University of Nevada, Reno

PASSIVE FUNCTIONAL MAPPING OF BRAIN LANGUAGE AREA AND MEASURING DEPTH OF ANESTHESIA USING ELECTROCORTICOGRAPHY

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by

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Abstract

Every year, thousands of patients undergo craniotomy as an indispensable operation for their treatment procedure. These individuals are consisted, and not limited to those who suffer from brain lesions, tumors or intractable pharmaco-resistant epilepsy. Given the complicated anatomical structure of human brain and considering the fact that every single spot on the cortex is responsible to support vital sensory and cognitive functions, minimizing collateral damage to brain tissue located in the vicinity of the surgical region and consequently reducing post-surgical complications, is considered as an ultimate goal by neurosurgeons. Although many techniques have been developed and utilized to create pre-surgical passive brain mapping which provides patient-specific functional information, direct Electro-Cortical Stimulation (ECS) is considered the most standard technique. Although ECS is proved to be a useful practical method for functional mapping, yet applying it, not only requires a great deal of experience, but also is usually followed by some complications. Specially in the case of epileptic patients who need to be awakened during the surgery in order to perform a cognitive task, applying ECS could be very problematic, since it significantly increases the chance of seizure. In this study, we develop a novel method based on Electrocardiography (ECoG) in order to do passive functional mapping under anesthesia. This approach which has been successfully utilized on about 20 patients, includes recording ECoG signals while performing a simple auditory task. The fact that this paradigm does not require attentive participation of patients, makes it possible to be performed under anesthesia. Moreover, this procedure results in calculating a quantitative index for measuring depth of anesthesia which could potentially be used alongside with BiSpectral Index (BIS).

Acknowledgment

First and foremost, I would like to thank my adviser Dr. Yantao Shen, for directing my research over the course of the last two years. I would also like to express my appreciation to Dr. Gerwin Schalkthe deputy director in National Center for Adaptive Neurotechnologies at Wadsworth Centerfor inspiring and encouraging me to complete this work. In addition, I would like to thank New York State Department of Health as well as Albany Medical Center for providing technical and medical support to conduct this research. Last but not least, I would like to thank my committee members, Dr Parvin, Dr. Xu, and Dr. Jiang for their time and valuable comments.

Dedicated to

MY BELOVED PARENTS

&

DEAR ERFAN

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Chapter 1

Introduction

Without a doubt, the neural network in human body and in particular human brain, is one of the most complicated structures in the whole universe. Human brain is a non-linear, self-organizing, self-assembled complex system, which despite its apparent tranquility, is dynamically involved in processing the receiving information from both internal and external world. The brain continues its perpetual activities, even in the absence of environmental and body derived stimuli. What we experience as the external world, is the result of extensive collaboration of different part of this self-sustained system to process enormous amount of data from all different sources. Learning, memorizing, reasoning, thinking and in general every single action that distinct us from other species and makes us human is due to our brain's capability in performing tremendous amount of computation in the fastest and the most accurate way. The non-linear chaotic nature of the brain makes it impossible to understand or predict its behavior solely by adding the outcome of its lower level constituents. In other words, although the local agents do cause the behavior of the whole, the overall outcome is far more complicated than a simple summation of its elements. The relation between the brain as a whole and its constituents can be described as a non-symmetrical yet reciprocal supervising process. What we know about human brain today is the result of decades of hard and non-stop endeavor done by neuroscientists, experimental psychologists, and many other scientists from different fields who have been collaborating closely to shed light on different aspects of our brain. This include both physiological structure and mechanisms that govern the cognitive functionality of the brain. Despite all the efforts that have been made to solve our brain's puzzle, there are still many unknowns about this mysterious system, yet to be discovered.

Among numerous research which are being done in the field of neuroscience deciphering the functional role that each part of our brain plays while performing a cognitive task, not only holds great promise for the ultimate understanding of its mechanism, but also could have a significant practical importance. Functional mapping in particular is at the center of attention of the neurosurgeons who perform brain surgeries. Every year, thousands of patients undergo craniotomy as a critical part of their treatment procedure. Craniotomy is a surgical operation in which surgeons remove a part of skull in order to have direct access to brain tissue. This operation is performed on patients who are suffering from traumatic brain injury (TBI), brain lesions, intractable epilepsy, cerebellar tumor or Parkinson's disease. Most of these operations, involve resecting brain tissue and/or removing a tumor. Given the fact that every known part of the brain is vital in running a related task, post-surgical complications due to probable damages to the collateral brain tissue in the vicinity of the surgical regions is highly likely. Functional mapping on the other hand, is a powerful technique that helps surgeons to perform surgery with higher accuracy and as a result reduce post-surgical complications.

Several techniques such as Positron Emission Tomography (PET) or functional Magnetic Resonance Imaging (fMRI), are currently being used to reach this goal, however, direct Electro-Cortical Stimulation (ECS) provides the golden standard for functional mapping. In order to perform ECS, which is most effective in determining the somatosensory as well as language area, patients needs to be awakened and perform simple cognitive tasks such as speaking, moving different body parts or using their memory. While patients are performing these task, their cerebral cortex is being stimulated by electric pulses. If stimulating a certain area renders the patient unable to continue performing certain tasks, there has to be a direct correlation between that specific cortical region and governing that cognitive task.

Although, in theory performing ECS sounds straightforward, it usually involves some serious complications when being done in a real-life situations. To mention but few, awakening a patient who is already under anesthesia requires a great deal of experience and can only be done by expert anthologists. besides, the experience of being conscious during a brain surgery could be painful, unpleasant and traumatizing. Moreover, experiencing a seizure is a highly likely when ECS being done on epileptic patients. Last but not least, this procedure can not be done in children under certain age [17].

Resolving this shortcoming has been the greatest motivation to run this study. The initial idea was to develop an alternative technique which makes functional mapping possible without direct cortical stimulation. In particular our focus was on determining the eloquent cortex which is responsible for processing auditory data and language area. The proposed method, was successfully tested on about 20 patients who underwent craniotomy and has been proved to be applicable and efficient from practical point of view. This thesis is a report of this scientific effort which describes the research procedure in depth. In the first section a brief review on anatomical structure of brain as well as their functional significance is presented. Rest of this chapter is dedicated to an overview on different techniques for measuring brain activities as well as a discussion regarding the importance of ECoG and its role in functional mapping. A comprehensive report regarding different steps of this research with further details, is presented in chapter 1. Another aspect of this study which was calculating a quantitative index for measuring depth of anesthesia is addressed in chapter 2. At the end, a chapter is dedicated to discuss the results and conclusion as well as directions for future research.

1.1 Brain Anatomical Structure

The nervous system in our body is made of two essential parts. The spinal cord and brain together form the Central Nervous System (CNS) and the rest forms Peripheral Nervous System (PNS).

1.1.1 Brain Divisions

There are three major divisions of the brain; namely: forebrain, midbrain and hindbrain. Among these three, the last two divisions are what we have in common with less evolved species. Forebrain, on the other hand, is the division which is significantly more evolved in human and is responsible for many of the capabilities and functions which are unique in our species and are lacking in others. Forebrain is consisted of two major parts. Diencephalon which contains thalamus and hypothalamus which are responsible for such functions as motor control, relaying sensory information and controlling autonomic functions. Other section is telencephalon which contains the largest part of the brain, the cerebrum which is discussed with further details in the following subsection. The other two divisions, midbrain and hindbrain together form the brainstem. Midbarin which is also known as mesencephalon, is the connecting bridge between forebrain and hindbrain. Hindbrain on the other hand, forms the spinal cord and other remaining part of the neural system. A comprehensive discussion regarding brain anatomy is beyond the scope of this thesis and could be found in related references. [36].

1.1.2 Cerebral Cortex

As it was mentioned earlier cerebral cortex in human brain is plays a key role in many cognitive functions. Therefore this section is dedicated to its structure and functions. As it is demonstrated in figure 1.1 cerebral cortex can be classified into four main regions: frontal lobe, parietal lobe, occipital lobe and temporal lobe.

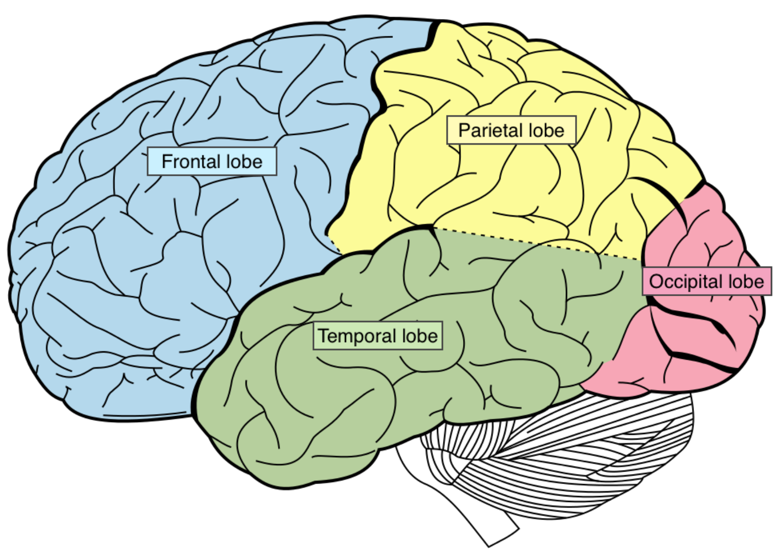


Figure 1.1: cerebral cortex

Frontal Lobe

It is mainly involved in movement, decision making, problem solving and planning and can be subdivided into two main areas. Prefrontal cortex which is responsible for personality expression and the planning of complex cognitive behaviors; and motor cortex controls movement in different part of the body.

Parietal Lobe

it plays a key role in processing sensory information, understanding spatial orientation and body awareness. Somatosensory cortex is found within the parietal lobe and is essential for processing touch sensation.

Occipital Lobe

It is positioned in the posterior side of the head and is the main center for visual processing. Some of its major functions include visual perception, color recognition, reading comprehension and depth perception.

Temporal Lobe

It is the last division in this categorization and plays an important role in organizing sensory input, auditory perception, language processing and speech production. Its other functions include but not limited to memory, emotional responses and facial recognition.

1.1.3 Auditory Cortex and Language Area

As it was mentioned before, among the four different topographical regions that cortex can be classified to, temporal lobe play the prominent role in processing auditory information. Temporal lobe is made of three gyri called superior, middle and inferior temporal gyrus which are separated respectively by superior and inferior temporal sulcus and they are shown in figure 1.2. Technically speaking, there are two main regions in brain which are responsible for processing and producing language. The receptive language area, also known as wernicke's area, is located in the posterior section of the superior temporal gyrus and is responsible for the comprehension of the written and spoken language. The expressive language area, also known as Broca's area, is located in frontal lobe and is responsible for speech production [36].

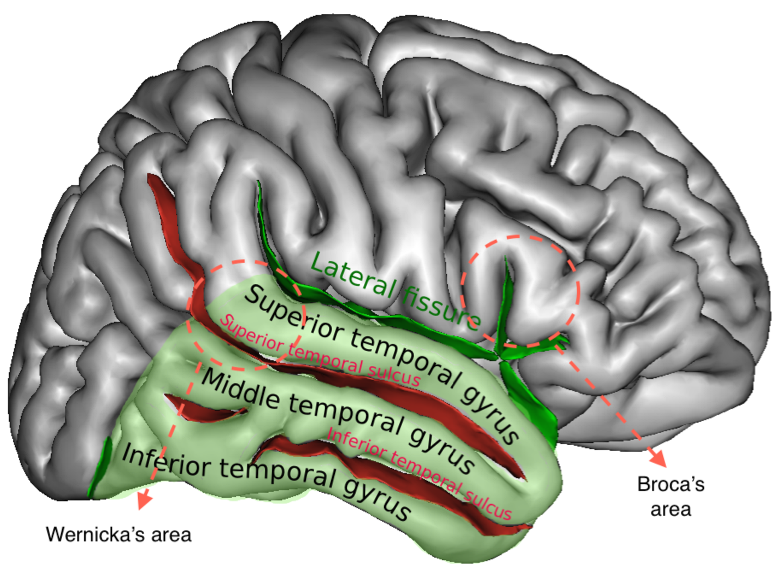


Figure 1.2: Temporal lobe regions

1.2 Techniques to Study Brain

Recent technological developments, have made it possible to study different aspect of the brain with remarkable resolution and with much more details. These techniques are generally classified into invasive and non-invasive. However, here we summarize summarize them based on the principle strategy behind their designs

1.2.1 Metabolic/Hemodynamics based Techniques

The main idea behind these techniques, which makes functional neuroimaging with remarkable spatial resolution, is to measure the hemodynamics or metabolic responses and activities in our brain.

Functional Magnetic Resonance Imaging

fMRI which is basically a modified version of the conventional MRI, uses blood-oxygen-level in different parts of brain as an indication for the level of activity. The main idea which fMRI is working based is, as a cognitive task being performed, certain cortical regions which are responsible for governing the ongoing activity, are more active and as a result, they consume more oxygen. In other word, the level of oxygen in a blood vesicle in an area in the brain, is correlated with its level of activity.

Positron Emission Tomography

The underlying idea behind PET, is more or less similar to fMRI and that is to measure activities in certain areas of the body. However, instead of blood oxygen level, PET targets fludeoxyglucose which is analogous to glucose. When a biological molecule is active, it consume more glucose as a source of energy and that is how it can be traced using the nuclear tactic which PET operates is based on.

1.2.2 Electromagnetic based Techniques

It has been a known fact since the beginning of the nineteenth century that human brain generates electromagnetic waves. A closer look at neurons which are the building blocks in our nervous system reveals the underlying mechanism which is responsible for the electric and magnetic field generation. To put it in a nutshell, selective exchange of different ions by neurons, which mostly happens through ion channels located around synapses, cause a potential gradient across the cell, which indeed results in a electric pulse traveling along the neuron. When this pulse reaches synaptic cleft, it is being transferred to other neighbor neurons which are connected. The fundamental mechanism behind this operation is still not fully understood but what could be asserted is that, the net behavior of big clusters of neurons which are aligned the same direction, can cause measurable electric and/or magnetic field even on the scalp [25]. Based on this measurable effect, several techniques have been developed to study and measure brain activities.

Magnetoencephelography

Although the strength of the magnetic field generated by brain is significantly smaller than the electric field, yet it has been used for functional neuroimaging. MEG with has high temporal resolution of the order of 10 millisecond and its primary use is the measurement of time courses of activity. This technique is usually used with fMRI in order to create brain map with more details. The advantage of MEG and in general any technique which is based on measuring magnetic field is, magnetic fields are less distorted then electric fields by the skull and scalp which results in better spatial resolution. However, there are some technical challenges in implementing such techniques. Creating a magnetic shield in order to cancel Earth magnetic field is one of them [16].

Electroencephelography

Electroencephelography (EEG) is the oldest and probably the first technique that was applied to measure brain activities. In the beginning of the nineteenth century, Hans Berger, who is known as the father of this field, started a series of experiment where he studies brain activities by measuring the electric potential on the surface of the scalp [15]. When cluster of neurons in a cortical region, which are aligned the same direction fire together, their electric field adds up and create a net electric field which is large enough to be measured even outside of the skull. EEG provide a non-invasive means to measure these electric activities. EEG has been developed and been extensively used for various studies such as sleep disorders, Brain-Computer Interface (BCI), brain death, depth of anesthesia and many others [24].

Local Field Potential

Although EEG provides a technique for measuring the overall behavior of ensemble of neurons, yet it is not suitable for studding the behavior of individual units of the nervous system. Single- and multi-cell recording techniques, however, provide this opportunity for us. These techniques rely on using fine micro-electrodes to measure the extracellular potential. This approach, not only allows for unparalleled selectivity and control of electrical properties, but also provides invaluable information that helps neuroscientists have a better understanding about the fundamental principle that our nervous system operates based on [14].

Electrocorticography

Electrocorticography (ECoG) records electric activities directly from the surface of the cortex. This approach indeed results in recording signals with unprecedented Signal to Noise Ratio (SNR). The electrode grids could be implanted surgically either on top of the dura layer (epidural) or beneath it (subdural) (figure 1.3). Considering the fact that skull and scalp are both electric insulator and therefore distort the electric field as it passes through them, recording brain's electric activity directly from the surface of the cortex is the only method that avoid this problem. The other great advantage of ECoG compared to other methods, is its excellent temporal resolution which is less than 1 millisecond. ECoG has been extensively used for brain studies as well as clinical applications. Specially in patients with epilepsy, ECoG provides valuable and precise information that helps tracking the cortical regions which triggers seizures in patients.

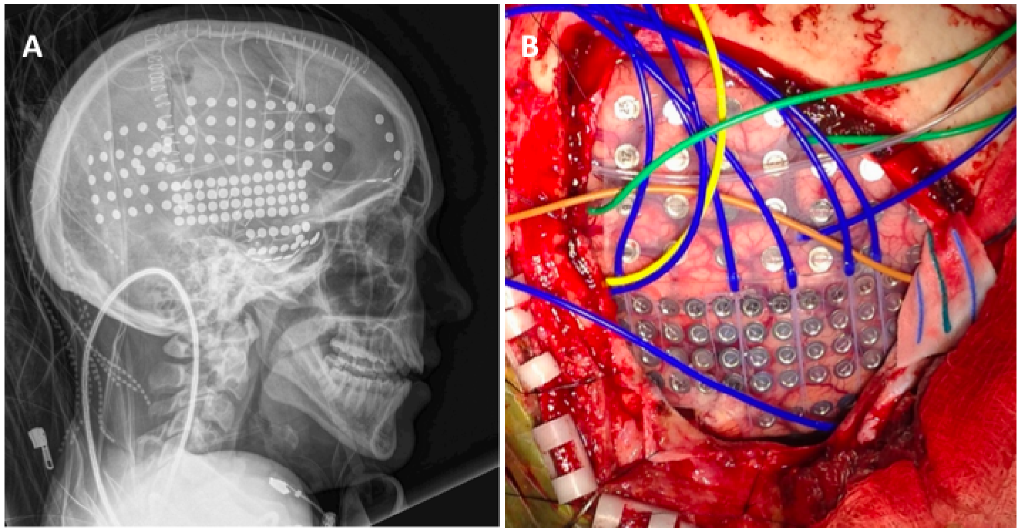


Figure 1.3: A) X-ray scan that reveals the gird poison B) Implanted gird on cortex

1.3 Brain Wave Frequency

The electric field which is being recorded using any of the above-mentioned techniques has one important feature. A quick look at these waves reveals the fact that they are no stationary. In other word, regardless of the physiological or mental state that our brain and mind have, oscillatory behavior is in the nature of brain waves. That being said, neuroscientists have been trying to link cognitive tasks with activities in certain frequency intervals. Using spectral analysis techniques such as Fourier transform, the main frequency components of the oscillatory rhythm of brain could be revealed.

Delta band

Oscillation with frequency between 0.5 to 4 Hz falls in this band. Previous studies revealed the fact that, when brain is not actively involved in performing cognitive tasks and specially during sleep or while being unconscious, larger patches of cortex behaves in a synchronized pattern. This synchronization yield in oscillation with low frequency and large amplitude [3].

Theta band

Oscillation with frequency between 4 to 7 Hz falls in this band. Activities in Theta band are associated with the idling, drowsiness in adults and teens and also it is higher in young children. Previous studies does not indicate any direct relationship between performing cognitive tasks and brain activities in Theta band [32].

Alpha band

Oscillation with frequency between 8 to 15 Hz falls into this category. The reason for this naming is that this it the very first frequency band which was studied by Hans Berger [5]. Studies shows activities in this band increases when eyes are closed, due to synchronization of larger cortical areas. One of the most important aspect of this frequency band is its potential role in modulating oscillation in higher frequencies. There is at least one major theory called gating-by-inhibition (GBI) which hypothesize the role of Alpha oscillation in modulating brain activities in other frequencies [19]. The other importance of this band is that most of motion related activities generate frequency between 8 to 12 Hz and due to its importance, this range is called My band.

Beta band

Oscillation with frequency between 16 to 31 Hz falls into this category. Low amplitude Beta rhythm is associated with active, or anxious thinking and active concentration. One of the important aspect of this frequency band is a phenomena called Event-Related Desynchronization (ERD). Previous studies revealed that prior to physical movement in one side of body, a decrease in beta amplitude could be detected over the contralateral motor cortex which usually followed by an increase in beta amplitude as the motion begins. The latter phenomena is also known as Event-Related Synchronization [28]. These known facts have been vastly used in designing BCI systems as well as for functional mapping [23].

Gamma band

Oscillation with frequency above 32 Hz falls in this band. Based on the power law, as the frequency increases, the amplitude of brain rhythmic activities decreases [9]. As a result, the amplitude of gamma oscillation is less than other frequency bands and therefore, gamma oscillations can not be detected using non-invasive techniques such as EEG. On the other hand, ECoG with the ability to record signals with high SNR, makes it possible to study brain rhythmic activities in gamma band. The other feature that puts gamma band in the center of attention is the fact that it is the only frequency band that shows localized behavior with in correlation with the ongoing task. This important characteristic is addressed with further details in the following chapter [21].

Chapter 2

Passive Mapping of Language Area

In the previous chapter a brief discussion regarding the practical importance of functional mapping in both research and clinical applications, was presented. In this chapter we narrow down the discussion to the topic that this study focused on which is mapping the language area. The first section surveys the results of the previous related studies and the rest of the chapters is dedicated to reporting the experimental paradigm and other related details.

2.1 Previous Studies

A survey on the literature, one can find several studies focused on mapping the language area using techniques based on hemodynamics activities. As mentioned earlier, fMRI provides an excellent spatial resolution [27, 22, 4, 6]. Although these fMRI and other similar techniques provide invaluable information regarding task specificity of various brain regions, yet studying other aspects require utilizing techniques with higher temporal resolutions such as ECoG. Broadly speaking, these factors are considered to be as their deficiencies: the lack of clear indexes of reliability and validity, lack of accordance with the result of other techniques and lack of ability to find immediate correlation between the ongoing task and active cortical regions [8, 34, 30]. The key role that broad band gamma activities play in neuroscientific studies was highlighted in the previous chapter. The practical importance of high-frequency activity is associated with language processes has been increasingly studied [11, 2, 10, 12, 37, 35]. Among all the available techniques, ECS is the only practical method which is widely being used by neurosurgeons as a golden standard for pinpointing eloquent cortex. Nonetheless, applying ECS could also be problematic. Here is the list of some of the serious issues [7]:

- time consuming
- can not be applied to young children
- requires experienced anesthesiologist
- could be very painful and traumatizing for patients
- could potentially triggers seizure in epileptic patients
- is not mostly efficient for language and somatosensory regions

2.2 Experiment Paradigm

Given all the deficiencies of ECS, developing an alternative technique was the main motivation of this study. The main idea was to design a paradigm in which task performance does not require attentive participation of the patient and therefore could be done even under anesthesia. The task which was used in our paradigm was simply listening to a certain number of words and gibberish which were randomly mixed. The group of words were simple nouns in English which were meaningful for patients such as rain, sky, water, ... On the other hand what we used as gibberish were technically the same meaningful words which underwent some manipulation in their vocal patterns and therefore they turn into meaningless sounds for patients. Normally expressive language area is only active when subjects speak, however, previous studies proved that there is a physiological and functional connectivity between receptive language area (Broca's area) and expressive language area (Wernicka's area) which is responsible for producing speech [1]. The basic null hypothesis was that, there is no statistically significant difference between different cortical regions' activities while listening to meaningful words compared to gibberish. The alternative hypothesis, on the other hand, was that a statistically significant difference should be detected between the recorded activities over different regions (expressive vs. receptive language areas). The goal was to search for reliable evidence to reject the null hypothesis and support the alternative hypothesis. Two different "test statistic" were used to further investigate the above-motioned hypothesis. One was the difference between the amplitude of broad band gamma activities recorded by each electrode during task performance, and the other one was the covariance between recorded signals over several different trials.

2.3 Subjects and Data Recording

The group of subject who participated in this research consisted of sixteen patients who were hospitalized in Albany Medical Center (located in NY). All of our patients underwent brain surgery and they fell into two categories: the first group consisted of those with intractable epileptic patients and the other group consisted of those who were suffering from brain lessons/tumors. All of the patients were above 20 years old and English was their first language. They were also asked to sign a written consent prior to participating in the experiment. Epileptic patients had be hospitalized in Epilepsy Care Unit (EMU) at AMC for about a week before the main surgery. They all underwent an initial surgery during which ECoG grids were implanted on their cortex in order to pinpoint cortical regions which needed to be removed in order to control the number of their seizures. This provided a golden opportunity for our team to further run the paradigm while they were at EMU and compare the results with those recorded under anesthesia. The second group of patients who were suffering from tumors, however, underwent a one stage surgery and therefore we could only run the paradigm during a limited time before, during and after the surgery.

Patients were implanted with high density ECoG grids with up to 256 electrodes which provided a substantial amount of useful data which later were used for further investigations. The software which was used to record the signal was BCI2000 which was developed in our lab more than ten years ago and have been updated ever since. All the patients went through MRI prior to the surgery which was used in order to create a brain model for each one of them. Brain models were created using ”Free Surfer” which is an open source software for the analysis and visualization of structural and neuroimaging data and was developed by Center for Biomedical Imaging at Massachusetts General Hospital.

2.4 Signal Processing

The recorded ECoG signals were saved in data files using BCI2000 package. The first step in processing the recorded signals were visual examination. The software which was used for visualizing ECoG signals was BCI viewer (figure 2.1).

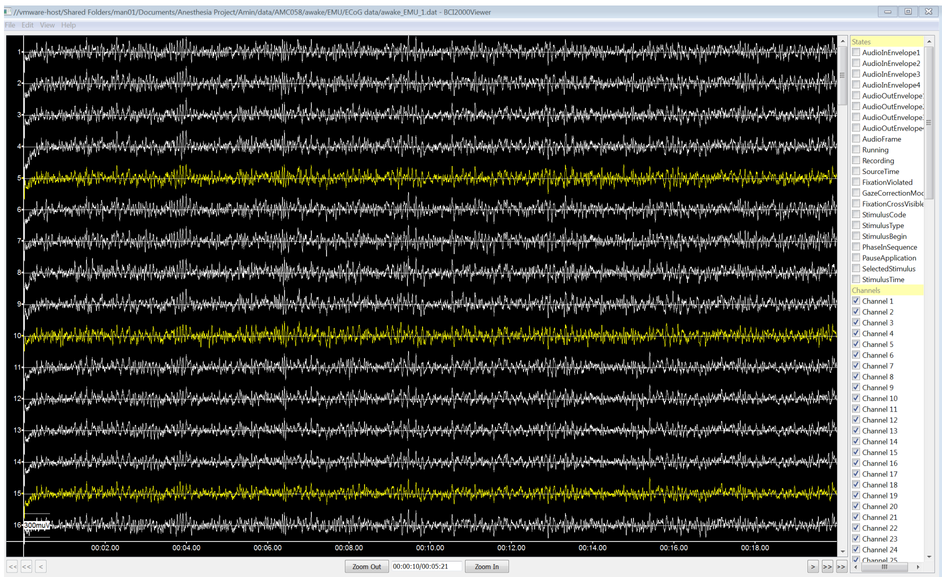


Figure 2.1: BCI viewer

The amplifier and ADC set up which were used to amplify the signal and convert the analog signal to digital with the sampling rate 2400 Hz, were made by g-tech company. Since ECoG signals are recorded directly from the surface of the cortex they are less prone to get distorted by artifacts such as blinking or facial movements and that is a unique advantage for ECoG. However, there were few cases in which the neurosurgeon or nurses in the OR accidentally touched the wires and this introduced a substantial artifact. These corrupted files were identified and removed from the process of analysis by the initial visual inspection of the recorded signals. Moreover, in order to improve SNR, signals were grounded with respect to one of the channels. The main criteria in choosing the ground electrode was to minimize the noise in other channels and it was different case by case. Figure 2.2 demonstrates the sequence of the basic steps in signal processing procedure. The last step prior to starting the the spectral analysis was to re-referencing the recorded signals. The main goal was to improve SNR by removing some common noise in all channels. Choosing the reference channels similar to ground channels was done based on optimum results.

Math Framework

Any sequence can be expressed as the sum of an even sequence and an odd sequence. Specifically, with $x_e[n]$ and $x_o[n]$ denoting the even and odd parts, respectively, of $x[n]$; therefore:

$$x[n] = x_e[n] + x_o[n] \tag{2.1}$$

$$x_e = \frac{x[n] + x[-n]}{2} \tag{2.2}$$

$$x_o = \frac{x[n] - x[-n]}{2} \tag{2.3}$$

if $x[n]$ is also stable, i.e., absolutely summable, then its Fourier transform exists. We denote the Fourier transform of $x[n]$ as

$$X(e^j\omega) = X_R(e^j\omega) + jX_I(e^j\omega) \tag{2.4}$$

where $X_R(e^j\omega)$ is the real part and $X_I(e^j\omega)$ is the imaginary part of $X(e^j\omega)$. This provides the basis for representing complex signals in terms of magnitude and

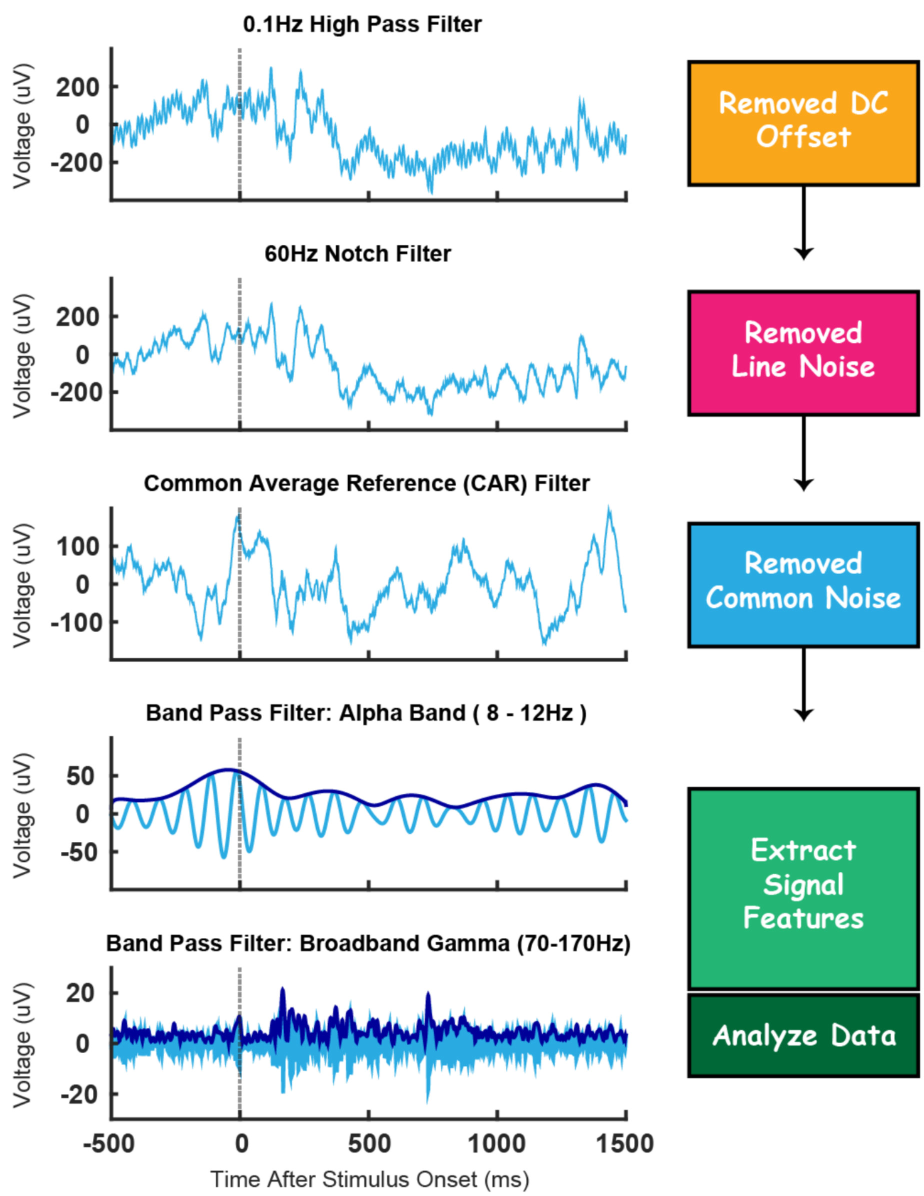


Figure 2.2: Signal processing steps

phase; i.e., $x[n]$ can be expressed as

$$x[n] = A[n]e^{j\phi[n]} \tag{2.5}$$

$$A[n] = (x_r^2[n] + x_i^2[n])^{1/2} \tag{2.6}$$

$$\phi[n] = arctan(\frac{x_i[n]}{x_r[n]}) \tag{2.7}$$

This indeed was used as an integral part of Hilbert transform to extract the signal envelop.

2.4.1 Spectral Analysis

Removing DC offset

After discarding channels with substantial artifacts, also grounding and re-referencing signals, the next step was to remove the DC offset. This was done by applying a highpass filter above 0.1 Hz. In performing the spectral analysis, Infinite Impulse Response (IIR) butterworth filter was utilized. The reason for choosing IIR filter over Finite Impulse Response (FIR) filter was the fact that they typically meet a given set of characteristics with a much lower filter order than corresponding FIR filter and therefore they are faster and lees computationally expensive [26]. Although IIR filters have nonlinear phase, nevertheless, this issue was resolved by applying non-causal, zero-phase filtering approach via some built-in Matlab functions which are available in the signal processing package.

Removing Line Noise

Consequently, signals were inspected for the Line noise. In order to detect channels with significant line noise, initially IIR filter were used to measure signals behaviour centering at 60 Hz and all other possible harmonics at 120, 180 and 240 Hz which could potentially introduce line noise to the signal. This followed by applying Notch filter on those channels with significant line noise to remove noisy signals.

Extracting Broad-Band Gamma

As it was mentioned in previous chapter, among all the frequency bands, broad band gamma is the one that has the most task specific and localized behaviour. As a result the signal were also band passed in order to omit all the frequencies below 70 Hz and above 170 Hz. Prior to applying the band pass filter, each channel was tested for the optimum filter order.

Spatial Filtering

After completing the spectral analysis, and in order to enhance the spatial resolution of signals, Common Average Reference (CAR) was applied. Broad band gamma waves, specially if recorded by ECoG, shows a localized characteristic. However, since the result of this study were applying to patients and possesses high clinical significance, we decided to improve the spatial resolution even further by applying a spatial filter.

2.4.2 Feature Extraction

After applying all the steps that were discussed above, and in order to extract signal power, Hilbert transform was used. The filtered signal as well as its power is demonstrated in figure 2.3. The reason for applying Hilbert transform and extracting the signal power is that, we were interested in the overall behaviour of the signal over short time intervals and not necessarily to Small scale oscillations. After this step, signals were down-sampled to 240 Hz and they were cut into epochs. The two important feature that were used in this study were signal power and also signal consistency. The idea behind the using these two characteristics as the main feature of our signal had its root in the form of our initial hypothesis which are discussed in depth in the following section.

2.5 Statistical Roadmap

Two main approaches were adopted in this study, each of which was based on a different hypothesis. In this part the technical details related to each approach are addressed and the results are reported in the following section.

2.5.1 Statistical Hypothesis

The first null hypothesis in this study was that, there is no statistically significant difference between the change in the broad band gamma activities, recorded from different electrodes over different cortical regions, due to performing the auditory tasks (listening to certain number of words and non-words which were randomly

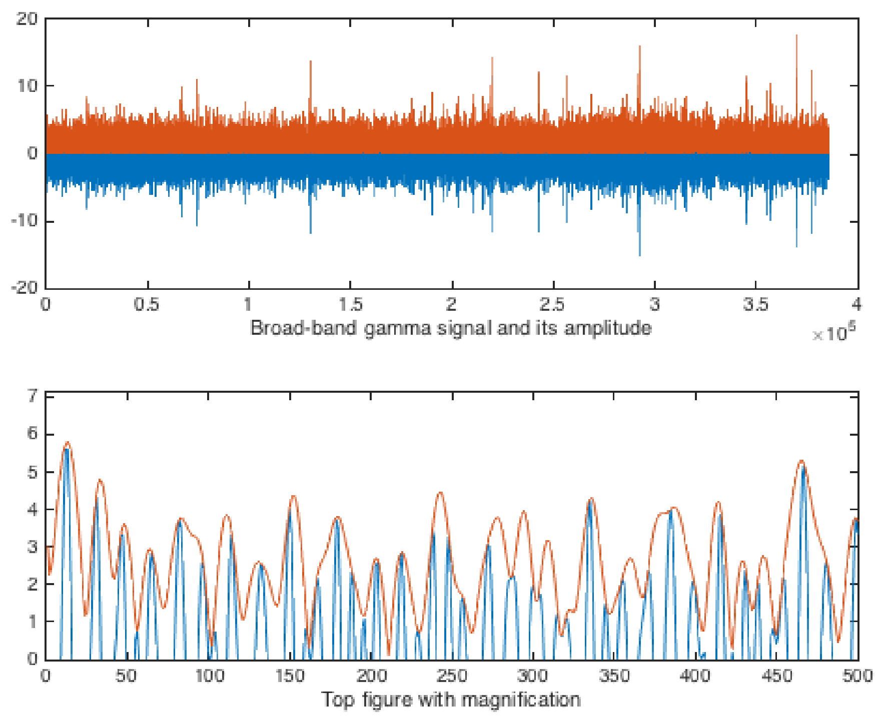


Figure 2.3: Top figure is the broad band gamma signal after applying filtering and also its amplitude. Bottom figure is the same figure after zooming in

mixed). Therefore we tried to investigate the available data from our patients to find evidence against this null hypothesis. On the other hand, the alternative hypothesis which we had the burden of its proof on our shoulder was, there has to be a statistical significant difference between the broad band gamma power, recorded over those cortical regions which are associated with auditory information processing (such as superior temporal gyrus) and other unrelated cortical regions, due to performing the semantic auditory task. The specific areas that were in center of our attention were the receptive and expressive language areas (Wernka's and Broca's area).

2.5.2 Defining Populations

Given that, the processed signals were cut into epochs and their power, as the main feature, were extracted. The timing pattern for creating the epochs was based on the onset of the auditory stimulus. Each run was consisted of 64 trials with meaningful words and 64 trials with gibberish. The total duration of 600 ms prior to the stimulus onset was considered as the baseline which later on were used as the main reference. The first 100 ms after the stimulus onset was discarded due to unstable behavior of signal and also the standard time that processing the auditory information takes [38]. The next 600 ms was considered as the time duration in which the task was being performed. Since two different separate tasks were defined in this paradigm (word vs non-word), the task intervals were treated separately. Subsequently all the baseline epochs and also all the tasks epochs were put together and formed the main three populations.

From this point there were two main steps which were to perform:
1 - Studying the difference between non-word population and the base line population to determine the auditory sensitive channels.
2 - Studying the difference between the word population and the baseline population to determine the language sensitive channels.
However, since language sensitive channels are expected to be auditory sensitive too, the investigation to answer the second question was limited to those electrodes which were already determined as being auditory sensitive.

2.5.3 Adopting Appropriate Statistical Approach

The test statistic which was used to answer above questions was the difference between populations mean value. The main concern in selecting statistical approach was to minimize the number of assumptions which were needed to be made before the analysis. Given the fact that all the Parametric statistical methods are based on basic assumption that sample data comes from a population that follows a probability distribution based on a fixed set of parameters all those techniques were off the table [29]. On the other hand the majority of the Non-parametric techniques are also based on some underlying assumption regarding the populations or sampling. These include Two-sample sign test, Wilcoxon sign-rank test, Mann-Whitney U-test, Wilcoxon rank-sum test, . . . [33]. The statistical approach which was adopted for this study was the Permutation test. Although Permutation test and other similar statistical techniques such as Randomization test and Bootstrap test are computationally expensive, however the fact that they applying them does not require making any major assumption regarding the populations, is a unique feature that makes them highly accurate.

2.5.4 False Discovery Rate

In hypothesis testing, one of the important things that need to be taken into account is when we run multiple comparisons. False Discovery Rate (FDR) controlling procedure is a method to control type I error which is false positive detection. In other word this procedure controls the rate at which the null hypothesis mistakenly gets rejected. The underlying idea behind FDR control is to make the significance level more stringent. By doing so, the burden of proof would be heavier and the stronger evidence would be required to reject the null hypothesis. The technique which was used in this study for controlling FDR, was Benjamini-Hochberg-Yekutieli procedure in which the false discovery rate is being controlled under positive dependence assumption [31].

2.5.5 Permutation Analysis

A comprehensive discussion regarding the Permutation analysis is beyond the scope of this thesis and could be found in the related literature [18]. Here, however, we briefly touch the base and summarize the way Permutation analysis was applied in this study. The idea here was that, if the null hypothesis would be correct and therefore there is no statistically significant difference between the populations mean values; mixing the two populations and shuffling their members should not change the difference in mean values. On the other hand, in case a statistically significant difference exist between the two populations, randomizing them should reduce the initial calculated value.

The extensive statistical calculations were performed using the algorithm developed by the author in Matlab. The tricky point which must be taken into account in performing the randomization test is the auto-correlation which usually exists in the data resulted from recording brain activities. This is due to the fact that different part of human brain and in particular those regions which are located in the vicinity of each other, works coherently and not as individual units [13]. This existing synchrony is what causes the auto-correlation which can be seen in figure 2.4. In order to take the auto-correlation into account, the randomization was performed without disturbing the order of epochs. In other words, in the populations, the order of epochs were shuffled and not their contents. The result of this analysis is discussed in the following section.

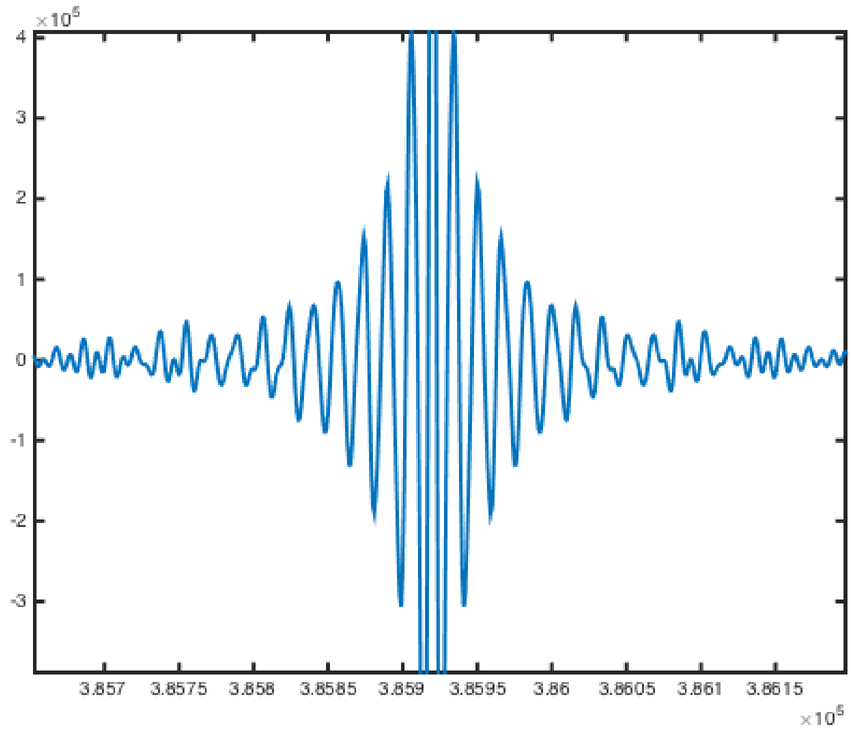


Figure 2.4: Auto-correlation in signal

2.5.6 Cross-Correlation

Although broad band gamma provides valuable information which is essential for functional mapping, nevertheless, when patients were under anesthesia, ECoG signal deteriorate and as a result of low SNR, analysis based on signal power would not be sufficient. The second approach which was tested in this study was based on the consistency of the signal and not on the power value.

The null hypothesis in this new approach was: The value of cross-correlation between different trials, is not significantly larger than those of baselines. The alternative interpretation of this statement is that, the signal consistency between the baselines and that of tasks is the same. On the other hand, the alternative hypothesis was, there is a consistency between the task-related signals compared to the baseline. The result of this approach is also reported in the following chapter.

Chapter 3

Results, Discussion and Conclusion

3.1 Brain Models and Activity Visualization

In order to depict brain activities a high-resolution brain model was created for each patient. In doing so the pre-operative MRI data were fed to ”FreeSurfer” which is a software package for the analysis and visualization of structural and functional neuroimaging data from cross-sectional or longitudinal studies and was developed by the Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging. The outcome of FreeSurfer software was then used to create the brain model(figure 3.1). Subsequently, in ordet to co-register the grid on the generated brain model, the CT scan was employed.

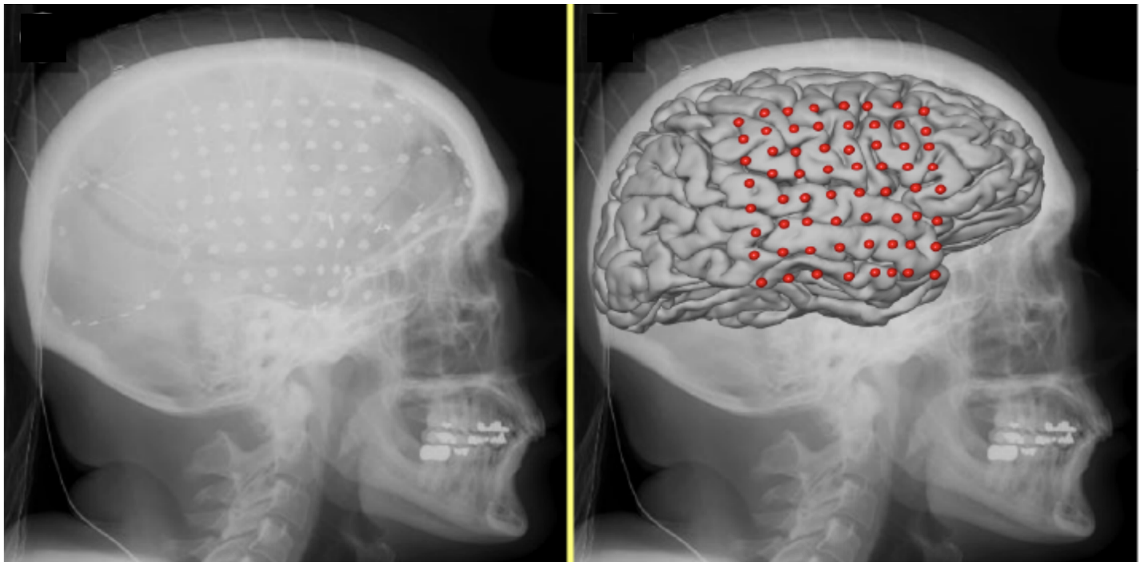


Figure 3.1: CT scan and co-registration of grid

3.2 Mapping Language Area Based on Signals Envelope

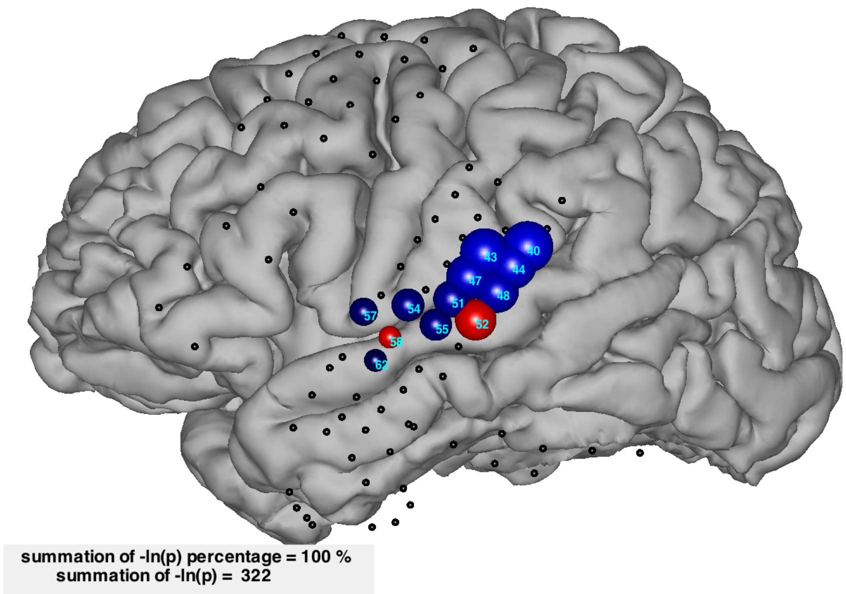
Figure 3.2 represents the brain map for one of the patients during awake condition. The activity of different cortical regions recorded by each electrode is visualized using spheres with two different colors. The blue color is associated with the activity while listening to non-word stimulus and the red color is associated with the activity while listening to word stimulus. The tiny black spheres, represent those electrodes with no significant activities. The size of each sphere is proportional to the level of activity recorded over that specific cortical spot beneath the electrode.

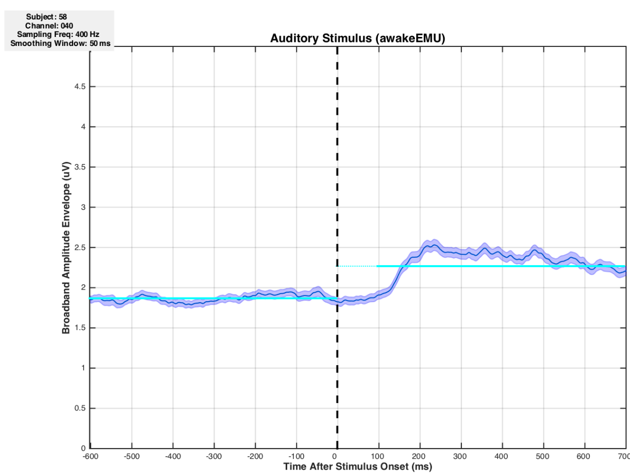
As mentioned earlier, the first approach in this study was based on the difference between the signal power recorded while performing the task, compared to the baseline (idle condition). The brain map in figure 3.2 and other similar maps which are presented in the following pictures, are the result of two steps:

- Comparing non-word activity and the baseline to identify the auditory sensitive areas and electrodes.

- For those electrodes which showed significant auditory sensitivity, comparing word activity vs non-word activity to identify language sensitive areas and electrodes

Therefore in figure 3.2 and all other similar brain maps, the blue electrodes represent those areas which are generally sensitive to auditory stimuli whereas the red electrodes not only are auditory sensitive but also they show sensitivity to semantic tasks. In order to realize the mechanism behind this analysis, the time series diagrams of broad band gamma powers both prior and after the stimulus onset are also included. The baseline epoch starts 600 ms before the stimulus onset and the task epoch starts from 100 ms after the stimulus onset and it continues for 600 ms (it terminates at 700 ms after the stimulus onset). However, for the sake of clarity, the first 100 ms after the stimulus onset is also included (although it was discarded for the analysis). Each run was consisted of 64 trials with word stimuli and 64 non-word stimuli. At the end of each run, the average of the broad band gamma power was calculated and plotted as the representative of activity of each electrode. Also the error bar at each time point was calculated and added to the diagram (the shaded area). In these time series, blue lines represent the auditory activity (non-word) and the red lines represent the activity recorded during the semantic task (word stimuli). For those channels without significant activities related to the semantic task, we only represented the blue trace and excluded the red trace.


40
43
44
47
48
51
52
54
55
57
58
62
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 322


Subject : 58
Channel: 040
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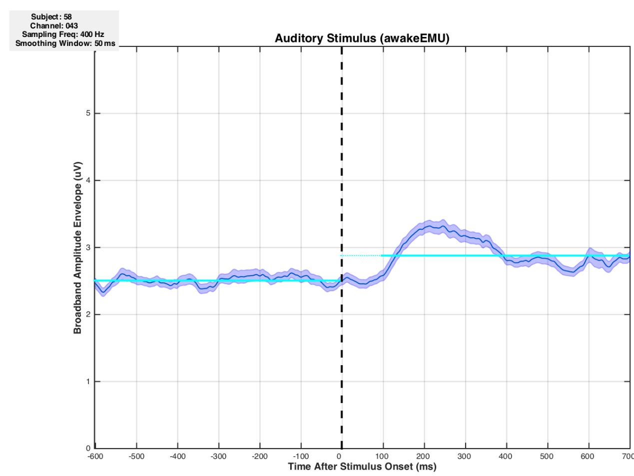
Smoothing Window: 50 ms
Auditory Stimulus (awakeEMU)
Broadband Amplitude Envelope (uV)
Time After Stimulus Onset (ms)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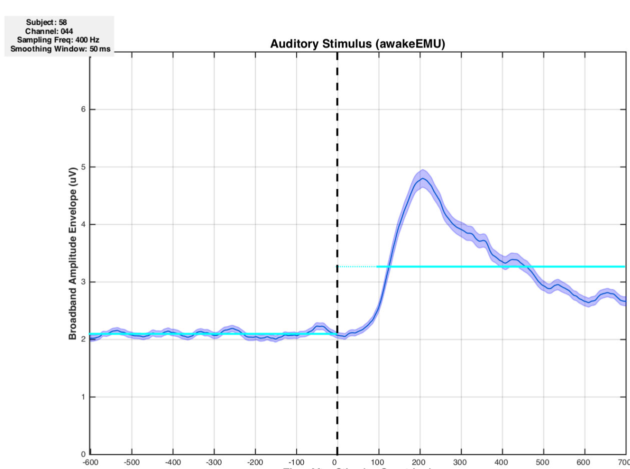
Auditory Stimulus (awakeEMU)
Broadband Amplitude Envelope (uV)
Time After Stimulus Onset (ms)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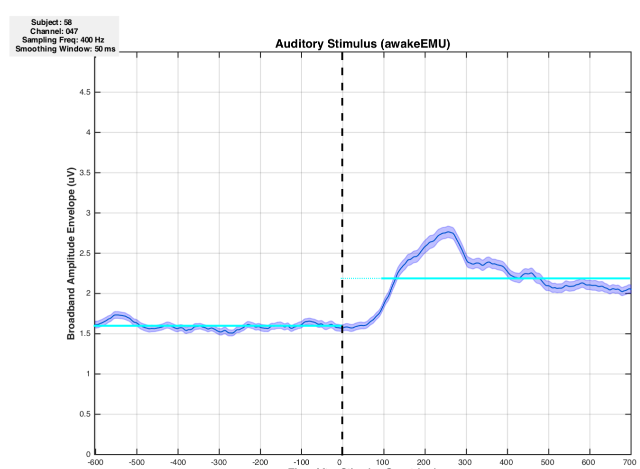
Auditory Stimulus (awakeEMU)
Broadband Amplitude Envelope (uV)
Time After Stimulus Onset (ms)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Broadband Amplitude Envelope (uV)
Time After Stimulus Onset (ms)

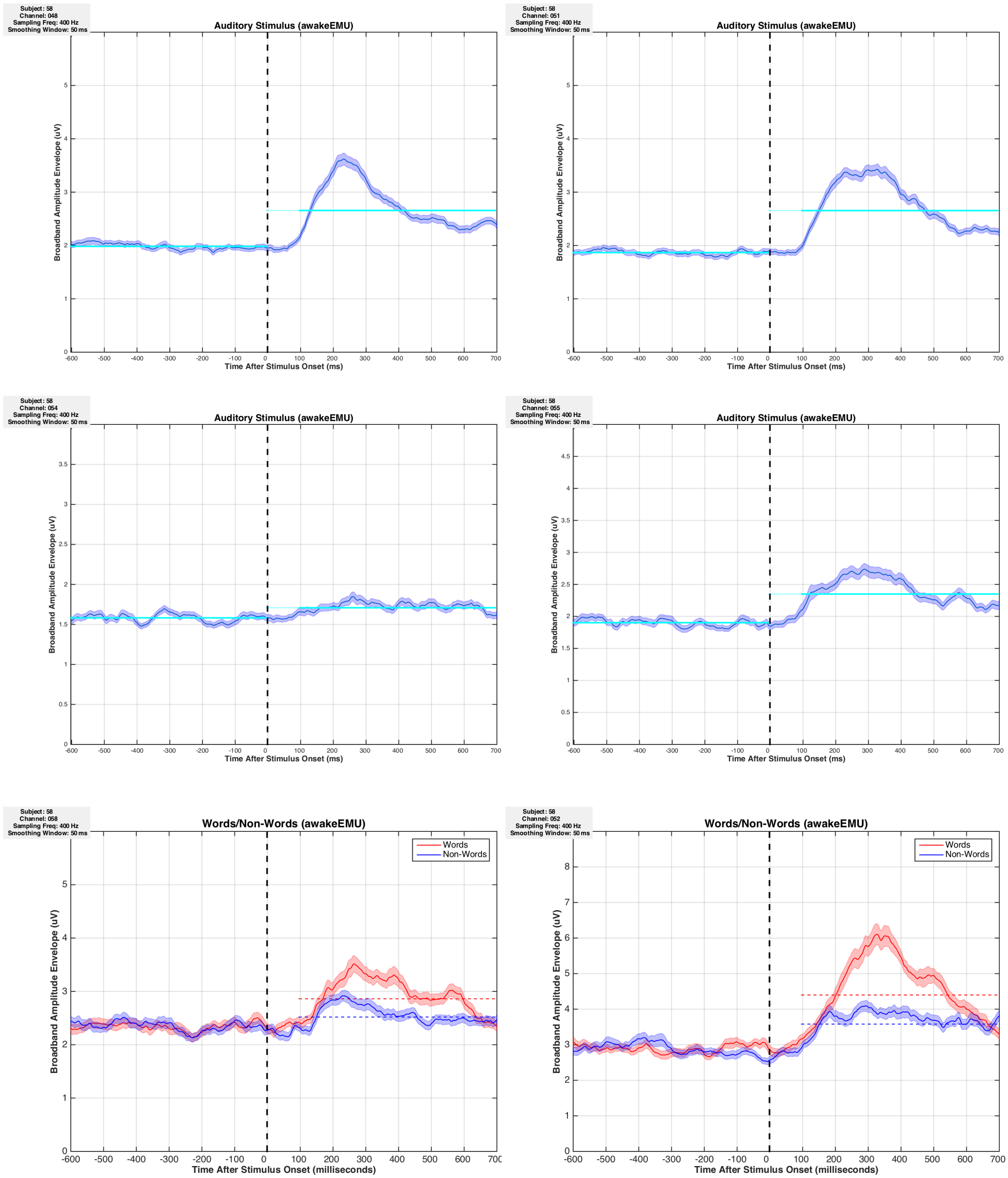


Figure 3.2: (Top figure)Brain map with active electrodes (blue electrodes are non-word (auditory) sensitive and red electrodes are word (language) sensitive) - Other diagrams represent the time series of broad band gamma activities prior and after the stimulus onset. Blue line represent activities during non-word stimuli and

The brain map in figure 3.2 along side with the created brain maps for other patients provide solid evidence to reject the null hypothesis and support the alternative hypothesis. The recorded activity from different electrodes are highly task correlated over those areas of cortex which are responsible for processing auditory information. As it can be understood from the figure, the number of blue spheres are maximum over the primary auditory cortex whereas on other cortical regions without any significant activities the number of colored spheres are minimum. The last two diagrams in figure 3.2 show the activity of both word and non-word tasks. Clearly, for these two channels, not only there is jump over the blue graph which represents auditory activity but also the change in the word related power is even more. Figure 3.3 demonstrates the brain map as well as time series of activities for the same subject under anesthesia. As it is expected, due to the presence of anesthetic agents, the signal power decreased noticeably. Although the number of active electrodes as well as their activity reduced due to unconsciousness, yet this method can be applied to identify the eloquent cortex. Our understanding is, in order to be able to perform the passive functional mapping under anesthesia, the analysis should be done before patients reach a certain depth of anesthesia. As patient goes deep under anesthesia, functional cortico-cortical and thalamo-cortical connectivities are blocked which renders the patient fully unconscious. Lack of these functional connectivities hinders processing data in our brain. Therefore, functional mapping should be performed before the stage of complete unconsciousness. This varies from case by case and is influenced by numerous factors which are currently under investigations. Figure 3.4 summarize best of the results for all patients in three condition: Epilepsy Monitoring Unit (AMC), Operating Room (OR), under anesthesia.

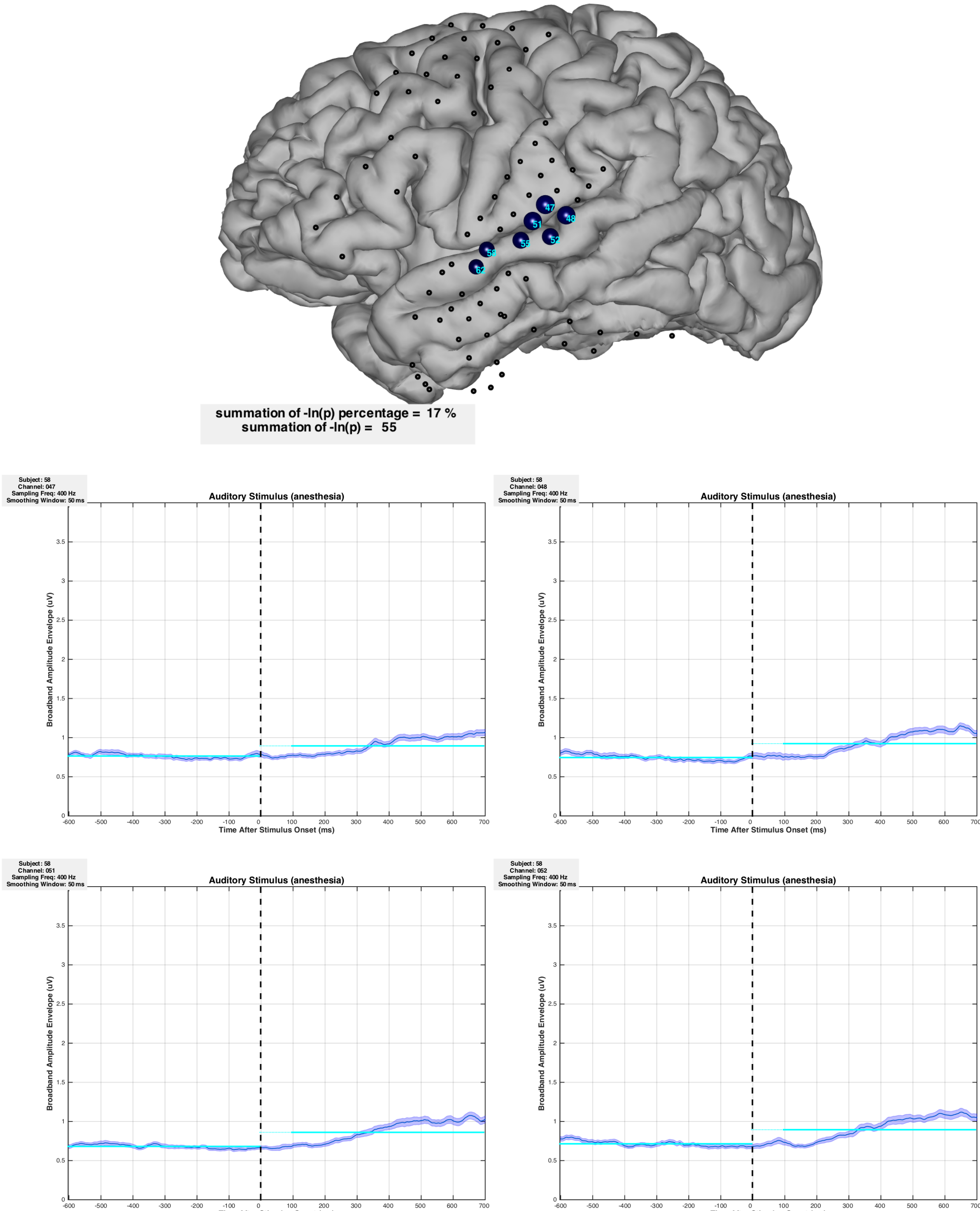
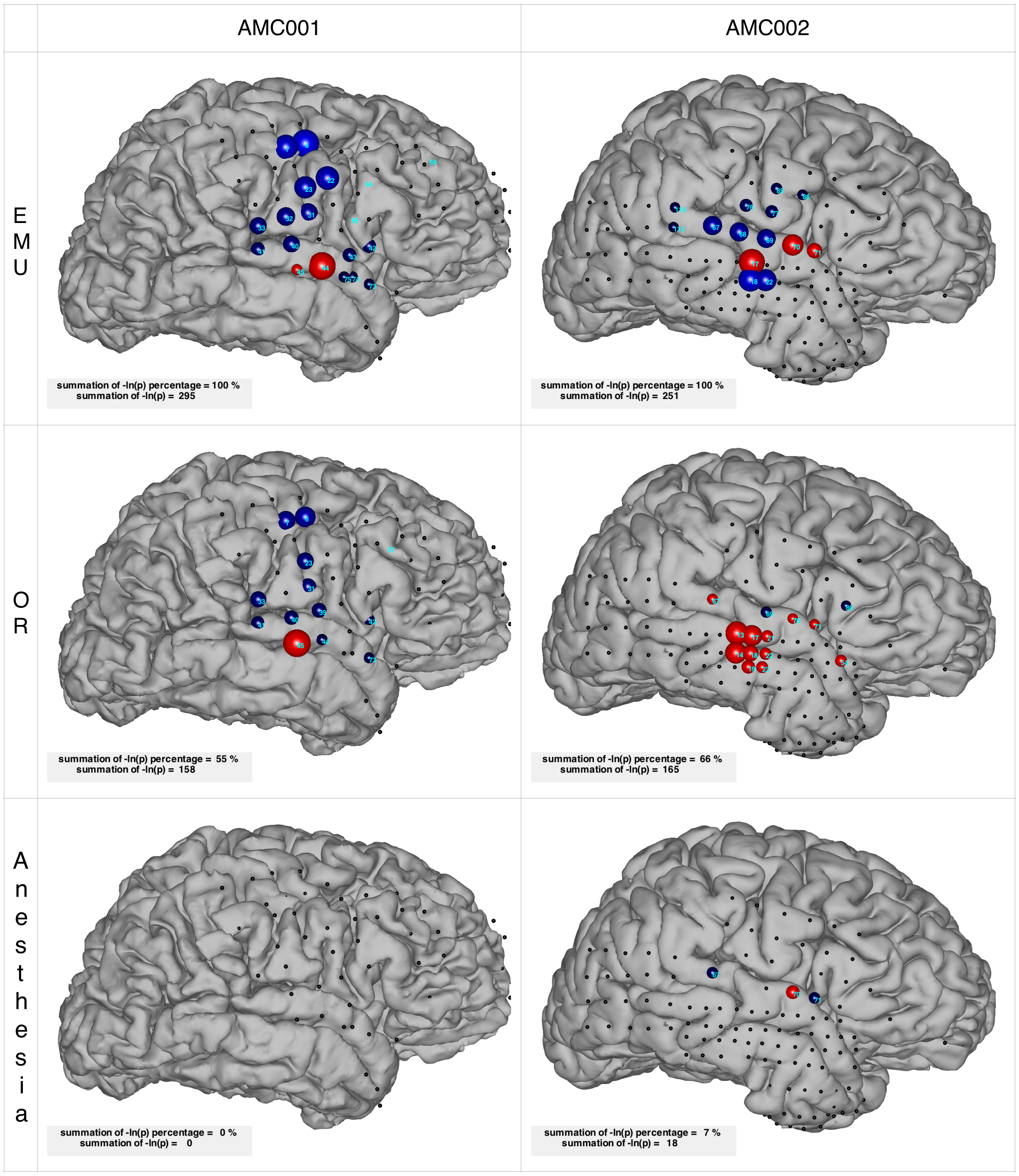
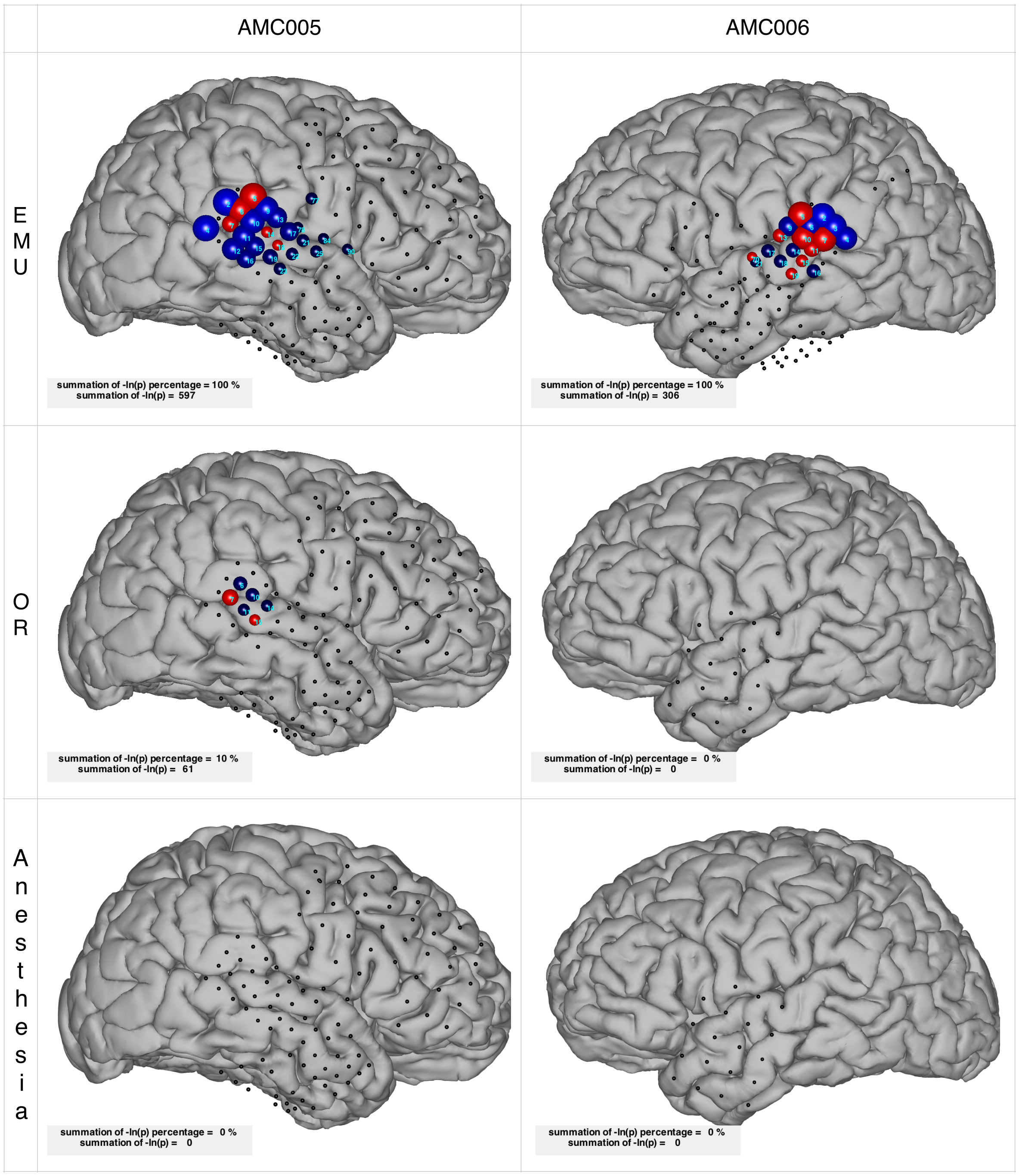
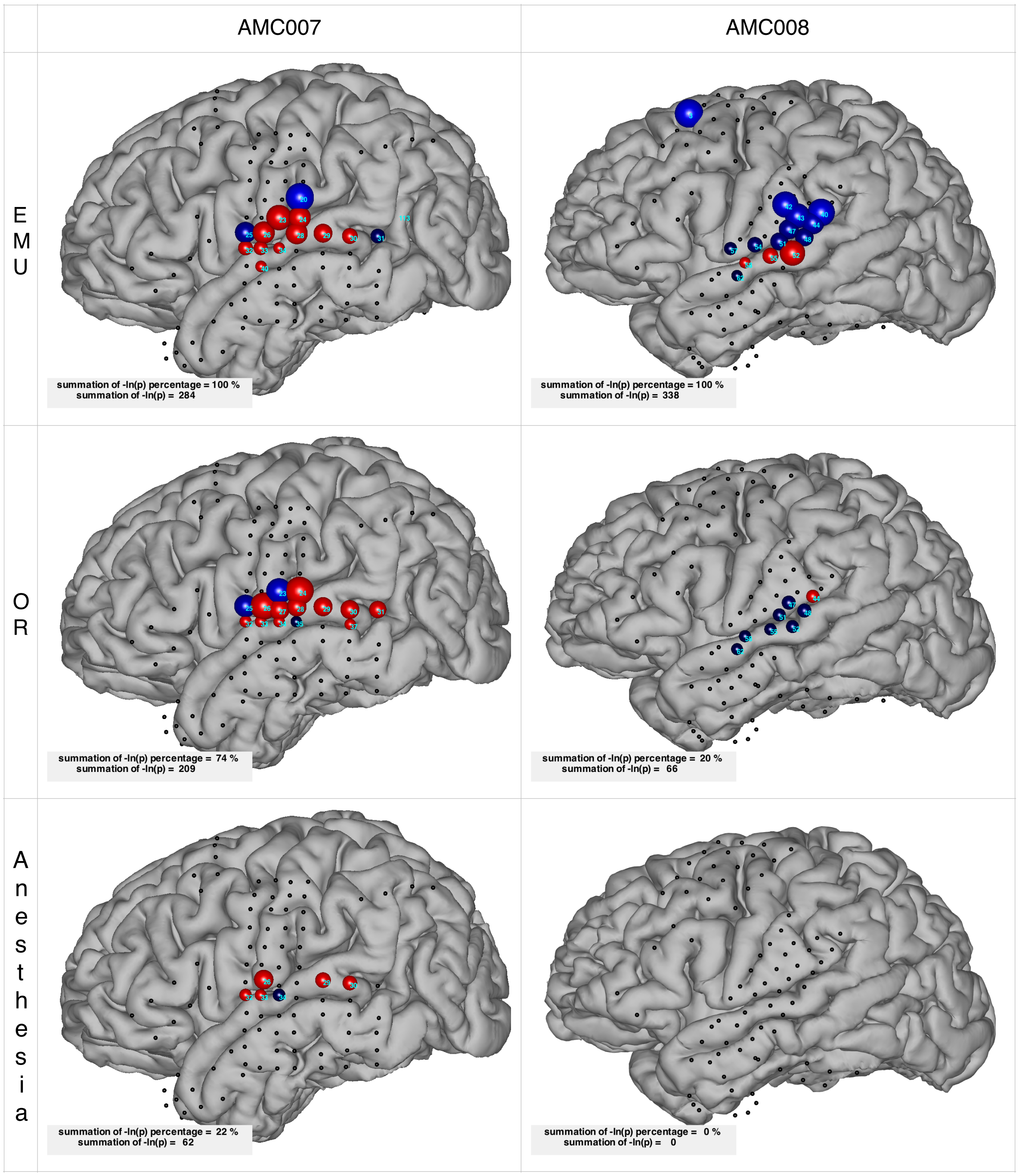


Figure 3.3: (Top) brain map under anesthesia, (Bottom): time series of signal power


AMC001
AMC002
EMU
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 295
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 251
OR
summation of -ln(p) percentage = 55 %
summation of -ln(p) = 158
summation of -ln(p) percentage = 66 %
summation of -ln(p) = 165
Anesthesia
summation of -ln(p) percentage = 0 %
summation of -ln(p) = 0
summation of -ln(p) percentage = 7 %
summation of -ln(p) = 18



AMC005
AMC006
EMU
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 597
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 306
OR
summation of -ln(p) percentage = 10 %
summation of -ln(p) = 61
summation of -ln(p) percentage = 0 %
summation of -ln(p) = 0
Anesthesia
summation of -ln(p) percentage = 0 %
summation of -ln(p) = 0
summation of -ln(p) percentage = 0 %
summation of -ln(p) = 0


AMC007
AMC008
EMU
OR
Anesthesia
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 284
summation of -ln(p) percentage = 100 %
summation of -ln(p) = 338
summation of -ln(p) percentage = 74 %
summation of -ln(p) = 209
summation of -ln(p) percentage = 20 %
summation of -ln(p) = 66
summation of -ln(p) percentage = 22 %
summation of -ln(p) = 62
summation of -ln(p) percentage = 0 %
summation of -ln(p) = 0

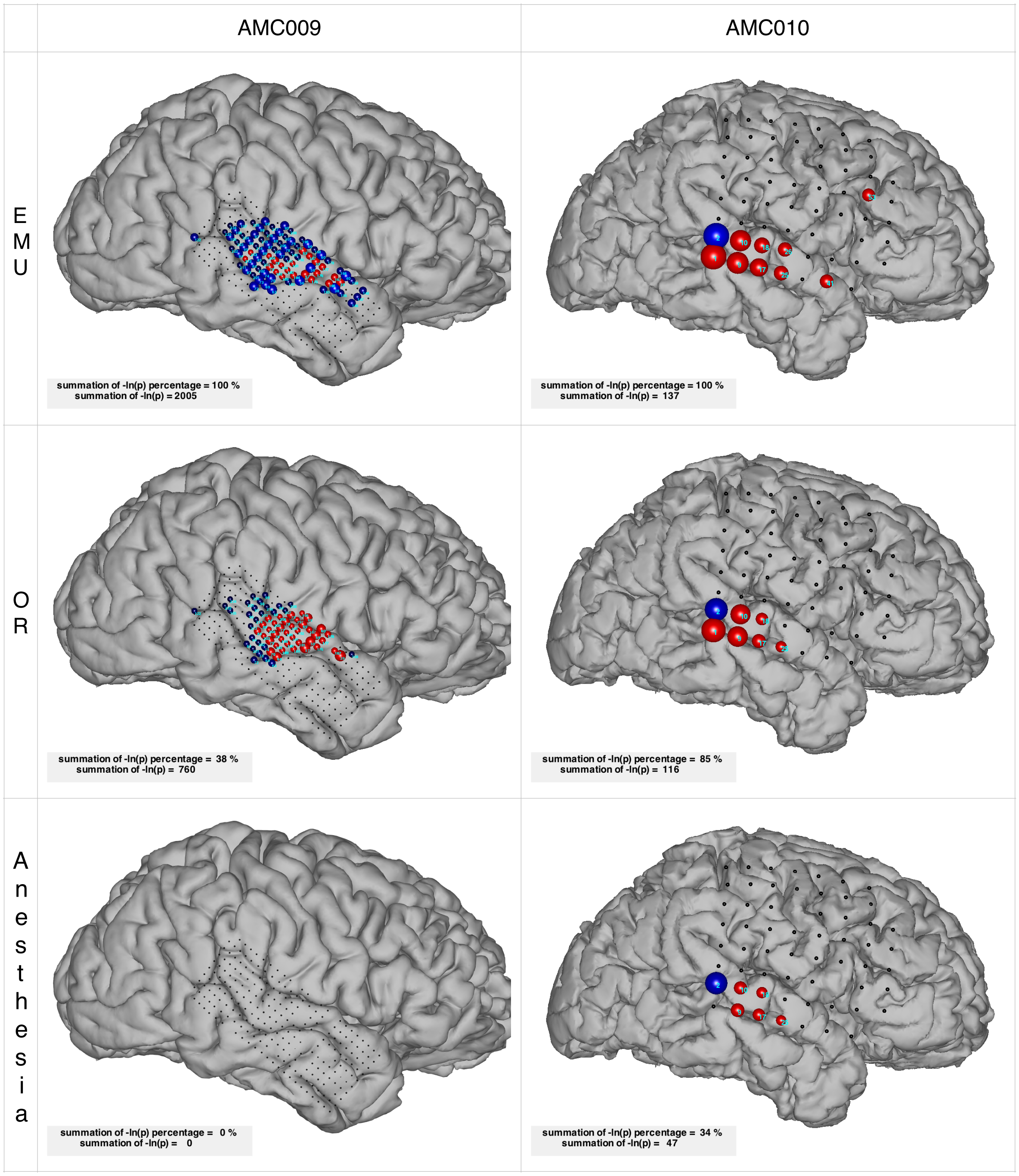


Figure 3.4: Table of brain activities for participants (blue spheres are auditory sensitive channels and red spheres represents channels sensitive to semantic tasks)

3.3 Measuring Depth of Anesthesia

Measuring depth of anesthesia is one of the important procedures that is crucial in any surgery that requires general anesthesia; However, the current methods are not accurate enough and their performance highly varies case by case. Most of these techniques are based on monitoring patient reaction to external stimuli which is considered as an indication for consciousness. Developing BiSpectral index (BIS) has been the first step towards modifying these methods. Although BIS has been vastly used, yet there is no general consensus regarding its reliability [20].

In this study we developed an index based on the p-value of the statistical tests which is an indication of depth of anesthesia. In figure 3.4, this index is reported for each condition and it is in absolute agreement with the consciousness of the patient. The calculated index for patients in EMU is 100, as they were fully awake. Other indexes were normalized to the value in EMU which helps to compare different conditions. The decrease in the value of the index as patients went through different conditions–from fully awake in EMU to some level of unconsciousness in OR–proves the fact that this index provides a practical means for measuring depth of anesthesia.

3.4 Conclusion and Future Works

The present study, provided a practical framework for the passive functional mapping of the language are in human brain. Identifying eloquent cortex is an indispensable process which is crucial in any brain study as well as brain surgeries. This indeed helps neurosurgeons to minimize collateral damage to brain tissue as they perform the surgery. ECS has been considered as the gold standard for brain mapping, nevertheless, this technique can be accompanied by complications. ECS can not be done in pediatric surgeries and also in epileptic patients, electrical stimulation could potentially triggers seizure.

To the best of our knowledge, this is the first time that the possibility of performing the functional mapping under anesthesia based on ECoG signals, was being investigated. The significance of this research stems in the fact that it demonstrates the feasibility of brain mapping under anesthesia. This eliminates the necessity for attentive participation of patient and facilitate the process of brain mapping. The reported promising results of this study not only proved the possibility of utilizing ECoG signals for functional brain mapping, but also paves the way for other teams to run research in this area.

Although, the primary focus of this study was on mapping language area, this procedure could be extended for to identify other cortical regions using ECoG signals. The potential roadmap for future research in this area includes designing various paradigms that could reveal the functional significance of various critical regions under anesthesia in order to generate a more comprehensive map.

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