman’s correlation coefficient $r$ between alpha power and the sound intensity/broadband gamma power time courses for each location. To assess the statistical significance of the obtained observed correlation coefficient, we performed a permutation test in which we circularly shifted the reversed time course of alpha power by a random value and calculated the corresponding Spearman’s correlation coefficient between the obtained time courses. We then computed this randomization step 500 times, generating a distribution of random $r$ values. We considered an observed $r$ value to be significant at the 95th percentile of that distribution ($p < 0.05$, Bonferroni-corrected for the number of auditory locations in each subject). Finally, for each subject, we computed the median delay and $r^2$ across locations displaying a significant correlation value, along with the percentages of those locations.

**Results**

**Spatial distribution of broadband gamma activations**

The locations that were reactive during the auditory and motor tasks for each subject are shown in Fig. 1. In line with previous research, in the human subjects, we found these locations primarily close to superior temporal gyrus (STG) or other perisylvian regions during the auditory task (Crone et al., 2001; Edwards et al., 2009), and close to premotor, motor and somatosensory cortices during the motor task (Crone et al., 1998; Miller et al., 2007). Thus, these results confirm that task-related increases in broadband gamma power can robustly localize functional cortical areas (Brunner et al., 2009; Crone et al., 2011; Miller et al., 2014). In the macaque monkey, these locations were largely concentrated
around STG during the auditory task and around primary motor cortex (F1), dorsal premotor area (F2) and ventral premotor area (F4) during the motor task.

Differential amplitude relationship of broadband gamma and alpha modulations across large-scale cortical systems

To approach the main questions posed in our study, we established the relationship of the amplitude of broadband gamma and alpha responses to the auditory and motor tasks, i.e., across two different large-scale cortical systems. According to our first prediction, we expected to locate decreased alpha power in task-related regions (identified by increased broadband gamma), and increased alpha power in task-unrelated regions. Our results confirm this prediction.

Fig. 2 summarizes the average power in alpha and broadband gamma across all task-related locations during auditory or motor tasks, respectively (auditory task: 200 to 800 ms following auditory stimulus onset; motor task: −300 to 300 ms relative to the button press). These results show that in the auditory locations, the broadband gamma power increase during the auditory task was accompanied by a decrease in alpha power (two-sided t-test; see Fig. 2 for significance values). Such induced depression of alpha power over the auditory cortex is consistent with previous studies reporting a decrease of the so-called tau rhythm centered around 10 Hz during the presentation of auditory stimuli (Tiihonen et al., 1991; Krause et al., 1994; Lehtelä et al., 1997). The same relationship was conserved in the motor locations during the motor task, where broadband gamma power increased and alpha power decreased (two-sided t-test; p < 0.001 for the humans). This finding is also consistent with the well-established event-related suppression of the mu rhythm (8–12 Hz) during motor movements (Pfurtscheller and Berghold, 1989).

These results also demonstrate that the reduction in alpha power in task-related areas was paralleled by an increase in alpha power in the task-related area of the opposite task (two-sided t-test; see Fig. 2 for significance values).
significance values). For example, during the auditory task, alpha power was increased in motor locations both in the human subjects (left panel) as well as the macaque (center panel).

Finally, we were interested whether this observed increase in alpha power would extend to cortical areas that were not involved in any of the two tasks investigated here. To provide a qualitative assessment, for each of the two tasks, we projected all the electrodes of the five human subjects or the macaque onto a three-dimensional template brain and rendered the color-coded alpha power during task onset at each location. The results are shown in Fig. 3A-B. Results indicate that alpha power decreased in the corresponding reactive locations and increased over the majority of the cortical areas not involved in any of the tasks. Notably, we observed large increases in alpha power over the prefrontal and the inferior temporal cortices. In addition, the decrease in alpha power was spatially more restricted than the increase in alpha power (two-sided t-test, p < 0.05 for both tasks): 56% of locations exhibited an increase in alpha power for the human subjects and 53% for the macaque during the auditory task; and 60% for the human subjects during the motor task (see Fig. 3C). These results show that the increase in alpha power occurs in a majority of the locations.

**Temporal relationship of broadband gamma and alpha modulations**

We next determined whether the task-related decrease in alpha power preceded or followed the increase of population-level activity in the task-related locations. According to our second prediction, the task-related decrease in alpha power should lag the increase of population-level activity in the auditory locations during the auditory task, but precede it in the motor locations during the motor task. This would be in line with previous studies that suggested that suppression in the alpha band follows auditory stimulation (Crone et al., 2001). In sum, alpha power lagged broadband gamma power in auditory regions during the auditory task but preceded it in motor locations during the motor task.

![Figure 3](image)

**Fig. 3.** A localized decrease in alpha power in the task-related locations is accompanied by an increase in the majority of the remaining locations. A, B) The topographies show color-coded alpha power averaged during the auditory task for all human subjects (200–800 ms; top left panel) and the macaque (200–800 ms; bottom left panel) and motor task (−300–300 ms; top right panel). Colored circles represent locations that were reactive during the auditory task (blue circles) or the motor task (red circles). AS, arcuate sulcus; CS, central sulcus; IPS, intraparietal sulcus; LuS, lunate sulcus; STS, superior temporal sulcus. C) The bar plots show the percentage of all locations for which alpha activity decreased (blue), increased (red) or did not change (green), for the human subjects during the auditory (left) and motor (middle) tasks, and for the macaque during the auditory task (right). Error bars represent the standard error.
top-down preparation for motor output and during bottom-up responses to an auditory stimulus. In both cases, alpha power modulations index these changes of cortical excitability.

Differential alpha modulations within the auditory system

Finally, if indeed oscillatory activity reflects a general mechanism that gates information flow throughout the cortex, similar task-related patterns of decrease and increase in alpha power should also be present within the small scale of a single cortical system (e.g., the auditory system).

Initial investigations suggested that this was the case. Specifically, while alpha power dropped consistently across the whole auditory system across all different types of auditory stimuli, alpha modulations in individual locations varied substantially across different types of stimuli. Fig. 5 gives exemplary time course of alpha and broadband gamma power over the whole duration of the stimulus for two exemplary locations and four different exemplary stimuli in subject A.

We first investigated how the moment-by-moment variations in alpha power, sound intensity and broadband gamma power related to each other. The results of our correlation analyses showed that alpha power was significantly negatively correlated with broadband gamma power in $69 \pm 7\%$ of the auditory locations (mean $r^2 = 0.13$, $p < 0.05$, Bonferroni-corrected for the number of auditory locations in each subject), and was lagging it by a median of 160 ms. In contrast, alpha power was significantly negatively correlated with sound intensity in only 2% of the auditory locations (mean $r^2 = 0.04$, $p < 0.05$, Bonferroni-corrected for the number of auditory locations in each subject), and lagged it by 170 ms. Because alpha power variations clearly trail broadband gamma power variations, our results suggest that during auditory stimulation, cortical excitability in the auditory locations is predominantly affected by variations in population-level cortical activity rather than variations in stimulus intensity.

To further quantify these modulations of broadband gamma and alpha power, we first sought to determine whether the alpha power decrease in response to each sound affected all locations within the auditory system or was instead limited to a subset of auditory locations. Hence, we computed the percentage of locations that displayed any type of change (i.e., increase or decrease) of alpha power during the auditory stimulation when compared to baseline. To do this, we first concatenated the whole alpha power time courses for stimuli of each category. We then computed the significance of a two-sided t-test on the obtained distributions ($p < 0.05$ Bonferroni corrected for the number of locations). We averaged across subjects the percentages of locations displaying a significant change of alpha power. This revealed that $91 \pm 4\%$ of auditory locations displayed a significant change of alpha power in response to auditory stimulation.

We then investigated how these changes varied with categories. When broken down across the 6 different sound categories, we observed that $68 \pm 15\%$ locations responded with a decrease of alpha power to speech stimuli, $58 \pm 12\%$ to music stimuli, $48 \pm 31\%$ to animal sounds, $35 \pm 25\%$ to engine sounds, $25 \pm 23\%$ to nature stimuli and $21 \pm 22\%$ to the white noise stimulus (one-sided t-test, $p < 0.05$, Bonferroni corrected for the number of locations and sound categories). Bar plots displaying the percentages of locations with a decrease, increase or non-significant change of alpha power for each sound category are presented in Fig. S2.

![Fig. 4.](image) **Fig. 4.** Alpha power suppression lags broadband gamma power in auditory areas during the auditory task, but precedes it in the motor areas during the motor task. The time courses depict the averaged responses in auditory locations during the auditory task in humans (left panel), macaque (middle panel) and in motor locations during the motor task in humans (right panel) for broadband gamma (blue) and alpha (red) bands. Semi-transparent shading represents the standard error. The vertical dashed lines indicate the timing of the positive peaks of the broadband gamma band (blue) and the negative peaks of alpha band (red) for each task.

![Fig. 5.](image) **Fig. 5.** The same auditory location can exhibit drastically different modulations of alpha and broadband gamma power according to the type of auditory stimulus presented. For two different auditory locations in subject A (left and right panels, respectively), the average time courses in response to four different auditory stimuli are shown for alpha and broadband gamma power (red and blue, respectively). Semi-transparent areas represent the standard error.
Next, we identified the locations within the auditory system that responded the most or the least to each particular auditory stimulus. To do this, we averaged the broadband gamma power of each stimulus across trials and time, which yielded one value for each auditory location, subject and stimulus. In each subject and for each stimulus, we identified those locations whose broadband gamma power was within the top and bottom 25% of these distributions (i.e., the most and least reactive auditory locations, respectively). In summary, this procedure identified the sets of locations that responded the most or the least to a particular stimulus. These reactive locations were largely different across stimuli; on average, only 30% of the most reactive locations were common across a pair of stimuli. Finally, we averaged the broadband gamma and alpha power across the most or least reactive locations and across all stimuli and human subjects. Results for human subjects are shown in Fig. 6. Notably, the alpha power decreased in the most reactive locations (two-sided t-test; \( p < 0.001 \)), and was increased in the least reactive locations (two-sided t-test; \( p < 0.05 \)), mirroring the increase versus decrease of alpha power previously observed across the auditory and motor systems. In the macaque, alpha power was higher than baseline in both the least and most reactive locations, which may be attributed to the lack of sustained attention to the auditory stimulus.

Finally, we determined whether these dynamics were also present on a single-stimulus basis. To do this, we determined, for each stimulus, whether the alpha power in the least reactive locations was indeed larger than the alpha power in the most reactive locations: we averaged alpha power across trials, time and the least or most reactive locations for each stimulus and subject. This resulted in two distributions (i.e., one for the most reactive locations and one for the least reactive locations), where each data point represented the alpha power for one stimulus and one subject. A paired t-test between these two distributions revealed that alpha power in the least reactive locations was indeed robustly larger than in the most reactive locations (paired t-test, \( p < 0.001 \)).

Discussion

Summary of results

In this study, we investigated the spatial and temporal dynamics of alpha and broadband gamma power modulation across two distinct systems (auditory and motor) and within the auditory system in both humans and one non-human primate. Our results confirm results from previous studies that showed increased broadband gamma power and decreased alpha power in task-related areas (Crone et al., 2001; Miller et al., 2007; Edwards et al., 2009; Potes et al., 2014). More importantly, our results demonstrated increased alpha power in task-unrelated areas, both across but also within large-scale cortical systems. In addition, the decrease in alpha power in the motor locations preceded gamma increases during the motor movement, but followed it in the auditory locations during the auditory task.

In sum, the results shown in this paper further highlight the critical role of oscillatory modulations in facilitating or inhibiting task-related processing, even within interwoven and spatially restricted networks.

Population-level activity, cortical excitability and the selection of functional networks

Throughout the study, we used modulations of broadband gamma power as a measure of population-level cortical activity. In contrast to the alpha band (8–12 Hz) and the canonical gamma band (30–60 Hz, Fries, 2005, Engel et al., 2001), broadband gamma is widely believed not to be an oscillatory phenomenon. Several studies have demonstrated that modulations in broadband gamma power strongly correlate with the asynchronous firing of neuronal populations in humans (Manning et al., 2009) and non-human primates (Whittingstall and Logothetis, 2009; Ray and Maunsell, 2011). As such, broadband gamma is a direct and robust measure of population-level activity. In addition, broadband gamma was used to localize areas that responded to the auditory and motor tasks. Our set of selected locations in the humans and the macaque monkey were in line with expectations based on prior studies investigating auditory processing (Crone et al., 2001, Edwards et al., 2009, for results in humans; Hackett et al., 1998, Crone et al., 1998, for results in the macaque) and motor movements (Crone et al., 1998, Miller et al., 2007, for results in humans; Rizzolatti et al., 1998, for results in the macaque). Moreover, the locations in the humans co-localized with the hemodynamic responses observed during fMRI studies investigating complex sound processing (Mukamel et al., 2005) and hand movement (Lotze et al., 1999).

Within the auditory network, we found that the responses in broadband gamma power during the auditory task were strongly specific to the type of auditory stimulus presented. Such specificity is in agreement with the compartmentalized representation of the auditory cortex derived from single-neuron studies in non-human primates (Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecker et al., 1995; Rauschecke
In summary, the results of our study showed that alpha power is decreased in task-related areas and increased in task unrelated areas, both across but also within large-scale cortical systems. We also showed that alpha power decreases lag gamma power increases in the auditory system during an auditory task, but precede gamma power in the motor system during a motor task. We conclude that our results further strengthen the view that oscillatory activity shapes task-related cortical networks by differentially biasing cortical excitability. Our results suggest that this mechanism might operate not only across but also within large-scale functional networks, and may be conserved across species. Future research could further determine the generality of this mechanism, establish the causal role of oscillatory activity in this process, and delineate both the origin of oscillatory activity as well as its guiding parameters.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.03.074.

References


Case Report

Intraoperative mapping of expressive language cortex using passive real-time electrocorticography

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A B S T R A C T

In this case report, we investigated the utility and practicality of passive intraoperative functional mapping of expressive language cortex using high-resolution electrocorticography (ECoG). The patient presented here experienced new-onset seizures caused by a medium-grade tumor in very close proximity to expressive language regions. In preparation of tumor resection, the patient underwent multiple functional language mapping procedures. We examined the relationship of results obtained with intraoperative high-resolution ECoG, extraoperative ECoG utilizing a conventional subdural grid, extraoperative electrical cortical stimulation (ECS) mapping, and functional magnetic resonance imaging (fMRI). Our results demonstrate that intraoperative mapping using high-resolution ECoG is feasible and, within minutes, produces results that are qualitatively concordant to those achieved by extraoperative mapping modalities. They also suggest that functional language mapping of expressive language areas with ECoG may prove useful in many intraoperative conditions given its time efficiency and safety. Finally, they demonstrate that integration of results from multiple functional mapping techniques, both intraoperative and extraoperative, may serve to improve the confidence in or precision of functional localization when pathology encroaches upon eloquent language cortex.

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1. Introduction

Precise localization of eloquent cortex facilitates optimal surgical outcomes in patients with tumors, epileptogenic foci, or vascular abnormalities. Operative planning balances removal of pathologic tissue that portends specific symptomatic morbidity with preservation of the eloquent cortex necessary for maintaining an acceptable quality of life. Historically, functional mapping has been conducted primarily with electrical cortical stimulation (ECS) [1,2], but also with functional magnetic resonance imaging (fMRI) [3], extraoperative (chronic) electrocorticography (ECoG) [4–6], electroencephalography (EEG) [7,8], magnetoencephalography (MEG) [9], or positron emission tomography (PET) [10]. Each of these techniques carries inherent limitations that impede widespread application in the approximately 111,000 patients that undergo brain surgery for removal of a brain tumor or epileptogenic focus each year [11].

Electrical cortical stimulation currently stands as the ‘gold standard’ for functional mapping. The technique is procedurally simple and has a relatively low cost. Its most notable limitation remains the extensive amount of time required to conduct the procedure. This issue becomes particularly apparent when ECS is performed under the time constraints of an awake craniotomy in the operating room. In addition, active stimulation of the brain with ECS can provoke after-discharges and seizures. Iatrogenic seizures can increase patient morbidity as well as the duration of mapping.

Functional MRI is another mapping technique that has garnered avid attention recently. Its primary advantage is its noninvasive nature and excellent spatial resolution. However, it only indirectly evaluates neuronal activity by measuring task-related BOLD changes [12,13]. Highly vascularized malignant tumors can alter cerebrovascular hemodynamics and BOLD patterns; hence, they may not accurately reflect eloquent cortical function [14,15]. Furthermore, clinical application of fMRI for real-time mapping is hindered by the extensive time and expertise required for the requisite post hoc analyses.

Electrocorticography, another passive functional mapping modality, is emerging and currently undergoing significant investigation. This technique identifies changes in cortical activity in response to specific
language, motor, or cognitive tasks. Recording these changes in cortical activity does not require application of electrical impulses to induce an effect, thereby eliminating the risk of seizures. Electrocorticography changes in the broadband gamma range (~60 Hz) are of particular relevance in this context of functional mapping [16]. They represent the average firing rate of neurons directly underneath the electrodes [17–19] and are highly task-specific [20]. They have also been shown to correlate well with the blood oxygen-level dependent (BOLD) response detected by fMRI [21]. Recent advances in neural signal acquisition [22,23] and processing [24] have provided the methodological basis for mapping of cortical activity in real time [25]. Despite these advances, ECoG-based mapping predominantly occurs in the epilepsy monitoring unit, remaining as an extraoperative endeavor. With few exceptions [26,27], the practicality and potential value of ECoG-based mapping in the operating room remains largely unexplored, particularly with investigation using high-resolution recordings. In this case report, we test the feasibility of intraoperative mapping using real-time ECoG.

In summary, accurate and practical functional mapping in the operating room still faces challenges in contemporary practice. Mapping based on ECoG promises rapidity, a high spatial specificity, and no increased morbidity. Combining data obtained from ECS, ECoG, and fMRI can provide complementary information that may be useful for surgical planning of complex cases. In the present case, we mapped expressive language function with ECoG using a high-density grid during an awake craniotomy. We confirmed the location of frontal language areas extraoperatively using fMRI, standard ECS mapping, and ECoG mapping. We integrated and visualized the results, producing highly detailed functional maps. These composite results suggested qualitative concordance of eloquent expressive language cortex across the different mapping modalities.

2. Case report

2.1. Initial presentation

The patient was a 33-year-old male who presented after a motor vehicle accident while experiencing a first-time seizure. The patient had a computerized tomography (CT) scan as part of his initial evaluation that suggested a hypodensity in the left frontal lobe. Magnetic resonance (MR) imaging revealed a nonenhancing left frontal mass (Fig. 1, left), and MR spectroscopy characteristics supported a low-to-medium grade tumor. Given the anatomic location of the tumor’s proximity to presumed Broca’s area, the patient underwent fMRI and diffusion tensor imaging (DTI). The fMRI confirmed the close relationship of the tumor to Broca’s area (within 3–5 mm) with verb generation and object naming tasks (p < 0.05, family-wise error correction) (Fig. 1, right).

The patient did not have any further seizures after the initiation of levetiracetam, and he remained neurologically intact without any focal deficits or aphasia. To comprehensively evaluate expressive language cortex for an optimal postoperative outcome, the patient elected to pursue a two-staged brain mapping procedure with the use of subdural grids and ECS. Prior to surgery, the patient had neuropsychological testing for baseline evaluation using the Wechsler Adult Intelligence Scale WAIS-IV [28]. The patient gave informed consent for a protocol that was reviewed and approved by the institutional review board of Albany Medical College as well as the US Army Medical Research and Material Command.

2.2. Stage 1 operation

The patient underwent implantation of an 8 × 8 cm silicon subdural grid embedded with 64 platinum iridium electrodes of 4 mm diameter (2.3 mm exposed) and interelectrode distance of 1 cm (PMT, Chanhassen, MN) (Fig. 2, panels A and B). Contacts 1, 2, and 9 were removed for better contour along the cortical surface. Contact 57 was located most anteriorly, contact 64 most superiorly, and contact 8 most posteriorly (Fig. 3). A four-contact electrode strip was placed on the skull to provide a ground for the clinical monitoring system. The patient tolerated the first stage well and was connected to an Nihon-Kohden Neurofax video-EEG monitoring system (Tokyo, Japan) that continuously recorded ECoG signals as well as accompanying clinical behavior. To ensure integrity of clinical data collection, passive splitter connectors simultaneously provided ECoG signals to eight optically isolated 16-channel g.USBamp amplifier/digitizer units (g.tec, Graz, Austria) with signal sampling at 1200 Hz. Clinical review of ECoG signals identified frequent left frontal spikes and spike and wave discharges at contact 23.

2.3. Clinical mapping

On postoperative day 2, the patient underwent extraoperative functional cortical mapping in the epilepsy monitoring unit (EMU) with ECoG and ECS procedures. For ECoG mapping, the broadband gamma signal at each contact location was measured and compared between rest and task epochs to establish the statistical difference across these tasks (see [29] for detailed methodology). The patient first rested...
quietly for six minutes to establish a model of baseline ECoG activity. The patient then performed several repetitive motor and language tasks as instructed by visual cues: 1) solve Rubik’s cube, 2) shrug shoulders, 3) stick out tongue, 4) purse lips, 5) listen to a narrative, 6) generate verbs, and 7) imagine generating verbs. This ECoG paradigm identified electrode contacts 11 and 12 (Fig. 3) as expressive language nodes within a few minutes.

For the ECS procedure, we used a digital Grass S12X stimulator with built-in stimulus isolation and constant current circuitry [Grass Technologies, Warwick, RI] to stimulate pairs of electrodes using a pulse duration of 0.3 ms, variable frequencies between 20 and 50 Hz, current ranging from 1 to 15 mA, and train durations of 5 s. Bipolar and monopolar modalities were assessed with increasing current until after-discharges or a functional response was elicited, or the maximum amount of current was reached at 15 mA. Stimulation of contacts 11 and 12 with 10 mA at 20 Hz rendered complete speech arrest, indicating eloquence. These nodes were confirmed on four separate occasions throughout the procedure. Oral motor function was also identified. An electrographic seizure was elicited with stimulation of contacts 23 and 41 during mapping; the patient was treated with 2 mg IV lorazepam, 1000 mg IV levetiracetam, and 500 mg fosphenytoin. Further mapping was delayed for approximately 90 min due to the stimulus-induced seizure and subsequent postictal period.

2.4. Stage 2 operation

Five days after the initial subdural grid implantation, the patient returned to the operating room for the second stage. Once the previous craniotomy flap was reopened and the cortical surface was exposed with good hemostasis, the standard subdural grid was replaced with a high-density 64-contact silicon grid (PMT Corp., Chanhassen, MN), measuring 2.5 × 2.5 cm embedded with platinum iridium electrodes of 2 mm diameter (1 mm exposed) and with an interelectrode distance of 3 mm (Fig. 2, panels C and D). To further refine the boundary of expressive language function, this high-density grid covered only the language cortex previously identified by extraoperative ECoG and ECS mapping. The patient was reversed from anesthesia for awake passive mapping. Within minutes, intraoperative ECoG mapping using verb generation and word repetition identified the most significant ECoG changes at locations corresponding to contacts 11 and 12 of the original standard subdural grid. These locations were outlined for preservation. The patient tolerated the procedure very well and was induced back under anesthesia for the remainder of the surgery.

2.5. Postoperative course

The patient experienced an excellent recovery and had very mild issues of transient confusion. Permanent pathology revealed focal anaplasia WHO III in the setting of diffuse fibrillary astrocytoma WHO II. The patient had adjuvant chemoradiation therapy.
neuropsychological testing (at 1 year) demonstrated a 28% decline in verbal fluency and a slight decrement in recent memory/new learning (although still within high average range). Surveillance imaging over 28 months has yet to demonstrate recurrence.

2.6. Coregistration of mapping techniques

The main results presented in this case report are the mapping results from fMRI, ECS, and extra- and intraoperative ECoG. They are summarized in Fig. 4. For fMRI data acquisition, preoperative scans were acquired on a Philips Ingenia 3 T scanner with an echo planar imaging (EPI) sequence (80 scans, acquisition voxel size 3 mm isotropic, repetition time (TR) 3 s, echo time (TE) 30 ms, flip angle 90°, field of view (FOV) 237 mm). Functional MRI data were preprocessed and analyzed using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). Images were realigned and coregistered with an anatomical scan using normalized mutual information [30]. Statistical analyses were performed on a single-subject basis, and therefore, no smoothing was applied. A general linear model was estimated with one regressor for verb generation (a 15 s box car for verb generation blocks convolved with a standard hemodynamic response function); data were corrected for low frequency drifts by a 128 s high pass filter and corrected for serial correlations with a first-order autoregressive model. Functional MRI results were rendered on the surface of the cortex (Fig. 4, left) in similar manner as before [21,31], plotting any activation up to 8 mm below the surface. Functional MRI activity was plotted with a threshold of t(150) > 5.51, p < 0.05.

We created a three-dimensional patient-specific cortical surface brain model by submitting the preoperative high resolution MRI scans to Freesurfer (http://surfer.nmr.mgh.harvard.edu). We identified the stereotactic coordinates of the standard subdural grid using SPM8 software (http://www.filion.ucl.ac.uk/spm/) and custom MATLAB scripts (The MathWorks Inc., Natick, MA), which coregistered the MRI scans with the postoperative CT scans. The high-density subdural grid contacts were coregistered with those of the standard subdural grid using scalp fiducial markers, an intraoperative neuronavigation system (Brainlab AG, Feldkirchen, Germany), and novel custom software [32]. The electrode locations were then projected onto a three-dimensional brain model and custom NeuralAct [33] software (Fig. 4, right) to render activation maps of corresponding ECoG activity.

3. Discussion

This case report represents the first application of high-resolution ECoG-based mapping in the operating room and demonstrates one of the most comprehensive examples of multimodal functional mapping to date. We mapped expressive language function in a patient using four different modalities: ECS, extraoperative ECoG, intraoperative ECoG, and fMRI. Recent technological advances enabled us to combine the results into an informative display that facilitated comparison across modalities. This comparison suggested qualitatively concordant functional language maps. In particular, ECS and extraoperative ECoG delineated identical critical language nodes using a standardized grid coordinate system. The same locations were confirmed with intraoperative high-resolution ECoG. Thus, our results highlight the value of passive ECoG-based mapping in the extraoperative as well as the intraoperative environment.

Electrical cortical stimulation currently represents the “gold standard” for functional cortical mapping even in the absence of standardization and validation by randomized controlled trials. Given the recent technological advances, ECoG-based mapping offers the potential for similar precision but with a greater safety profile, better patient

![Fig. 4](image_url). (Top left) Functional MRI showing increased BOLD activity (shown in yellow and orange) in Broca’s area, as well as auditory/Wernicke’s area, precentral gyrus, supplementary motor/premotor cortex and prefrontal cortex. ECS (white circles) caused speech arrest in Broca’s area, adjacent to increased BOLD activity. (Top right) Small black dots represent electrode contacts of the standard extraoperative subdural grid. Results from extraoperative ECoG-based functional mapping (shown in green) demonstrated increased activity in Broca’s area, precentral gyrus, supplementary motor/premotor cortex and postcentral gyrus. (Bottom) Results from intraoperative ECoG-based mapping are shown in red. The diameter of each circle is proportional to the activity under the corresponding electrode contact. The largest circles identify locations that are qualitatively concordant with those from intraoperative ECoG-based and ECS mapping. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
tolerability, and faster data acquisition time. Several studies have compared the mapping results of ECoG with those of ECS, reporting sensitivities ranging from 0.43–1.0 and specificities of 0.72–0.94 for sensorimotor mapping [4,5,16,29,34,35]. However, we attribute this decline in verbal outcomes for patients with brain tumors who undergo surgery [30–32] to the high-density grid. This work was supported by the NIH (EB006356 (GS) and W911NF-14-1-0440 (GS)) and Fondazione Neurone.

As with ECS and ECoG, the concordance between ECS and fMRI varies, with reported sensitivity and specificity measurements for language mapping varying between 59%–100% and 53%–97%, respectively [40–45]. Our case report demonstrated strong concordance between fMRI, ECoG, and ECS for the language sites identified on the pars opercularis but not as well for the language sites on the pars triangularis. Multiple issues can influence this mismatch on the pars triangularis. First, we used a conservative fMRI threshold, and only the most robust sites reached this threshold in the analysis (see Supplementary Fig. 1 that demonstrates BOLD activation in the pars triangularis when a lower threshold is used). Second, blood flow artifacts can obscure the fMRI signal, making it more difficult to measure in certain regions compared with others [14,15]. Lastly, previous fMRI studies often used a battery of language tasks to localize language areas [46], whereas we only evaluated verb generation and word repetition. A more comprehensive battery across modalities may provide better-matched results.

To our knowledge, this is the first instance of using a high-density subdural grid in the intraoperative environment for language mapping. With its superior spatial resolution, we were able to create a highly refined boundary between the tumor and expressive language cortex. These results are encouraging, but important questions are not yet resolved. How does this improved spatial resolution translate into improved patient outcomes? What is the optimal electrode diameter size and interelectrode distance for best spatial resolution that will provide nonredundant recordings [47–49]? At what point will the spatial resolution of high-density subdural grids exceed the operative resolution of neurosurgery with available techniques?

Even with mapping of Broca’s area and the specific language nodes, our patient still suffered a 28% decline in verbal fluency at one year. Can we attribute this decline in verbal fluency as a postoperative deficit (as seen in 3–13% of patients with brain tumor who undergo surgery [50–52]) or to that of radiation necrosis potentiated by chemotherapy (that afflicts 2.5–5% of patients [53])? Our patient had undergone formal neuropsychiatric evaluation. Functional limitations or clinical observations (as used in some other studies) would likely have missed these subtle changes.

Functional language mapping during an awake craniotomy remains a challenge. Here, we demonstrate that functional mapping with high-resolution electrocorticography can readily be performed in the intraoperative environment and that its results appear qualitatively concordant with ECS. At this juncture, there is no universal standard of care for functional language mapping. Taking into account the unique strengths and limitations of each modality, no one technique is clearly superior to the others. The rate of investigated functional modalities for functional brain mapping is at its zenith, with the impetus to improve clinical outcomes for patients with epilepsy, tumors, or vascular malformations.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejbar.2016.03.003.

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Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Case Report

Electrocorticographic mapping of expressive language function without requiring the patient to speak: A report of three cases

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ABSTRACT

Objective: Patients requiring resective brain surgery often undergo functional brain mapping during perioperative planning to localize expressive language areas. Currently, all established protocols to perform such mapping require substantial time and patient participation during verb generation or similar tasks. These issues can make language mapping impractical in certain clinical circumstances (e.g., during awake craniotomies) or with certain populations (e.g., pediatric patients). Thus, it is important to develop new techniques that reduce mapping time and the requirement for active patient participation. Several neuroscientific studies reported that the mere auditory presentation of speech stimuli can engage not only receptive but also expressive language areas. Here, we tested the hypothesis that submission of electrocorticographic (ECoG) recordings during a short speech listening task to an appropriate analysis procedure can identify eloquent expressive language cortex without requiring the patient to speak.

Methods: Three patients undergoing temporary placement of subdural electrode grids passively listened to stories while we recorded their ECoG activity. We identified those sites whose activity in the broadband gamma range (70–170 Hz) changed immediately after presentation of the speech stimuli with respect to a prestimulus baseline.

Results: Our analyses revealed increased broadband gamma activity at distinct locations in the inferior frontal cortex, superior temporal gyrus, and/or perisylvian areas in all three patients and premotor and/or supplementary motor areas in two patients. The sites in the inferior frontal cortex that we identified with our procedure were either on or immediately adjacent to locations identified using electrical cortical stimulation (ECS) mapping.

Conclusions: The results of this study provide encouraging preliminary evidence that it may be possible that a brief and practical protocol can identify expressive language areas without requiring the patient to speak. This protocol could provide the clinician with a map of expressive language cortex within a few minutes. This may be useful as an adjunct to ECS interrogation or as an alternative to mapping using functional magnetic resonance imaging (fMRI). In conclusion, with further development and validation in more subjects, the approach presented here could help in identifying expressive language areas in situations where patients cannot speak in response to task instructions.

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1. Introduction

Language is crucial for meaningful interaction and communication. Key language abilities, such as perception and production, are governed by multiple regions in the brain. These abilities can quickly become jeopardized in people with brain tumors, epilepsy, or other structural abnormalities. Many of these patients require resection of pathological tissue near eloquent language areas to prolong or improve quality of life. Inevitably, such resection carries inherent risks to language function. Thus, functional language mapping for precise localization of eloquent language areas is necessary for achieving optimal surgical outcomes in such patients.

Functional language mapping for perioperative planning in individual patients is of utmost importance given the high variability in structural anatomy and function across individuals [1]. Most typically, language mapping is achieved using electrical cortical stimulation (ECS) mapping. While ECS is widely considered the gold standard [1,2], it does
have noteworthy limitations. First, a thorough ECS interrogation is very time-consuming. Second, ECS increases the risk of after-discharges or seizures that result from “active” stimulation of the cortex using electrical impulses. Finally, ECS can be difficult to accomplish in the subset of pediatric patients and patients with psychiatric and cognitive comorbidities. These issues have prompted recent and increasingly encouraging investigations suggesting that “passive” methodologies, such as electrocorticography (ECoG) or functional magnetic resonance imaging (fMRI), may prove useful for functional mapping and may have distinct advantages in efficiency, morbidity, or the range of patients that can benefit from it [3–11].

Unfortunately, traditional mapping of expressive language function with any of these existing techniques carries the additional requirement that patients actually speak, i.e., fully participate in specific tasks such as verb generation, object naming, or counting. This requirement currently precludes the use of these techniques in many patients, such as those with aphasia or cognitive deficits or very young patients.

Together, these limitations and requirements preclude or greatly impede functional mapping of expressive language areas in certain clinical circumstances (such as during awake craniotomies) or with certain populations (such as pediatric patients). Hence, it is desirable to have access to a technique that does not electrically stimulate the brain and that eliminates or reduces the requirement for patient participation. Such a technique may eventually reduce ECS mapping time by guiding the clinician with a preliminary map of eloquent expressive language areas. Identification of eloquent expressive language cortex without requiring the patient to speak is supported by several findings. Previous fMRI studies reported activations of the left (12,13) and bilateral (14–17) inferior frontal cortex while subjects listened to speech stimuli but did not perform any overt speaking task. In addition, Suarez et al. demonstrated using fMRI that a passive listening task recruited similar cortical areas as a verb generation task in a cohort of 15 pediatric patients [17]. However, fMRI is still expensive and requires substantial expertise that is not available in all centers, and its reliability in the context of functional mapping is still uncertain [18,19]. Thus, to date, fMRI-based mapping has not achieved widespread acceptance.

Electrocorticographic recordings also provide opportunities for functional mapping in the context of mapping of motor [23,20–22] or language [3,20] function, in pediatric patients [23], and in the operating room [3,6]. Together, these studies demonstrated that ECoG-based mapping can be achieved in real time (i.e., while signals are being recorded), does not require expertise in signal analysis, and can produce clinically useful results that can readily be compared with ECS results in a few minutes. However, evidence for its utility in identifying expressive language without subject participation was lacking. Indeed, only two previous neuroscientific ECoG studies reported activations in the inferior frontal cortex during a passive listening task [24,25], but they did not determine whether these activations could be identified using a common analysis approach, establish the concordance between locations resulting from ECoG- and ECS-based mapping, or discuss the feasibility of such passive mapping ECoG protocol in the context of presurgical or intraoperative mapping. The present report provides initial evidence on this topic from three subjects.

2. Methods

2.1. Patients

Three subjects (A–C) participated in this study. All three subjects were patients at Albany Medical Center (Albany, New York). Subject A was diagnosed with a low-grade glioma in the left frontal lobe after presenting with new-onset seizures. Subjects B and C suffered from intractable epilepsy. All subjects underwent temporary placement of subdural electrode grids to localize seizure foci and eloquent cortex prior to surgical resection. The subjects’ clinical profiles are summarized in Table 1. The electrode grids were approved for human use (Ad-Tech Medical Corp., Racine, WI and PMT Corp., Chanhassen, MN) and covered different areas within frontal, temporal, and parietal lobes of the left hemisphere. Most importantly, all three subjects had coverage of frontal lobe language areas, and two of the three (subjects B and C) also had coverage of temporal lobe language areas. Electrodes consisted of platinum–iridium discs (4 mm in diameter, 2.3–3 mm exposed), were embedded in silicone, and were spaced 6–10 mm apart. The total number of implanted electrodes was 61, 98, and 134 in subjects A–C, respectively. Following subdural grid implantation, each subject had postoperative anterior–posterior and lateral radiographs, as well as computer tomography (CT) scans to verify grid location. Preoperative language lateralization (IL) had been assessed previously with fMRI in subject A and with WADA testing [26] in subjects B and C. Based on these evaluations, language was lateralized to the left hemisphere in all three subjects. All subjects signed informed consent to participate in the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command.

2.2. Data collection

Once subjects recovered postoperatively, we recorded ECoG signals at the bedside using a general-purpose BC2000 software [27,28], which controlled eight 16-channel g.USamp biosignal acquisition devices (g.tec, Graz, Austria). To ensure integrity of clinical data collection, a connector split the electrode cables into two separate sets. One set was connected to the clinical monitoring system, and another set was connected to the g.USamp acquisition devices. The ECoG signals were amplified, digitized at 1200 Hz, and stored by BC2000. We used electrode contacts distant from epileptogenic foci and areas of interest for reference and ground.

2.3. Anatomical mapping

We created 3D cortical brain models for each subject by submitting preoperative high-resolution magnetic resonance imaging (MRI) scans to Freesurfer software (http://surfer.nmr.mgh.harvard.edu/). We coregistered MRI scans with postoperative CT images using SPM software (http://www.fil.ion.ucl.ac.uk/spm/) and identified the stereotactic coordinates of each grid electrode using custom MATLAB scripts (The MathWorks Inc., Natick, MA). Finally, we visualized the cortical surface of each subject and ECoG grid locations using NeuralAct software [29].

2.4. Task and stimuli

In our study, we asked the subjects to listen to four short stories narrated by a male voice (stimulus duration: 17.15–55.70 s; interstimulus interval (ISI) of 10 s) which were part of the Boston Aphasia Battery [30]. The stimuli were digitized at 44.1 kHz in waveform audio file format and binaurally presented to each subject using in-ear monitoring earphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Hand</th>
<th>LL Seizure Focus</th>
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<td>A</td>
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Table 1  Clinical profiles of the 3 patients. “LL” reflects language lateralization.
environmental noise). The sound volume was adjusted to a comfortable level for each subject. The subjects did not perform any overt task (such as repeating words and generating verbs in response to the words they heard).

2.5. Feature extraction

We identified ECoG activations by detecting task-related changes in the broadband gamma (70–170 Hz) band. Activity in this band has been shown to be related to the average firing rate of neuronal populations directly underneath an electrode [31–33]. A large number of studies have shown that broadband gamma activity increases reliably in task-related cortical areas [20,34], including locations traditionally thought to be active during speech perception [24,35,36].

To identify those locations that responded to auditory stimulation, we first removed channels that did not contain clear ECoG signals (e.g., ground/reference channels, channels with broken connections, or channels corrupted by environmental artifacts or interictal activity). Of a total of 61, 98, and 134 channels, this left 59, 79, and 132 channels for subjects A–C, respectively, which we submitted to subsequent analyses. In these analyses, we high-pass filtered the signals at 0.1 Hz to remove drifts and re-referenced the signals to a common average reference (CAR) montage. We band-pass filtered the results in the broadband gamma band using a Butterworth filter of order 16. We then obtained the power of these signals by computing the square of the analytical signal of the Hilbert transform, followed by a low-pass filter at 4 Hz and down-sampling to 120 Hz. Finally, we normalized the resulting broadband gamma power estimates by subtracting from them the signal mean calculated from a baseline period (−6 to −0.5 s prior to the onset of the auditory stimulus) and by dividing them by the standard deviation of the signal during the baseline period.

2.6. ECoG-based mapping of expressive language cortex

We determined those locations whose ECoG broadband gamma activity following onset of the auditory stimulus (i.e., the response period) was different from that during the baseline period. Several studies have shown that, in receptive auditory areas, broadband gamma activity reliably tracks the time course of the envelope of the intensity of the auditory stimulus [37,38] or speech stimulus [39]. A few isolated reports documented discrete and brief broadband gamma activations in inferior frontal cortex after the onset of an auditory speech stimulus [24,25] that occurred after the activations in receptive auditory areas [25]. Based on these reports, we defined the response period as 250–750 ms following the onset of the auditory stimulus. Then, for each location, we determined the magnitude of the change in ECoG broadband gamma power that was related to auditory stimulation by calculating the coefficient of determination (Pearson’s \( r^2 \) value). Finally, we determined the statistical significance of each \( r^2 \) value, i.e., the probability that ECoG broadband gamma samples differed in amplitude between the response and baseline periods, using a permutation test. In this test, we cut the ECoG broadband gamma power time courses into blocks of 500 ms (thereby preserving the autocorrelation of the signal), randomly permuted the resulting blocks, and finally calculated the corresponding random \( r^2 \) value. We repeated the permutation step 1000 times, thus generating a distribution of 1000 random \( r^2 \) values at each location. We considered \( r^2 \) values to be significant at the 95th percentile of that distribution (\( p = 0.05 \), Bonferroni-corrected for the total number of electrodes in each subject). The result of this procedure was a set of locations whose ECoG broadband gamma activity was significantly different between the baseline and the response periods and, hence, responded to the speech stimuli. Among the resulting locations, we identified those that were situated within inferior frontal cortex. This included all electrodes whose Talairach coordinate was within \( x = −28 \) to \( −55 \), \( y = −8 \) to \( +34 \), and \( z = 0 \) to \( +28 \), consistent with previous observations [41].

2.7. ECS-based mapping of expressive language cortex

Standard electrocortical stimulation mapping of expressive speech was performed extraoperatively for clinical purposes. The subjects took part in two simple tasks commonly used for this purpose: a picture-naming task, during which subjects were asked to verbally name sequentially presented pictures of simple objects and a verb generation task, during which subjects had to verbally generate verbs associated with simple nouns presented auditorily. Different electrode pairs were stimulated to establish whether a given pair induced a disruption of expressive language function, e.g., speech arrest or hesitation. Stimulation intensity typically started at 2 mA and was increased in incremental steps of 2 mA until the neurologist observed clinical effects or after-discharges or reached the 10 mA threshold.

3. Results

The main results of our study are presented in Fig. 1. This figure highlights those locations that were identified by our analyses of the ECoG signals corresponding to the presentation of the speech stimuli (filled circles) and locations that produced arrest of expressive language function using ECS mapping (yellow circles).

Locations identified by ECoG mapping included the expected locations (highlighted by gray-filled circles) in superior temporal gyrus and/or perisylvian areas (all subjects) as well as in premotor and/or supplementary motor areas (subjects A and C) [28]. Consistent with previous observations (see Fig. 8 in [18]), our method also identified responsive locations on or close to superior precentral gyrus (Patient C). Most relevant in the context of the present study, our ECoG-based mapping identified locations (highlighted by blue-filled circles) in inferior frontal cortex (pars triangularis and/or pars opercularis) in all three subjects. Fig. 1C also presents exemplary time courses of ECoG broadband gamma activity in Patient C.

Electrical cortical stimulation mapping identified 1–2 locations in which stimulation produced expressive language arrest in each subject (yellow circles). These locations were also located in or around pars triangularis and pars opercularis. The ECS-positive sites overlapped with the sites identified using ECoG or were located no more than one contact away.

4. Discussion

In our study of three patients with chronically implanted subdural electrode grids, we provide initial evidence that it is possible to use passively recorded ECoG in response to presentation of speech stimuli to identify not only locations in the receptive language network that are located primarily in the temporal lobe but also locations within the expressive language network in the inferior frontal cortex.

With further refinement of the protocol and validation in more subjects, the passive mapping approach described here could lead to a mapping method that may have important clinical implications. The ability to map expressive language cortex with greatly reduced needs for patient participation expands the utility of functional language mapping. Specifically, it enables functional mapping of expressive language in patients who are unable to cooperate productively such as pediatric populations or patients suffering from aphasia or psychiatric and cognitive comorbidities. We envision passive language mapping using ECoG to either complement existing ECS or fMRI mapping protocols or provide an alternative when other expressive language mapping techniques are inadequate. The ECoG passive mapping may also have distinct advantages in the time-limited settings of the intraoperative environment. A preliminary map of eloquent expressive language cortex could inform ECS mapping, likely resulting in reduced ECS mapping time and thereby diminishing the risks of patient morbidity, discomfort, and iatrogenic seizures. This would prove extremely useful in an intraoperative decision-making situation. Recent studies already
demonstrated the feasibility of intraoperative real-time mapping of motor [3,5] and language [3,6,42] mapping using acutely placed subdural grids.

4.1. Variable congruency between ECS and ECoG

One important general question that remains to be answered is the reason for the variable congruency between ECS and passive ECoG in the context of language mapping. Using traditional ECoG-based mapping tasks (such as verb generation, picture naming, and passive listening), previously reported concordance rates between ECoG and ECS range from 38%–89% in sensitivity and from 48%–92% in specificity [4, 23,43,44]. This variability in concordance reported in the literature can be attributed to several factors. These include the different language tasks used with each modality [44,45]. Other potential explanations for the discrepancies between ECS and ECoG involve the statistical issues that necessarily result from the comparison of the single-electrode ECoG method with the pair-wise ECS method [2,45] and the fundamental difference between a lesion-based model approach versus a task-based physiologic approach [34,43]: while ECoG should identify all locations at which neuronal populations subserve the specific function, ECS will only identify the (potentially small) subset of those locations that completely disrupt function. Thus, ECoG can be expected to define a larger area for preservation and underestimate the margin for safe resection. In this context, it is worth noting that patients have been reported to have postoperative language deficits after resection of an ECoG(+) /ECS(−) node [4,23,43,44,46,47]. In a study of 77 patients, postoperative language deficits could be predicted by the number of ECoG(+) language nodes resected [48]. At present, most resections are based primarily on ECS results even though ECS has never been validated in randomized, clinical trials [2]. This reality implies that, with continued refinement and validation, the ECoG method may play an even larger role in presurgical functional mapping in the future. At the same time, without additional information, we currently do not suggest replacing exhaustive ECS mapping but rather argue that ECoG-based mapping provides useful and complementary information.

4.2. Additional evidence from other studies supports the mapping of expressive language function without requiring the patient to speak

Another critical question raised by the present study is to what extent the encouraging results presented here generalize to a larger number of patients. For two reasons, we are optimistic that the results in a larger number of patients will echo the initial results reported here. First, several groups have reported activation of the inferior frontal gyrus in response to presentation of passive speech stimuli [12–15,17,49]. Mazoyer et al. first demonstrated activation of the left inferior frontal gyrus on positron emission tomography (PET) scans in 16 subjects while listening to lists of words and stories [12]. Several fMRI [13–15,17,49] and ECoG [24,25] studies have replicated these results using similar tasks. Furthermore, it is well known that the blood-oxygen level-dependent (BOLD) signal changes detected using fMRI correlate very well with the broadband gamma increases in ECoG [50–56], which are the basis of ECoG-based functional mapping. Second, recent evidence indicates that ECoG-based mapping can identify locations in expressive language areas when sites in receptive language areas are stimulated using electrical stimulation (corticocortical evoked potentials (CCEPs)) [57–60]. For example, Matsumoto et al. [57] described the technique of delivering a single pulse electrical stimulation in the inferior frontal language area and recording a cortical evoked potential in the temporal–parietal area, establishing structural neuronal connectivity between the two functional regions. In a smaller subset of patients, they were able to elicit CCEPs in the inferior frontal and basal temporal regions with stimulation of the temporal–parietal language area. This bidirectional connectivity is likely mediated at least in part by the arcuate fasciculus, although the anatomical distribution of the arcuate fasciculus may be more complex than historically assumed [61–64]. More generally, the language network connectivity model appears to be much more complex than initially believed, with
an interplay of numerous cortical regions and white matter tracts [62,65–67].

4.3. Study limitations

While our initial results are encouraging, different circumstances could temper the significant positive implications of expressive language mapping using passive stimuli. When applied in intraoperative scenarios, different surgical realities (such as intermittent irrigation on the subdural grid, cable adjustment, variable clinical or cognitive status of the patient) may lead to lower signal-to-noise ratio and a resultant decrease in ability to detect task-related ECoG changes. The duration of mapping may be increased if the grid requires repositioning with reinitiation of tasks. Furthermore, it is possible that passive engagement of expressive language function may not elucidate the whole expressive language network. Finally, the current study is only reporting results for expressive language function may not elucidate the whole expressive language network. The duration of mapping may be increased if the grid requires repositioning with reinitiation of tasks. Furthermore, it is possible that passive engagement of expressive language function may not elucidate the whole expressive language network. Finally, the current study is only reporting results for functional mapping of expressive language function that could greatly reduce the need for subject participation. With further refinement and validation, the approach described here may lead to a simple, easy-to-use protocol that would simultaneously identify receptive and expressive language areas for surgical planning. This protocol would be widely applicable in a significantly greater number of patients. Finally, because our approach does not require the patient to speak, it opens up the possibility for applying it to patients under general anesthesia. Thus, this approach has the potential to completely revolutionize functional language mapping in neurosurgery; the initial results presented here clearly encourage further investigation.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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