Bachelor's Thesis

Bachelor's degree in Industrial Technology Engineering

Effects of electrical stimulation in childhood epilepsy

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Abstract

Epilepsy affects around 0.5% of children worldwide. At least a third of them are resistant to antiepileptic drugs and may have to undergo surgery. This condition is called refractory epilepsy. Beforehand, many tests have to be carried out to localise where the seizures are originated and whether surgery would damage functional areas. The amount of area that have to be resected by clinicians is called the epileptogenic zone (EZ). Nowadays, invasive and non-invasive tests are used to identify the EZ. In some cases, non-invasive evaluation suggests an uncertainty about where the seizures origin is. For this cases, invasive methods need to be carried out to complete the diagnose. Among the different invasive methods, stereoelectroencephalography (SEEG) has been used.

Electrical stimulation using SEEG can aid clinicians in the determination of the EZ. In this study, the SEEG signals during electrical stimulation will be used to elaborate the three-dimensional activation maps from a 19-year-old patient suffering from refractory epilepsy. The study will be held out with Matlab and Brainstorm.

Firstly, we will segment the signals and we will remove the noise by filtering it. Secondly, we will conduct a time-frequency analysis where the activations at different frequency bands (low and high frequencies) will be taken into account to map the brain activity in the brain cortex.

The observations from the conducted work allow narrowing down the epileptogenic zone that was firstly observed with non-invasive tests. The observations at high frequencies provide a more focalized pathological region, suggesting that clinicians should use these frequency bands in order to delimit the EZ.

Key words: refractory epilepsy, brain mapping, electrical stimulation, epileptogenic zone

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1. List of acronyms

AED	Antiepileptic drug
SEEG	Stereoelectroencephalography
DRE	Drug-resistant epilepsy
EZ	Epileptogenic Zone
VEEG	Video-electroencephalography

2. Preface

2.1. Project's origin

This project comes from the current NEURABLING project that the Polytechnic University of Catalonia is developing along with Sant Joan the Deu's Hospital. One of the project objectives is to develop new tools for the diagnosis and treatment of children suffering from intractable epilepsy.
Paediatric patients with intractable epilepsy are sometimes surgery candidates. For this reason, there is a necessity of defining where the seizures are originated. This information could allow to operate patients to resect or remove the affected area.

2.2. Motivation

When a patient is diagnosed with refractory epilepsy one of the most common and effective treatment is surgery. Before undergoing into a surgery, many tests have to be carried out to identify where the epileptogenic zone is and determine if surgery is possible. To do so, electrical stimulation can be used. There are many different ways of stimulating the brain differing by being invasive (introducing electrodes trough the skull into deep brain regions) or non-invasive (measurement of electrical stimulation through the skin). Stereo-EEG is an invasive method which allows to get information from different deep brain structures.

Once the stimulation has been completed, the interpretation of the results it is still difficult because the SEEG signals are still in a raw format. For this reason, brain mapping is very important. Brain mapping allow to map the functional and pathological areas and give clinicians a better visualization on how the patient's brain is responding to stimulation.

2.3. Previous requirements

This thesis is mostly addressed to biomedical engineers and doctors who want to gain information on brain mapping in patients who suffer from refractory epilepsy. Although it is not necessary, knowledge on Matlab and Brainstorm are recommended.

3. Introduction

According to the World Health Organization, epilepsy is a disease that affects 1% of the population, however, at least a third of these patients does not respond to antiepileptic drug (AED) [4]. The condition of not responding to AED is called refractory epilepsy.
This project comes from the current one that the Universitat Politècnica of Catalunya (UPC) and Sant Joan de Déu Hospital are developing on children's epilepsy and strokes. Epilepsy affects around 0.5% of children and young people under 18 [19]. In this project we will focus in children's refractory epilepsy and how to map the brain using electrical stimulation signals. This mapping could help doctors localize and resect or remove the area where the seizures originate, the epileptogenic zone (EZ).
Electrical stimulation can use either invasive or non-invasive tests. Although non-invasive tests are safer for the patient, sometimes the gathered information is not enough for a diagnose. In the 60s [9], stereoelectroencephalography (SEEG) was used for the first time. This technique allows to monitor the brain electrical activity in deep regions and can also be used as an invasive electrical stimulation method. Electrical stimulation gives raw signals whose interpretation is not obvious and needs a thorough study to identify where seizure originate. For this reason, using brain mapping could allow doctors to have a better visualization on the EZ and bound the functional and pathological areas of the patient. This information is useful to determine whether operating the patient could cause any damage on any other functional brain area.

3.1. Project Objectives

This project aims to provide information from the patient's disease using biomedical signals and images to aid clinicians in the presurgical evaluation of epilepsy. This information may be very useful for them in order to determine where the problem is originated and if surgery can be performed.

The specific objectives of this dissertation are:

Segmentation of biomedical signals: SEEG signals can be very long (~3 hours recordings) although just a few seconds may be relevant to our study. It is important to study what happens after the stimulation of each one of the channels. Moreover, we may take into

account that noise can alter our results so after segmenting the signals we may eliminate it using different methods.

Delimitation and mapping the Epileptogenic Zone: Biomedical signals give us an idea of what is going on in the patient brain but there has to be a study and an interpretation of those signals as to assure where is the region where the epilepsy seizure is triggered. The EZ is a theoretical area where it is thought that seizures originate that has to be resected as a solution to fight epilepsy. The study of where the EZ is arduous. Electrical signals from the brain after stimulation may give us some idea of how the pathological neurological networks activate and where do they originate.

Mapping of functional areas: Depending on the region that is stimulated, the patient's brain may trigger some electrical activity followed by some physical symptoms. Not all the stimulation from the different channels originate a pathological seizure similar to the ones that the patient has in a spontaneous way. By observing the symptoms and the areas that are activated when a stimulation is performed, we can map the physiological areas of the brain, that is, knowing which brain regions are activated when a function (language, motor, visual…) is taking place. This information is essential to know which are the limits where clinicians can resect the pathological brain tissue without compromising any physiological function.

3.2. Project's scope

This project has the intention of mapping electrical stimulation from children who suffer from refractory epilepsy. Before doing it there will have to be some previous knowledge about:

- The illness
- The electrical stimulations
- The software needed
- The anatomy of the brain

After that, the conditioning and study of the signals provided will be done before mapping them.

4. Epilepsy

4.1. Definition

World Health Organization defines epilepsy as a chronic disorder of the brain characterized by recurrent seizures that affects approximately 1% of the population. But this is not the only definition there is. According to the International League Against Epilepsy, epilepsy is a disease of the brain defined by any of the following conditions: at least two unprovoked seizure occurring less tan 24 hours apart, one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years or diagnosis of an epilepsy syndrome. Even though it may have been a controversial decision, epilepsy may be considered to be resolved according to the ILAE for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those remained seizure-free for the last 10 years.

For most of the patients who are diagnosed with epilepsy its cause is unknown.

4.1.1. Refractory epilepsy

This type of epilepsy is known by different terminologies such as drug-resistant epilepsy (DRE), intractable epilepsy, among others. As its name shows, this type of epilepsy cannot be treated with the common medication. [4]

It is difficult to diagnose because most of the patients have different outcomes. While reading different articles about this subject you can tell that there has no perfect definition. Although there is a highly agreement among those definitions, there are still some discrepancies. They mostly differ on how many treatments the patient has to fail as to diagnose him/her with DRE. However, most of latest articles referred to this type of disease, require a failure of two antiepileptic drug.

So we could conclude with an example of probably one of the most common definition used nowadays which Pindrik et al. have put together in their article. They define DRE as inadequate seizure control despite adequate trails of two antiseizure medications. [8]

4.1.2. Medical tests and methods to diagnose epilepsy

Seizures can be developed by different diseases or conditions. When a patient goes to a hospital after having a seizure, doctors are able to run different tests as to come up with a diagnose.

There are several tests that could help diagnose epilepsy such as electroencephalography (EEG), a magnetic resonance imaging (MRI), blood tests or a computed tomography scan (CT). However, no test on its own can determine for certain if a patient has or not epilepsy.

As seen before, when a patient suffers from epilepsy has failed at least two antiseizure drugs and is diagnosed with refractory epilepsy, one of the treatments may be going under surgery to remove the EZ. Before doing so, a pre-surgical work-up has to be done including a non-invasive and an invasive phase. The non-invasive phase does not need to puncture the skin and so tests such as MRI, EEG recordings, will be conducted. But sometimes the latter tests are not enough to identify the EZ and invasive tests such as the stereoencephalography (SEEG) method have to be carried out.

4.1.3. Electrical stimulation and Stereoelectroencephalography

Electrical stimulation is a technique that uses electrical impulses to produce a reaction in the highly connected neurological tissue. These impulses are discharged through electrodes that can be placed on the skin or directly on the brain. The position of the electrodes depends on the method that is being used: invasive and non-invasive.

The previous method can be used to map different brain areas and find where the seizures originate. Doctors use it to map the functional and the pathological areas of the brain.

Functional areas are specific brain areas which are responsible for different body aspects such as the motor control area, the speech area, the smell area, the hearing area, etc. [16]

Pathological areas are those brain regions that are affected by epileptic seizures. Once these areas are bounded, doctors may be able to operate the patient. In order to localize them, doctors stimulate different brain areas using electrical stimulation to see whether that zone produces similar patterns than a recurrent seizure or not.

Once doctors have an overview of the patient's brain and it is known where the pathological areas are, they can verify if it affects a functional area. When this happens, sometimes it is not possible to undergo under surgery to eliminate the epileptogenic zone because it would damage a healthy functional brain area.

As previously said, the pediatric studied in this thesis have undertaken the SEEG method, an invasive method.

SEEG is quite a new method because it was invented around 50 years ago by Jean Bancaud and Jean Talairach at the Sainte-Anne Hospital in Paris. [9]

According to Ho et al. [7] the SEEG method allows the insertions of multilead depth electrodes into cortical and subcortical areas of interest. Before the insertions of the electrodes there has to be a full diagnose of the patients as to know where will be the right brain area to place them.

SEEG is used for the following reasons, 1) to explore the deep cortical/sulcal structures; 2) to have bilateral recordings; 3) to define the epileptogenic zone; and 4) to map the brain's cortex as to plan a surgical procedure.

As previously commented, before performing the SEEG method there has to be a full diagnose of the patient, not only to know where the electrodes have to be placed but also to know if the patient requires to go through this highly-invasive medical procedure. From Ho et al. we can provide some discrepancies from non-invasive diagnostics that would ensure the doctor to carry through with the SEEG method:

> ''1) ictal or interictal electroencephalograpghy (EEG) findings discordant with clinical semiology; 2) absence of cortical lesions on MRI despite convincing EEG seizures localization; 3) incongruence between abnormalities seen on MRI and EEG and clinical semiology localization, suggesting extralesional involvement; 4) focal abnormality seen on MRI discordant with electroclinical hypothesis; 5) hypothesized EZ involved with or close to eloquent areas; and 6) large, hemispheric, and/or multifocal abnormalities revelled by MRI that are discordant with localized ictal onset''[7].

After many tests during the last years, it is known that SEEG is ideal for predicted subcortical or bilateral EZ involvement.

During the procedure, doctors place depth electrodes in brain areas where they suspect that seizures are taking place. Usually, the patient is monitored for several days to observe and study their interictal epileptic activity (between seizures) and their ictal activity (during seizures). In addition, during these days various tests can be carried out such as cognitive tests, visual stimulation or electrical stimulation.

Through the SEEG electrodes, single pulses can be delivered pseudo-randomly or periodically at a certain intensity and during a short period of time. Although this method may sound risky, it is much more safe than other methods, for example placing subdural electrodes. Derray S et al. in Allen L. Ho et al. [7] writes about having a mortality rate range between 0-1.4% by performing the SEEG method. This method has also a low rate of intracranial haemorrhage and surgical infections.

Although SEEG has been used for some time in investigation, is still a new technique used to map patients' brains who suffer from refractory epilepsy. Because of the previous reason, there are still variations among the centres that use it as to how deep are the electrodes or which type of subdural grids to use. There can also vary the methodologies used: frame based, frameless, and robot assisted. [7]

Overall, this method allows doctors to make an effective diagnose to those patients who suffer from refractory epilepsy. In this dissertation, as we are focusing on children, we can assure that is one of the safest invasive techniques because it avoids large craniotomies and as previously seen, it is very safe.

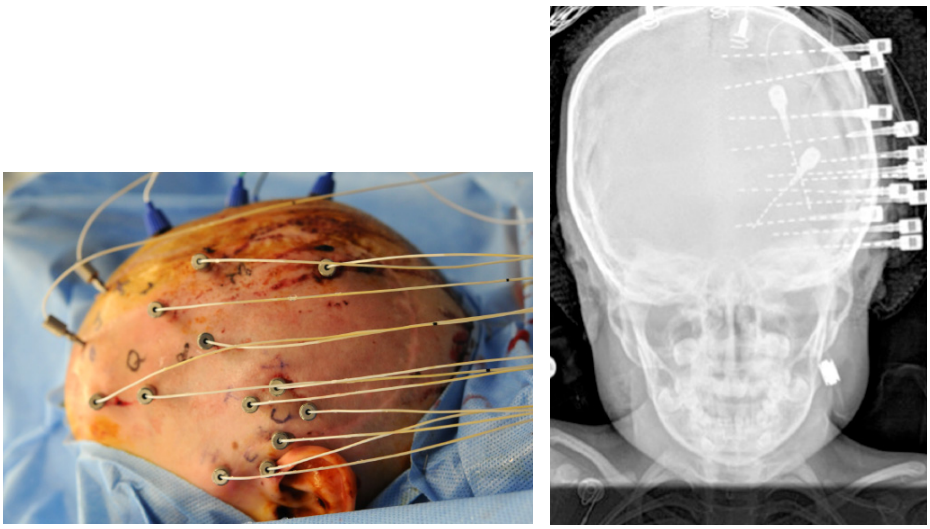


Figure 1. Patient at the end of the procedure, after the implantation of depth electrodes and skull X-ray with the positioning of the electrodes [14]

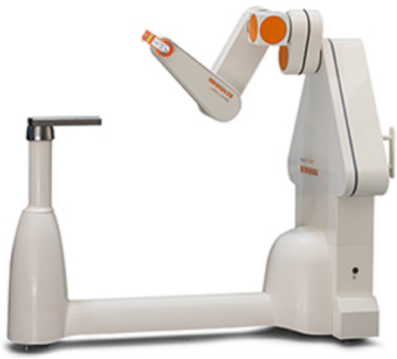


Figure 2. Stereotactic robot for electrode implantation [15]

5. Simple guide to the anatomy of the brain

The brain can be divided into different areas that will be stated below. The following figure show the right terminology that have to be used when referring to brain parts and regions.

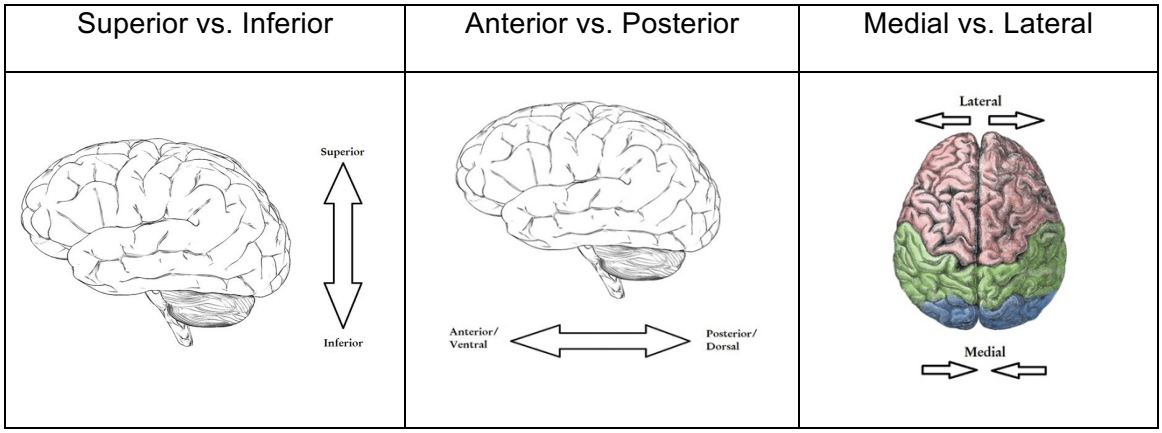


Figure 3. Locations of the parts of the brain [11]

The brain is composed by three parts: the cerebrum, the cerebellum and the brain stem. The cerebellum is under the cerebrum and is responsible for the body movements, involving coordination and muscle tone modulation [12].

The cerebrum comprehends the biggest part of the brain which is divided into to halves: the right one and the left one. But it is also subdivided in other six parts, known as lobes: the frontal lobe, the parietal lobe, the temporal lobe, the occipital lobe, the insular lobe and the limbic lobe[12]. Sometimes we may find that Scientifics only speak about four lobes not contemplating the insular and limbic lobes.

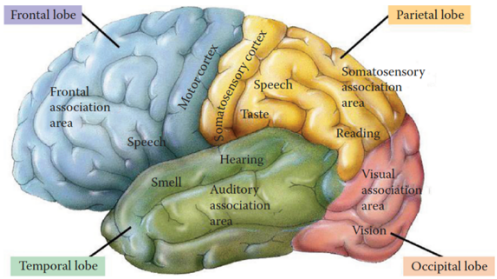


Figure 4. Representation of the lobes of the brain [12]

The frontal lobe is responsible for the body movement, the personality, concentration, planning, problem solving, the meaning of words emotional reactions, speech and smell. The parietal lobe is responsible for touch and pressure, taste and body awareness. The temporal lobe for hearing, recognizing faces, emotions and long-term memory. Lastly, the occipital lobe is responsible for the vision area [16].

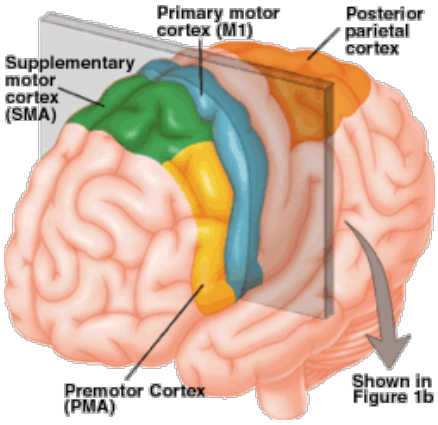


Figure 5. Principal cortical domains of the motor system [2]

One of the objectives of this thesis is knowing which parts of the brain are affected by seizures. This is one of the reasons to investigate which parts of the brains are responsible of the functions of different parts of the body.

As the primary motor cortex control some of the body movements, we will focus on this part. The primary motor is found between the somatosensory cortex and the premotor cortex, and it generated neural impulses that allow the body to make several movements.

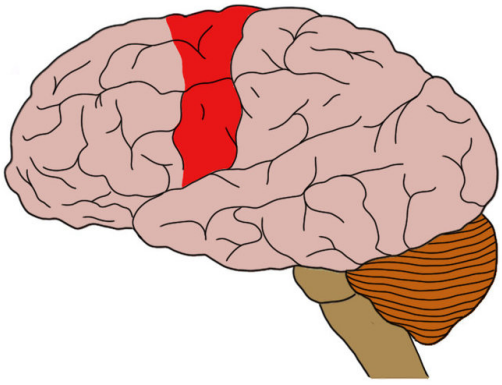


Figure 6. Visualization of the motor cortex in red [26]

Some useful tool to investigate which brain parts affect the body parts is studying the map of the body in the motor cortex which is called homunculus. This will give us an idea, once we study the electroencephalograms, of which brain zone may be creating seizures in its respective body part.

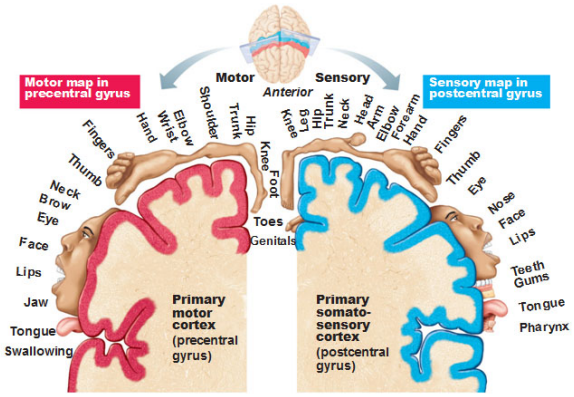


Figure 7. Homunculus of primary somatosensory cortex [1]

6. Data Science: MATLAB and Brainstorm

6.1. Why MATLAB?

MATLAB has several advantages not only for those who start using this program but also for those ones who have already use it. From the book Neural Data Science, we can see why the usage of MATLAB will be a must for this dissertation.

1. ‘’Well-developed help function’’
2. ‘’High-level language although not a limitation for beginners’’
3. ‘‘MATLAB provides a particularly strong suite of visualization routines and functions that would take a long time to program de novo in a low-level language like C.’’
4. ‘‘MATLAB is particularly optimized to represent matrices md the liner algebra operations that can be performed on them, which lends itself to handling neutral data’’.
5. ‘‘MATLAB functions as an obvious Schelling point in neuroscience’’. [3]

The application we will introduce works with MATLAB because as we have commented there are many useful tools that allow to read the electrophysiological recordings and perform advanced analysis.
On the other hand, the easiest way to work with neuroscience data is using matrices and MATLAB can work perfectly with them.

6.2. Why Brainstorm?

Brainstorm is an open source application dedicated to the analysis of brain recordings. Using this application, we are able to analyse multimodal data coming from different modalities: Magnetoencephalogram (MEG), Electroencephalogram (EEG), Fnirs, Electrocorticography (ECoG), depth electrodes (SEEG) and animal Invasive Neurophysiology [13].
Brainstorm is developed with MATLAB although users do not need their own license.
Brainstorm is a graphic user interface (GUI) that allow the visualization of raw and processed data from different perspectives: we are able to visualize time-series data while, at the same time we are able to visualize the activations in different areas of the brain. Furthermore, we are able to compute several processes to data: source analysis, time-

frequency analysis, connectivity analysis, etc. Due to the great number of options and functions that this application provides, the learning curve can be steeper, for this reason, there is a variety of online tutorials from the basics until the most complex tools. These tutorials were useful to learn the basics of brainstorm. The *SEEG epileptogenic maps* tutorial [17] was especially useful for a deeper understanding of the topic of the current project.

This application will allow to study the patients' stereotactic EEG (SEEG) recordings and to visualize them throughout 2D and 3D images during electrical stimulation. These resources will be very helpful in order to determine which brain zones are active, in which frequency bands and when.

7. Methodology

In this study, we are trying to analyse the activations and inhibitions of the electrical activity recorded by SEEG during electrical stimulation. We will perform this analysis dividing the signal into different frequency bands and observing how the different areas of the brain are activated. We will obtain 3D activation maps for each one of the stimulations that clinicians performed. These volumetric activations will allow clinicians to map the eloquent areas of the brain and also the pathological areas that produce similar patterns than a recurrent seizure, providing useful information for the surgical planning and a better view on the patient's illness.

7.1. Patients, signal acquisition settings and previous preprocessing

The Epilepsy unit of Sant Joan de Deu Hospital (HSJD) provided all the signals and data from this study. One pediatric patient (age 19) diagnosed with intractable focal epilepsy was selected for this study.
The sampling frequency used is from 1024Hz, the number of electrodes are 34, the number or needles are 9 and the Video-EEG monitoring lasted for 6 days.

7.1.1. Patients medical records and previous information

Patient's diagnose:
Refractory focal epilepsy, probably right medial peirolandic cortical dysplasia, with somatosensory aura +/- dystonic crisis +/- myoclonus in her left foot +/- left leg or left hemibody +/- bilateral convulsions, that begun at the age of 15.
Suspicion of right focal medial perirolandica cortical dysplasia. Negative Magnetic Resonance.

She was monitored with 9 DIXI electrodes during 6 days using a 128 channel Micromed system using the stereotactic technique. Table 1 shows the position of the electrodes and the number of contacts for each one of them. Furthermore, the magnetic resonance after (Figure 10) the implantation was also provided. This information allowed to localize the electrodes in a 3D configuration using Brainstorm software (Figure 11). This procedure was carried out by other members of BIOART lab.

Also with the MRI coordinates, we generated a default canonical surface following the recommendations provided in the *SEEG Epileptogenicity maps* Tutorial [17]. Using the obtained canonical surfaces, we will extend (interpolate) the functional information of the electrodes along the brain surface.

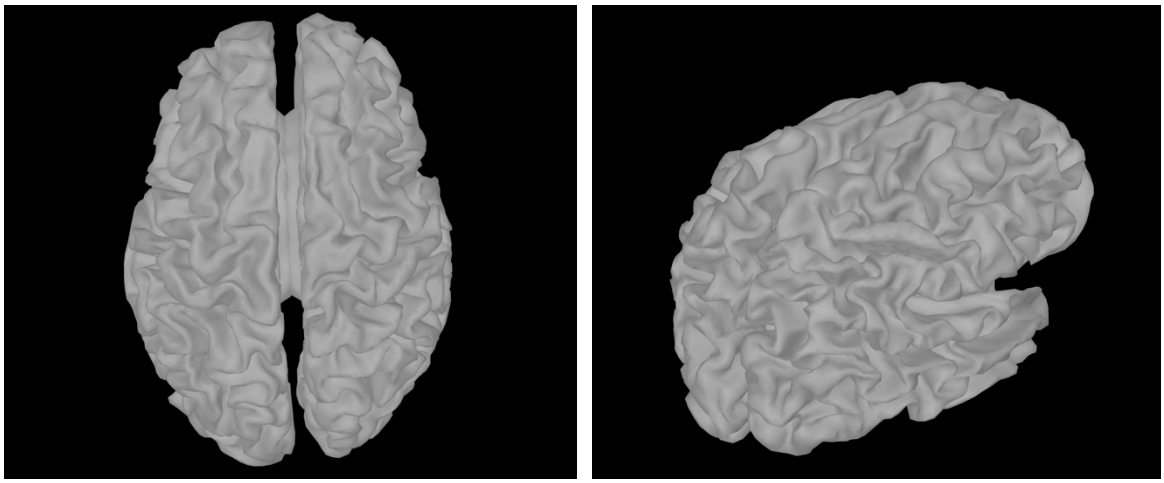


Figure 8. Brain surfaces generated with *Brainstorm*

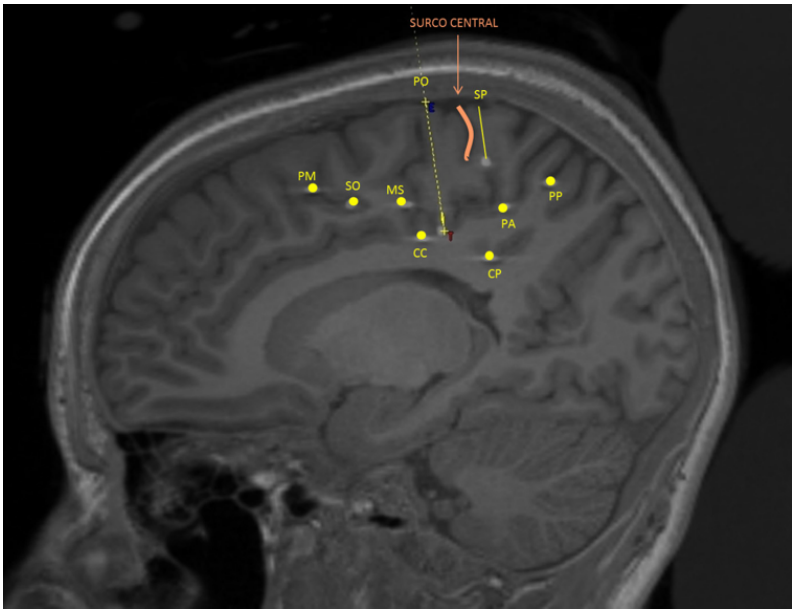


Figure 9. Visualization of the 9 DIXI implanted electrodes

Electrode	Area	Number of contacts
PM	Right premotor	12
SO	Right supplementary motor area, oblique	10
MS	Right supplementary motor area	15
CC	Right central cingulate	18
PO	Right primary motor area, oblique	12
SP	Right primary sensory area	10
CP	Right posterior cingulate	18
PA	Right anterior parietal	12
PP	Right posterior parietal	10

Table 1. Electrode names, position in the head for each one of the needles and number of contacts. [24]

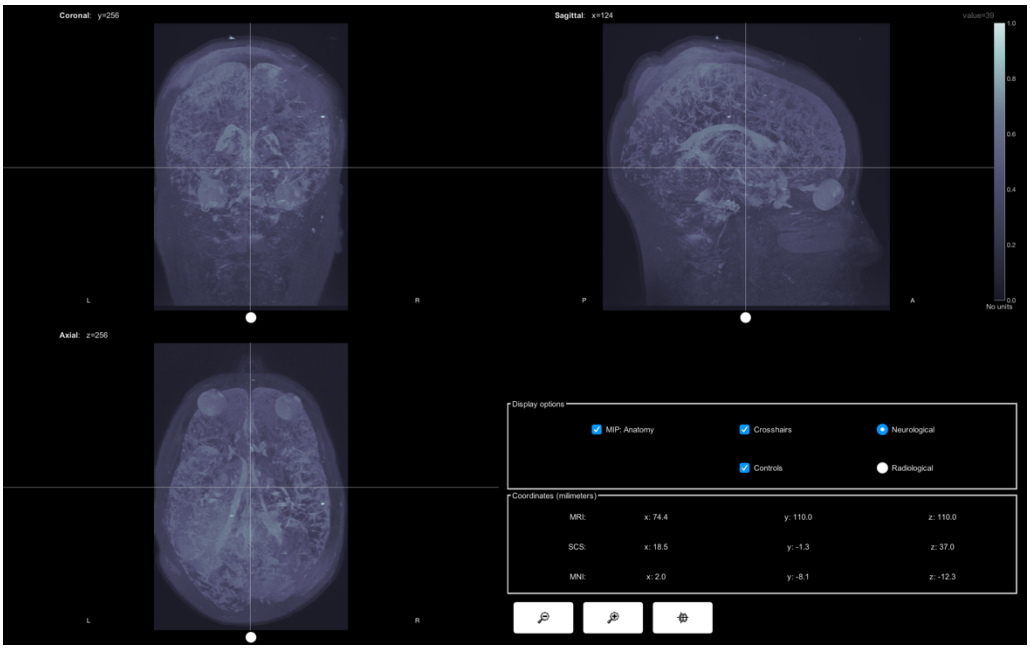


Figure 10. Magnetic resonance imaging (MRI) from the patient after the implantation of intracranial electrodes.

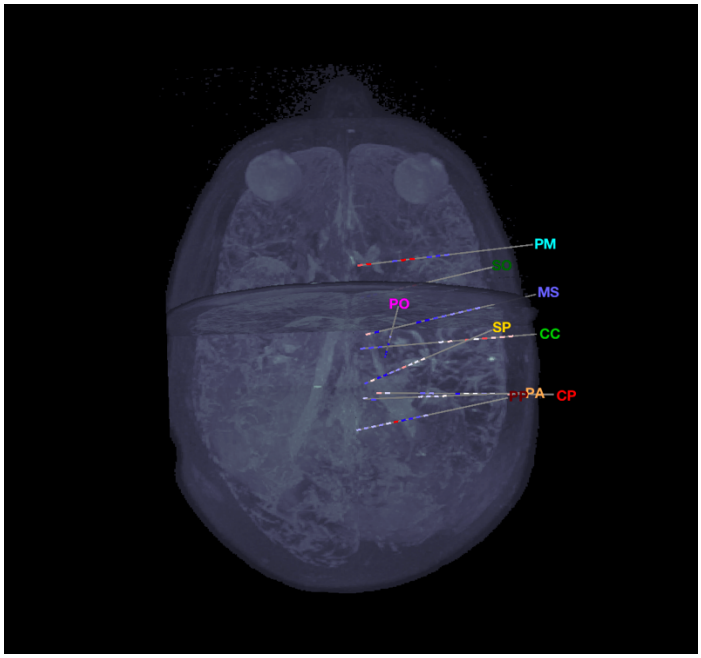


Figure 11. Visualization of the 3D configuration of electrodes and its contacts in *Brainstorm*

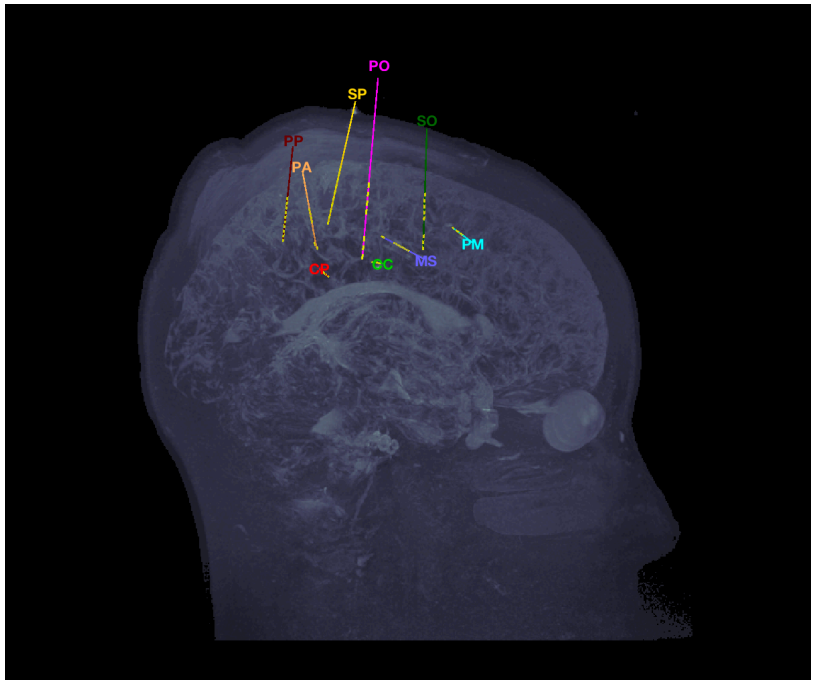


Figure 12. Left side visualization of the 3D configuration of electrodes and its contacts in *Brainstorm*

Clinicians stimulated different contacts of the brain while recording the SEEG activity in the other contacts simultaneously. They used for all the channels the same different time stimulation, frequencies and amperages.

Contact	Stimulation parameters
X	500micros.40” 1Hz 3mA
	500micros.5” 50Hz 1mA
	500micros.5” 50Hz 2mA
	500micros.5” 50Hz 3mA

Table 2. Example of a channel’s electrical stimulation

After the stimulation, clinicians observed which the changes in SEEG signals were and which were the observable changes in the patient. They included all this information in the clinical record.

The purpose of this study was to observe which areas of the brain are activated or inhibited after the electrical stimulation. To do so, we will compare the power in different frequency bands before (baseline) and after the stimulation.

7.1.2. Segmentation and cleaning of SEEG signals

The next step was to segment de SEEG signals. The segmentation involves the extraction of the segments of the RAW EEG that we will use. We will extract thirty seconds before and thirty seconds after from each one of the stimulations performed by clinicians (Figure 13). Each stimulation has a different length. For this reason, each one of the segments will have variable time length.

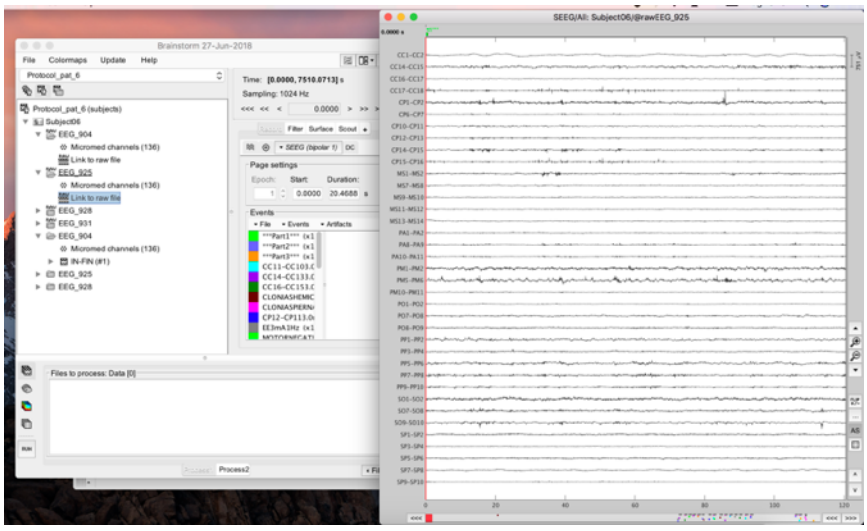


Figure 13. Example of a raw stimulation file

After creating these segments, we will delete the channel that has been stimulated. The stimulated channel records the stimulation that is much bigger than the electrical activity. This cause an artifact that may affect our further studies.

Once these segments were created, we saw that there was too much noise in the frequency peaks and we decided to use a frequency filter. We ran the notch and low-pass filter in the files as a way of correcting the noise in specific frequencies (50, 100, 150, 200, 250, 300 Hz).

We used the notch filter because it is suited to find contaminations when we are working with stable frequencies.

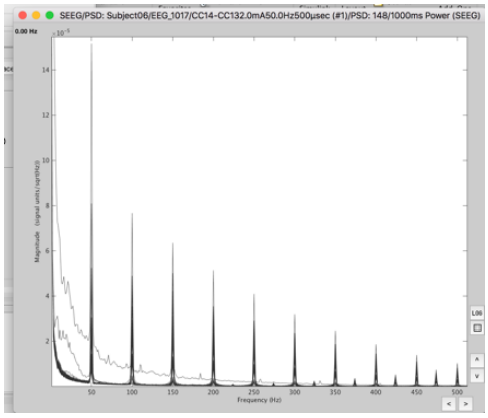


Figure 14. Example of a power spectrum density (PSD) graphic

7.1.3. Time-frequency analysis

After the segmentation and cleaning of the signals, we will perform the time-frequency analysis. For this step, we used two types of analysis: Multitaper analysis and Wavelets.
A time-frequency analysis allows to study both the time-course of the signal and frequency domain at the same time. Generally, biomedical signals show simultaneously fast oscillations in short periods of time and slow variations in long intervals. For the previous reason the wavelet transformation will provide a variable resolution regarding time-frequency. [20]
The multitaper function allows to reduce the noise by smoothing the frequency and as more tapers are used, better is the smooth achieved. The usage of this technique is highly indicated while working with values of frequency over 30 Hz. **Error! Reference source not found.**
Another technique used to develop the time-frequency analysis is to use Morlet wavelets that uses a complex exponential multiplied by a Gaussian window. This technique also allows to have access to time related changes and more temporal precision while working with high frequencies. [21]

> ‘‘The crucial difference between wavelets and multitapers is that in wavelets the signal is *convolved* with the basis function, whereas for multitapers the signal is *windowed* with the basis function and then subjected to a Fast Fourier Transform (FFT) procedure.’’[23]

For the Morlet Wavelets there has to be a definition of time bands and it is known that some brain functions can be associated to some brain waves. The human brain electrical activity can be divided into five brain waves and each of those have a particularly frequency range: [12]

- Delta waves range from 0.5-4 Hz. These waves happen frontally in adult and posteriorly in children.
- Theta waves range from 4-8 Hz. They are more commonly in young children than in older ones or adults. If many are observed it may be a sign from abnormal brain activity.
- Alpha waves range from 8-13 Hz. Alpha means first and these waves were discovered in 1908 by Dr. Hans Berger [12]. They are normally seen in the posterior half of the brain and have higher amplitude over the occipital areas.
- Beta waves range from 14-26 Hz. Apart from other aspects, these waves are

associated with sensory motor rhythm. They mostly found in the frontal and central brain regions.

- Gamma waves range from 30-90 Hz.

Epileptic patients have abnormal electrical activity that, depending on the shape and intrinsic signal frequency, can be classified as spikes and high-frequency oscillations. The latter are extracted by amplifying the recording and are divided into ripple (80-200 Hz) and fast ripples bands (250-500).

We will divide into different ripple bands the frequencies which comprehend from 80 Hz to 300 Hz. [18]

7.1.3.1. Steps to develop a time-frequency analysis in Brainstorm

Firstly, we will study the signal using the multitaper analysis following the *Brainstorm* tutorial. It suggested using a frequency (start: step: stop) of 10:30:220 Hz but we will be using 10:20:220 Hz to have more intervals of study. That would mean that the first frequency would be the 'start' on and it would change its value every 'step' Hz until reaching the 'stop' value.

After that we will create power spectrum density graphics to analyse the evolution of the recording.

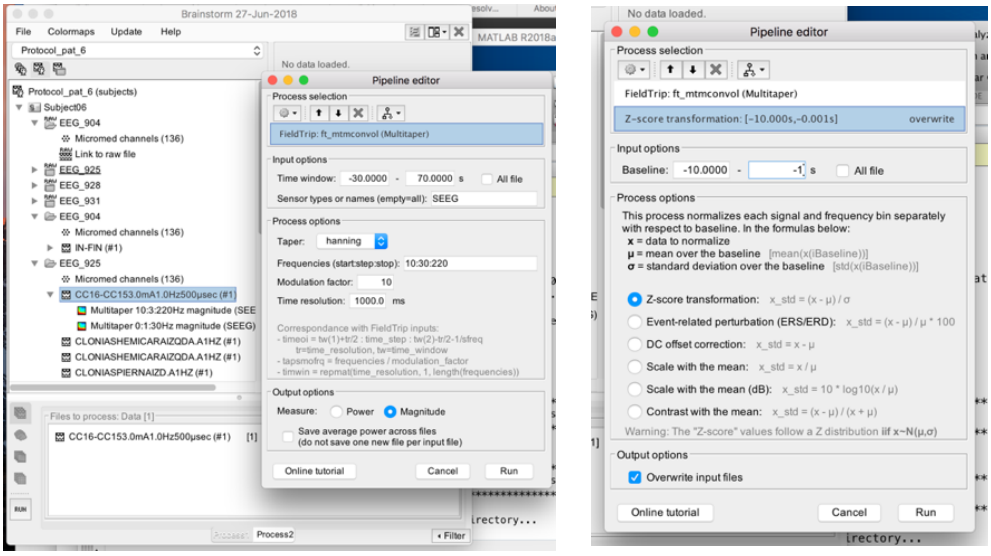


Figure 15. Creation of Multitaper and Power Spectrum Density in *Brainstorm*

Secondly, we will develop a time frequency decomposition of the EEG recordings using Morlet Wavelets. These have sinusoidal shapes which allows to 'capture local oscillatory components in the time series'. [13]

To define this, we will be focusing in time and frequency definition. As for the former, we will divide the signal into two different time bands to have different overviews. In the first one, each time band will have 3000ms and as for the second one we will be splitting the recording in three bands (before, during and after the stimulation). The second method will allow us to see an average of the behaviour in the three studied phases (before, during and after the stimulation).

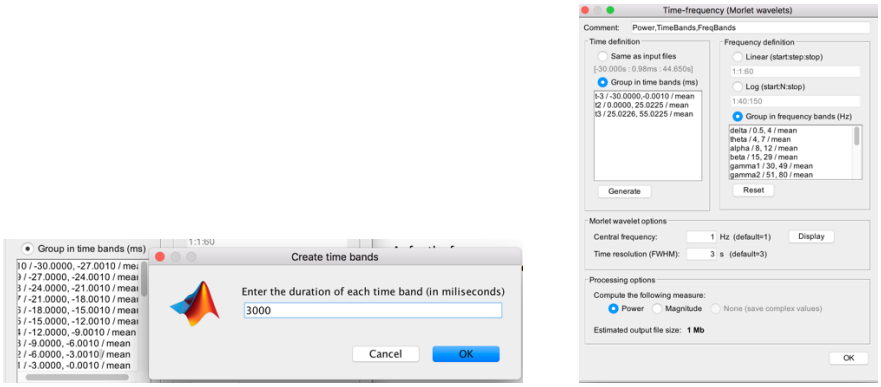


Figure 16. Time-band and time-frequency in the creation of Morlet Wavelets

As we explained, the EEG recordings show different types of oscillations known as brain waves. Brain waves are categorized into bands according to their frequency or number of 'waves' per second. To create the Morlet Wavelet is necessary to define the frequency bands. As we have seen that there is noise in the frequency peaks, even though we have filtered it before, we will not consider those frequencies for our study.

In Brainstorm we will place:

Frequency band	*From*	*To*
Delta	0.5 Hz	4 Hz
Theta	4 Hz	7 Hz
Alpha	8 Hz	12 Hz
Beta	15 Hz	29 Hz
Gamma 1	30 Hz	49 Hz
Gamma 2	51 Hz	80 Hz

Ripple 1	80 Hz	99 Hz
Ripple 2	101 Hz	120 Hz
Ripple 3	120 Hz	149 Hz
Ripple 4	151 Hz	170 Hz
Ripple 5	170 Hz	199 Hz
Ripple 6	201 Hz	220 Hz
Ripple 7	220 Hz	249 Hz
Ripple 8	251 Hz	270 Hz
Ripple 9	270 Hz	299 Hz

Table 3. Frequency-bands placed in Brainstorm to create the time-frequency analysis with Morlet Wavelets

After developing the time-frequency analysis there are still some modifications that have to be done to correctly visualize how the stimulation affects the patient's brain. To do so, the power maps need to be normalized with respect to the baseline. The baseline is defined as the brain activity without stimulation (the last 30 seconds after the stimulation).

To normalize the data, we will extract the 3000ms time band graphic to Matlab and will subtract the pre-stimulation to the post-stimulation.

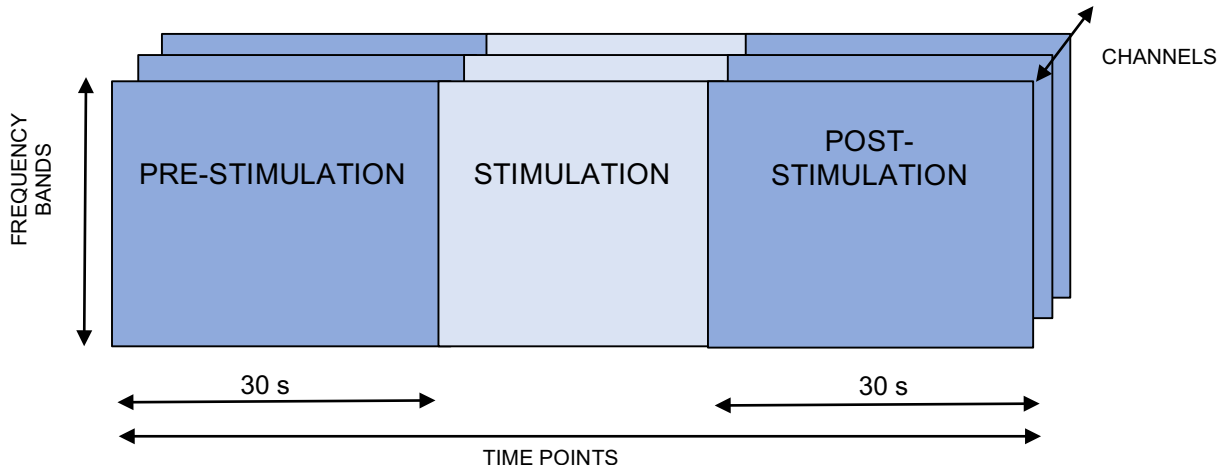


Figure 17. Schematic representation stimulation paradigm

As this type of normalization is not available in brainstorm, we will normalize the data directly in Matlab, developing a script (Figure 19). We will export the data from brainstorm. This data will be saved in a structure, whose one of its fields is called "TF" (channels*time points

* frequency bands). The first nine time points correspond to the pre-stimulus. We will subtract the average pre-stimulus to all the data.

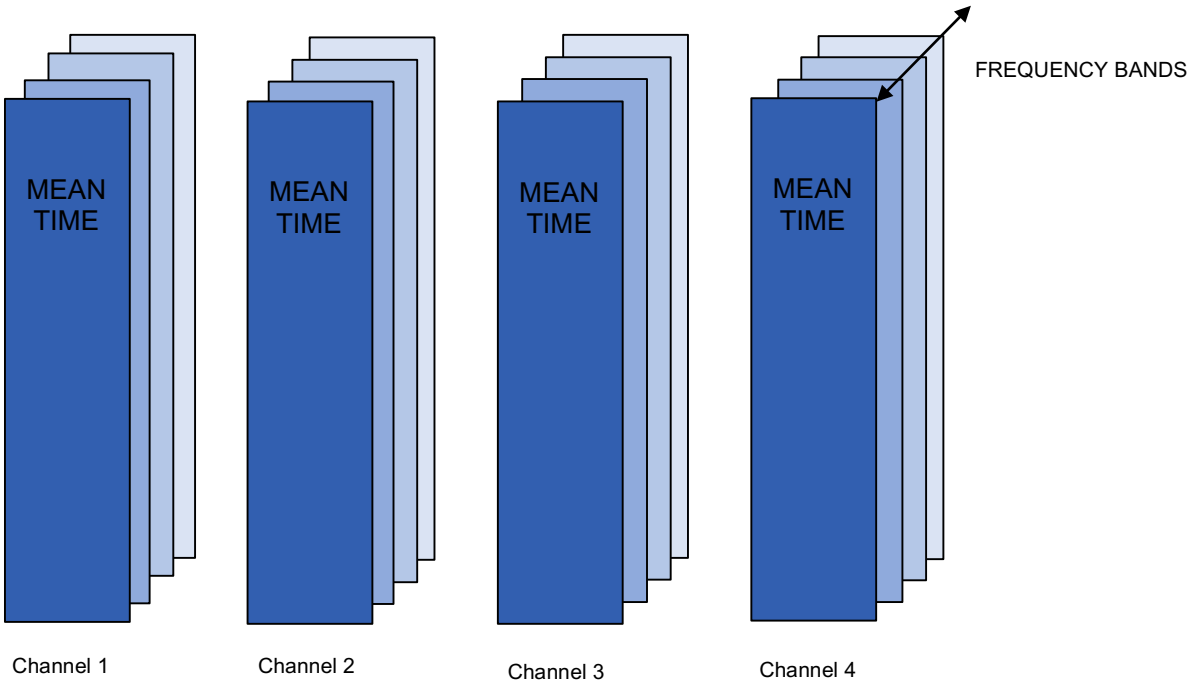


Figure 18. Visualization of the channels' composition per each frequency

```
mean_baseline = permute(mean(variable.TF(:,1:9,:), 2), [1 3 2])
baseline_corrected = permute(variable.TF, [1 3 2]) - (mean_baseline)
variable.TF = permute (baseline_corrected, [1 3 2])
variable.Comment = 'Power, TimeBands, FreqBands (SEEG) | baseline'
```

Figure 19. Matlab code

Once the powers had been normalized, we will import it again to Brainstorm and extract the time value from the end of the stimulation to that time plus thirty seconds. Brainstorm allows to interpolate the activity of the sensors into the scalp if a three-dimensional canonical surface is provided. By doing this, we will be able to visualize a comparison inside the cortex (activation and inhibition of cells) from how the stimulation affects the patient's brain with respect to the baseline.

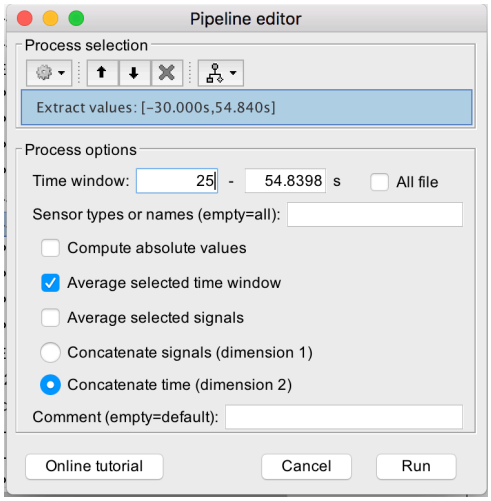


Figure 20. Extraction from time values from the Baseline file

8. Results

The electrical stimulation signals provided for this research were raw and needed to be conditioned before doing the analysis.

Firstly, the signals were segmented in a period that included thirty seconds before the beginning of the stimulation and thirty seconds after its ending. After the segmentation, we cleaned the channel interference and eliminated the noisy channels.

Finally, we have created the normalized time-frequency maps using two methods:the Multitaper and Morlet Wavelets.

After visualizing the results from the time-frequency we have dismissed the Multitaper images because they did not give any relevant information. There was no pattern followed in the images and the results were inconclusive.

8.1. Detection of functional areas, pathological areas and epileptogenic zone

The *Brainstorm* software was used to study the electrical signals from the patient in the medical trial. For the evaluation of the signals, coordinates from the electrodes' localization and the patient MRI were uploaded to the software.

Electrical stimulation is commonly used for two main purposes: to map the functional areas of the brain and to delimit the epileptogenic areas. When an electrode is stimulated it may induce a seizure or not. If the electrodes cause a seizure, the activations will be treated as epileptogenic or pathological areas and if not, the activations will be treated as functional areas.

The visualization of the results will be done through the following brain three-dimensional images:

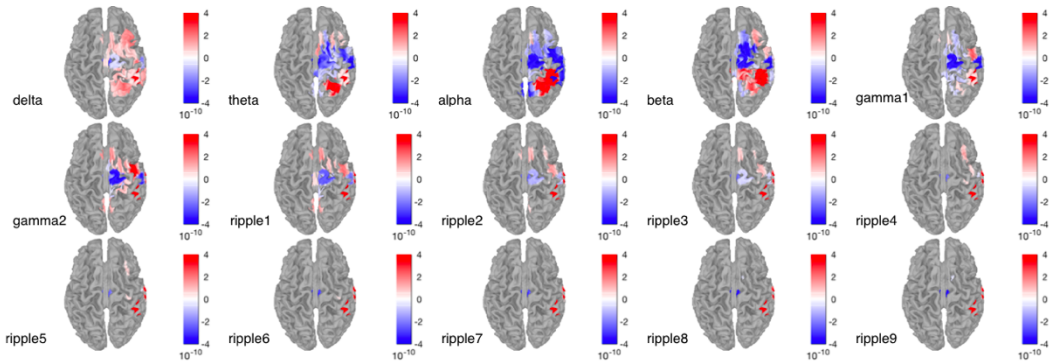


Figure 21. Example of a visualization of brain capture

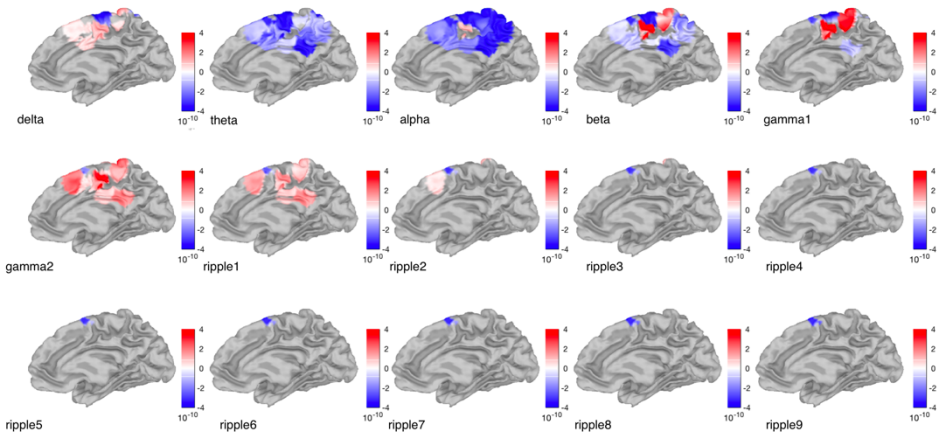


Figure 22. Example of visualizations of brain captures

The previous images show the brain activity when stimulating. In Figure 21 we can observe the lateral and medial part. The Figure 22 allows seeing the superior internal part. Both of them allow to visualizing the anterior and posterior part of the brain.

These brain images show the increase (reddish) or decrease (bluish) of activity that the brain experience after the stimulation in comparison to the baseline. White zones correspond to the areas that have not changed with respect to the baseline.

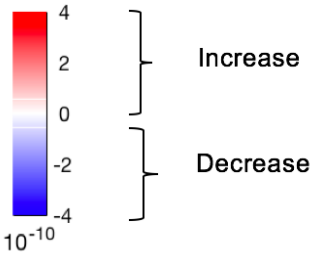


Figure 23. Example of a brain map scale

Each of the taken snapshots refers to each one of the described frequency bands. By doing this, we are able to visualize if there may be different patters regarding each one of the frequencies.

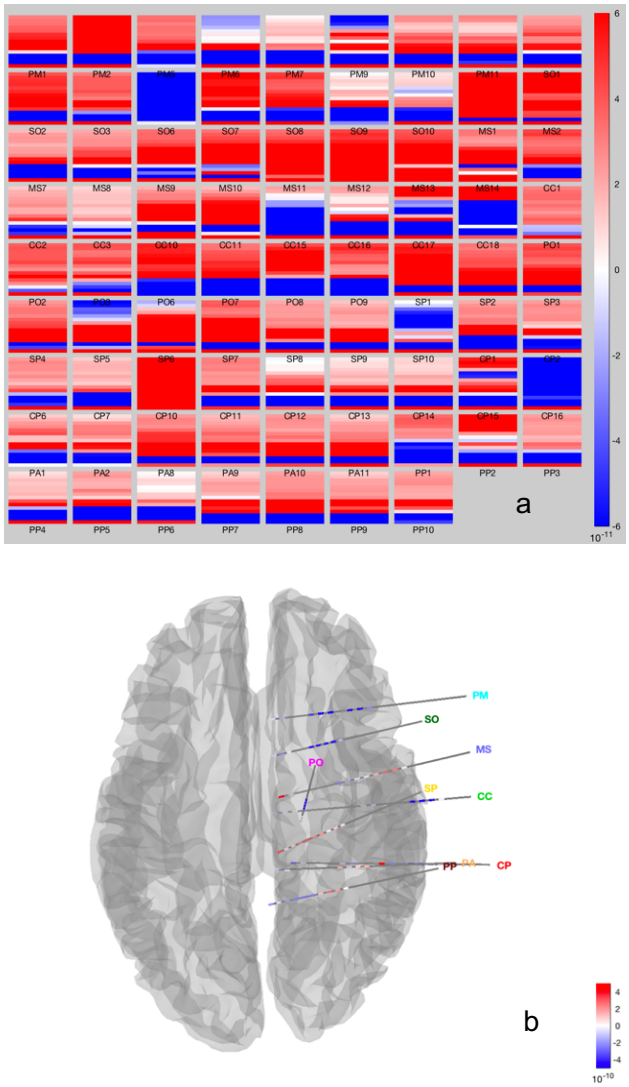
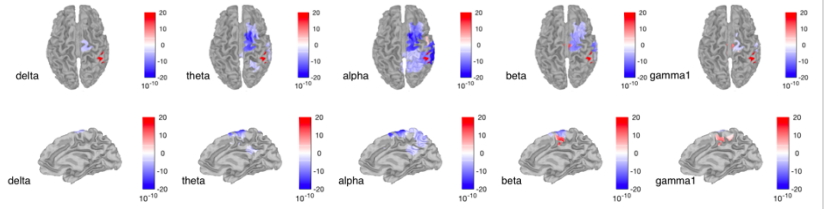
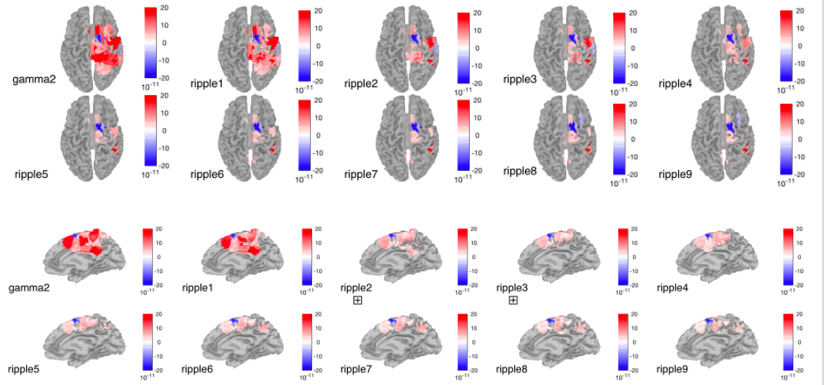
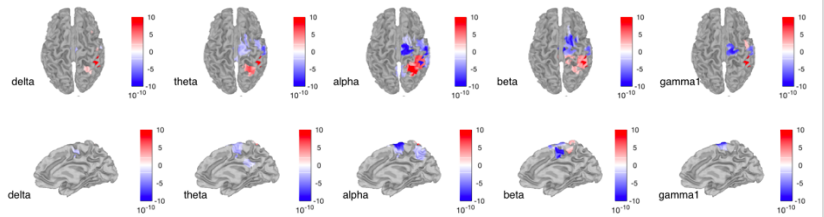
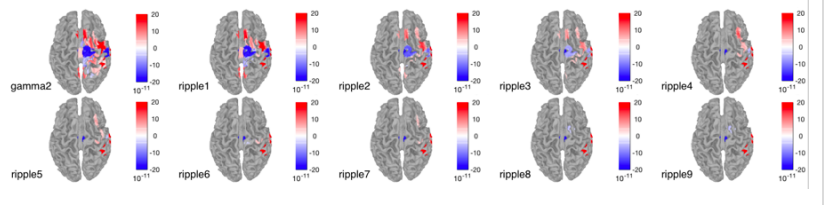
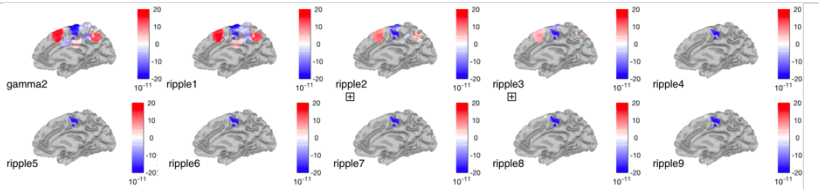
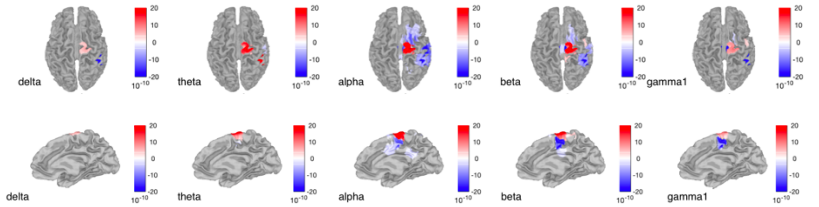
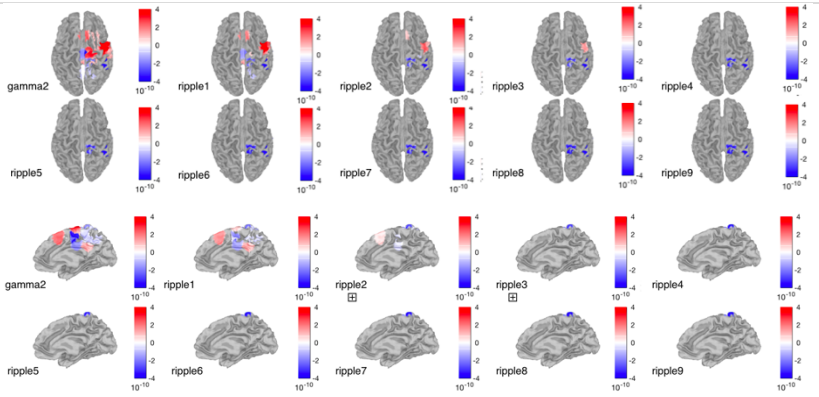
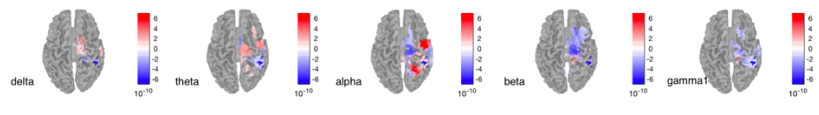


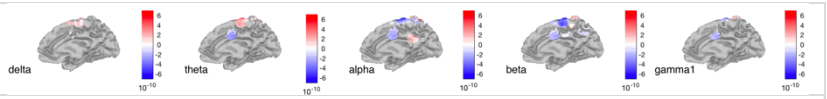
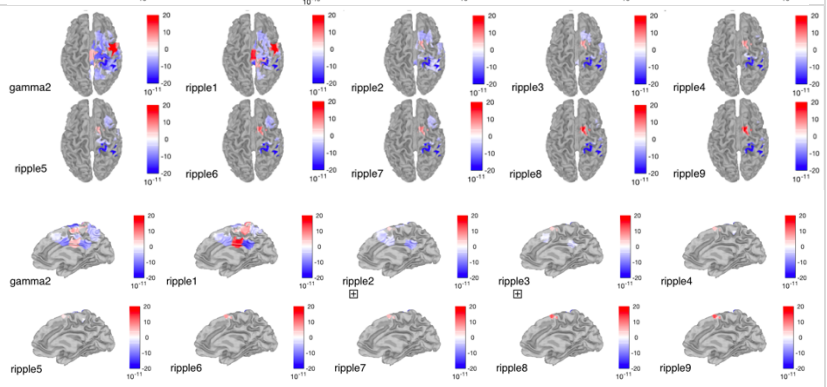
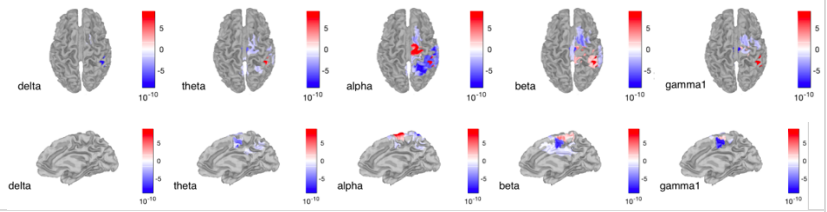
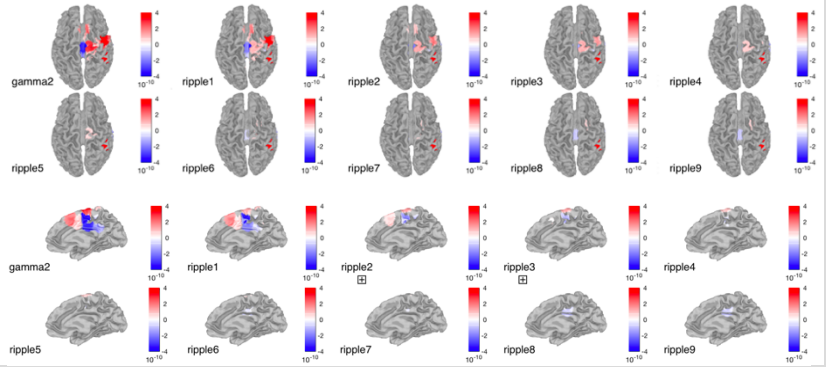
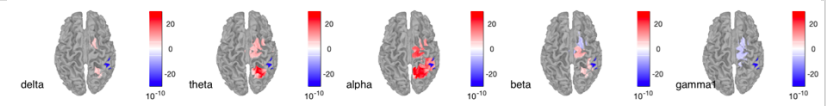
Figure 24. Visualization of all channels in a specific contact stimulation a) temporal visualization and b) visualization per each contact

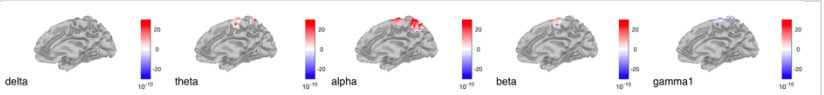
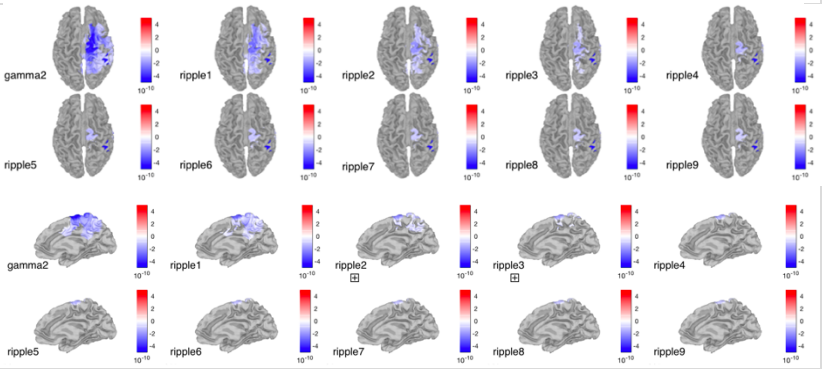
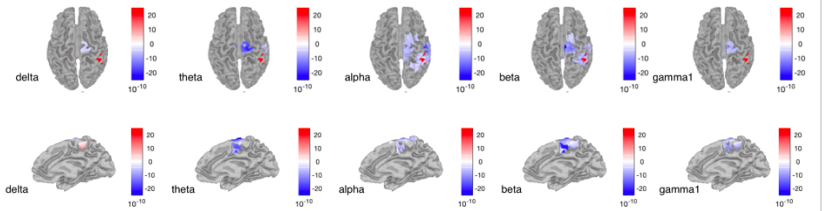
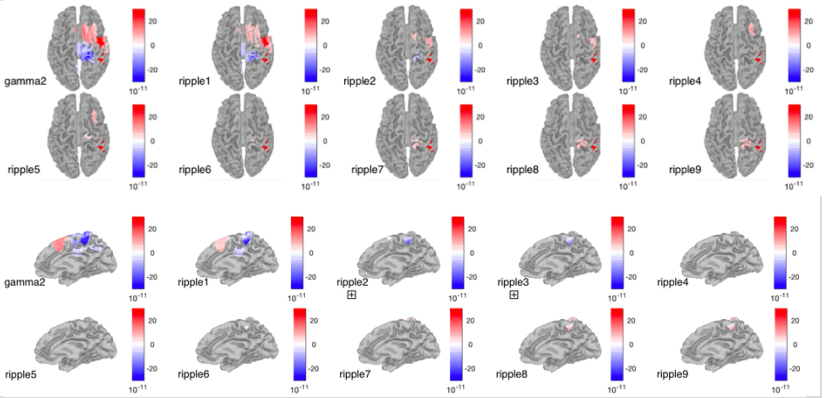
8.1.1. Functional areas

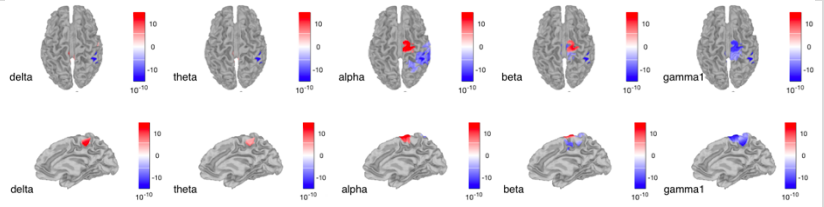
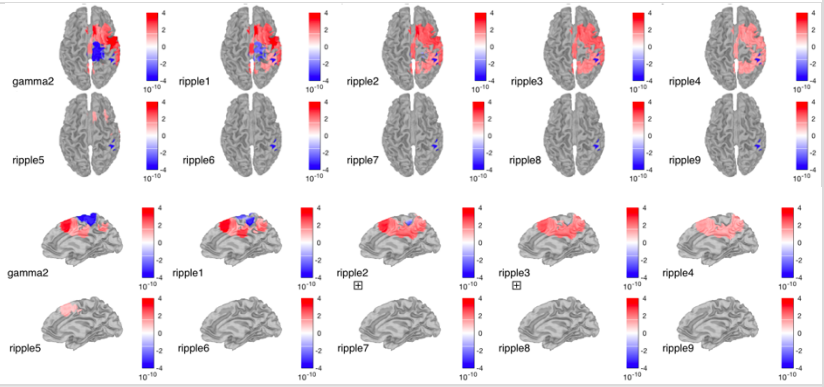
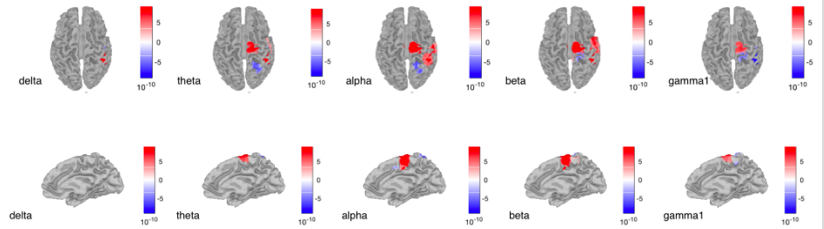
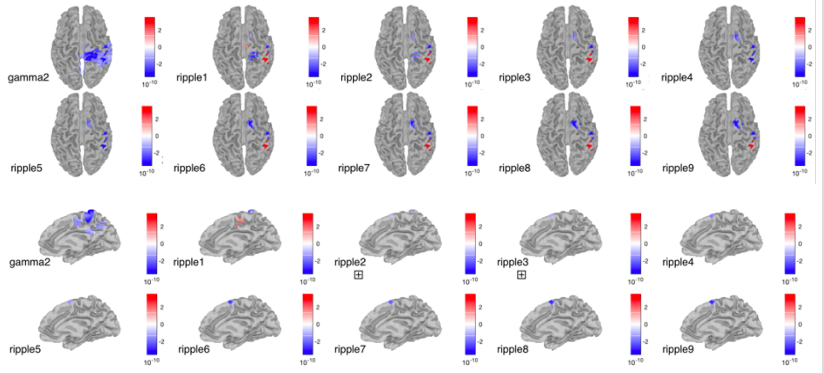
As previously commented, functional areas are the ones that when stimulated, do not originate regular seizures. Even though a seizure is not induced, the patient still feels some other physical outcomes that will be studied. The information provided by the patient along with the information extracted by the brain maps is useful to provide a better delimitations of the functional areas of the patients.

Contact		CC13-14
Clinical observation		Quick left peribucal myoclonias and left elbow and forearm movements while the spiking lasts. It does not look like her usual seizures.
		Areas of the body involved | Peribucal area, left elbow and forearm.
Brain map	Low Frequencies	
	High Frequencies	
Contact		CC15-16
Clinical observation		Quick left peribucal myoclonias and also strange sensation on the tip of the tongue while the spiking lasts. It does not look like her usual seizures.
		Areas of the body involved | Peribucal area and tongue.
Brain map	Low Frequencies	
	High Frequencies	

		
Contact		CC2-3
Clinical observation		Unpleasant sensation, contraction and quick myoclonias in the anterior part of the left thigh and then in the left leg and arm while the spiking lasts. Hemiparesis that lasts 20''. It does not look like the beginning of her seizures.
		Areas of the body involved Left thigh, leg and arm.
Brain map	Low Frequencies	
	High Frequencies	
Contact		MS1-2
Clinical observation		Low amplitude myoclonias in left hand fingers following from pronation and myoclonias of the left arm and left side face while the spiking lasts. It does not look like the beginning of her seizures.
		Areas of the body involved Left hand fingers, arm and side face.
Brain map	Low Frequencies	

		
	High Frequencies	
Contact		PO1-2
Clinical observation		High frequency myoclonias in the arm and quick blinking of both eyelids. Tone rise in left arm and at a lower level in left leg while the spiking lasts. After that, left hemiparesis that predominates in the left arm during 20-30''. It does not look like the beginning of her seizures.
		Areas of the body involved Left arm and leg.
Brain map	Low Frequencies	
	High Frequencies	
Contact		SO6-7
Clinical observation		No observations
Brain map	Low Frequencies	

		
	High Frequencies	
Contact		SP5-6
Clinical observation		Contraction in the left hemiabdomen and the left leg root and then from arm and left hemiface while the spiking lasts. It does not look like the beginning of her seizures.
	Areas of the body involved	Left hemiabdomen, leg, arm, hemiface.
Brain map	Low Frequencies	
	High Frequencies	
Contact		SP5-6 (3mA)
Clinical observation		Contraction in the left hemiabdomen and the left leg root and immediately also from the left arm and the left hemiface while the spiking lasts. It does not look like the beginning of her seizures.

		Areas of the body involved	Left hemiabdomen, leg, arm and hemiface.
Brain map	Low Frequencies		
	High Frequencies		
Contact		SP7-8	
Clinical observation		Myoclonias in left hemiabdomen while the spiking lasts. It does not look like her usual seizure.	
		Areas of the body involved	Left hemiabdomen
Brain map	Low Frequencies		
	High Frequencies		
Contact		SP8-9	

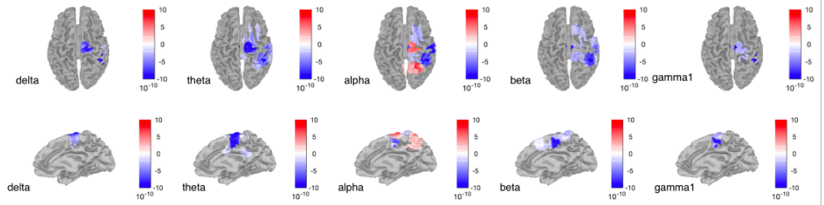
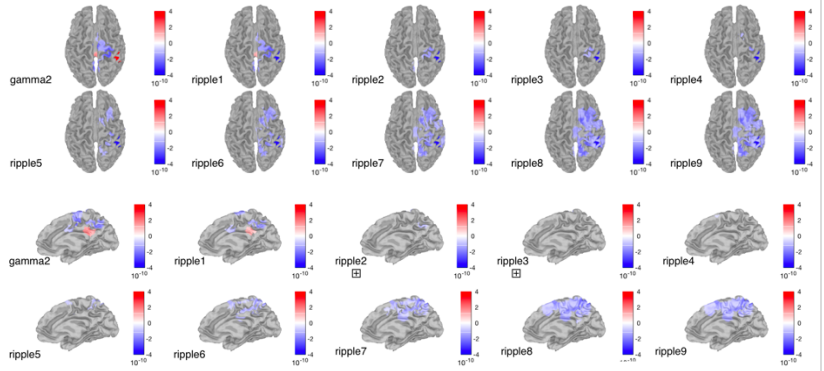
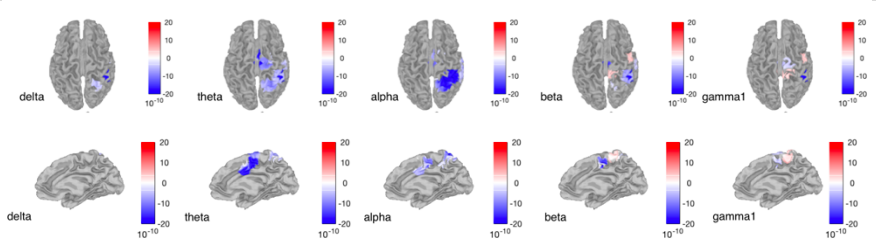
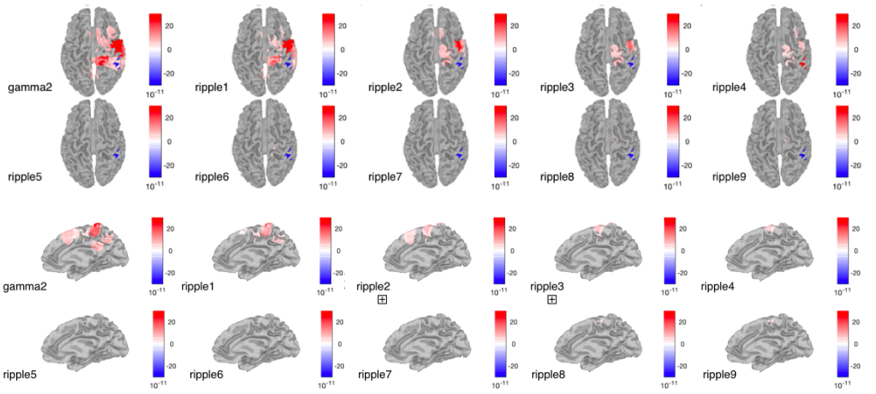
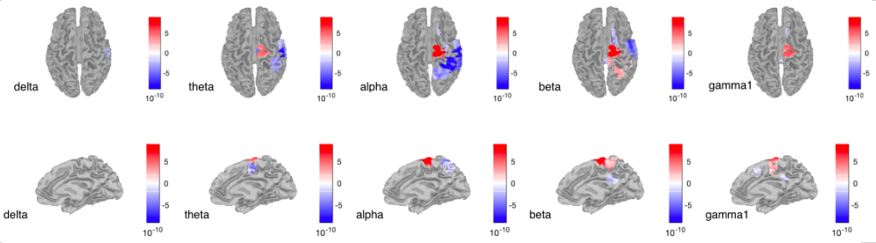
Clinical observation		Contraction in left chest while the stimulation lasts, it does not look like her usual seizure.
		Areas of the body involved Left chest
Brain map	Low Frequencies	
	High Frequencies	

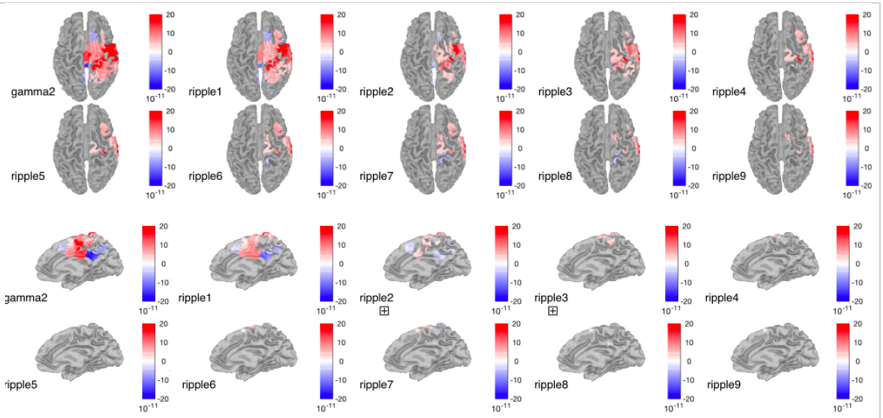
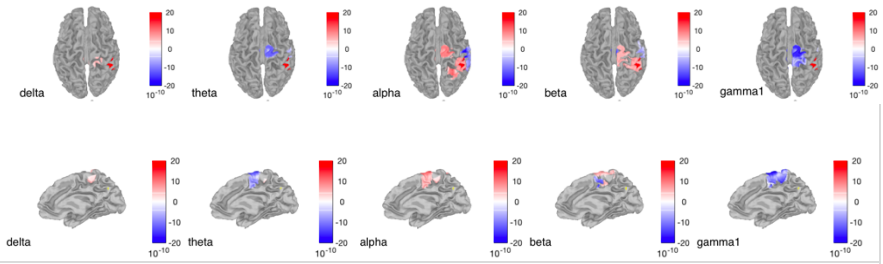
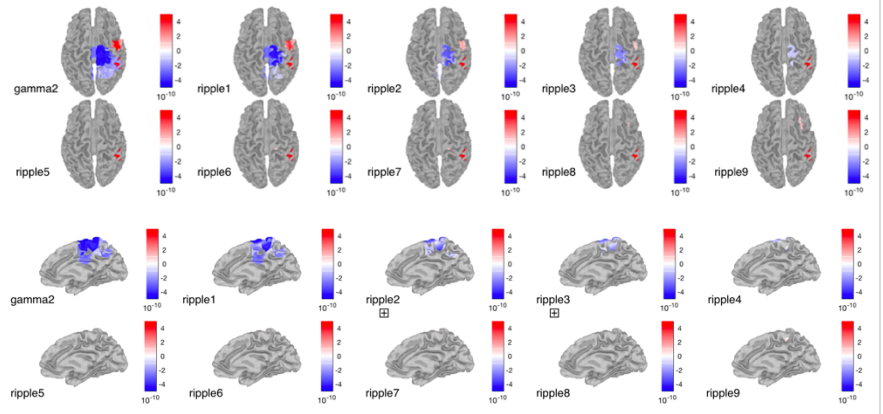
Table 4. Contacts, clinical observations and brain maps figures from the patient [24]

8.1.2. Pathological areas

Sometimes, when some of the electrodes are stimulated, the patient's usual seizure is triggered. The stimulated electrodes that trigger a usual seizure are the most interesting ones because is highly probable that the EZ is near the contact. Furthermore, we can observe which brain zones are affected, this allow clinicians to evaluate if the removal of the epileptogenic zone is feasible or not.

Contact	PO6-7
Clinical observation	It is similar to her usual seizure, but with tonic contractions firstly in the left arm and immediately after, contraction with flexion and rotation from the inside part of the left foot and lower from the left leg. Also from all the left hemibody and myoclonias. She preserves her consciousness and speech. Postictal hemiparesis that predominates in her left arm during 1-2''.

		Areas of the body involved	Left arm, inside part of theft foot, left leg and hemibody.
Brain map	Low Frequencies		
	High Frequencies		
Contact		PO7-8 (1mA)	
Clinical observation		Seizure almost like her usual one, but immediately tonic contraction with flexion and rotation from the inside part of the left foot and lower from her left leg. And almost simultaneously left hemibody contraction and myoclonias. She preserves her speech and consciousness. Postictal hemiparesis that predominates in her left arm during 1-2''.	
		Areas of the body involved	Inside part of left foot, left leg and left hemibody.
Brain map	Low Frequencies		

	High Frequencies	
Contact		PO7-8 (1.5mA)
Clinical observation		Seizure almost like her usual one, but immediately tonic contraction with flexion and rotation from the inside part of the left foot and lower from her left leg. And almost simultaneously left hemibody contraction and myoclonias. She preserves her speech and consciousness. Postictal hemiparesis that predominates in her left arm during 1-2''.
	Areas of the body involved	Inside part of left foot, left leg and hemibody.
Brain map	Low Frequencies	
	High Frequencies	
Contact		PO8-9

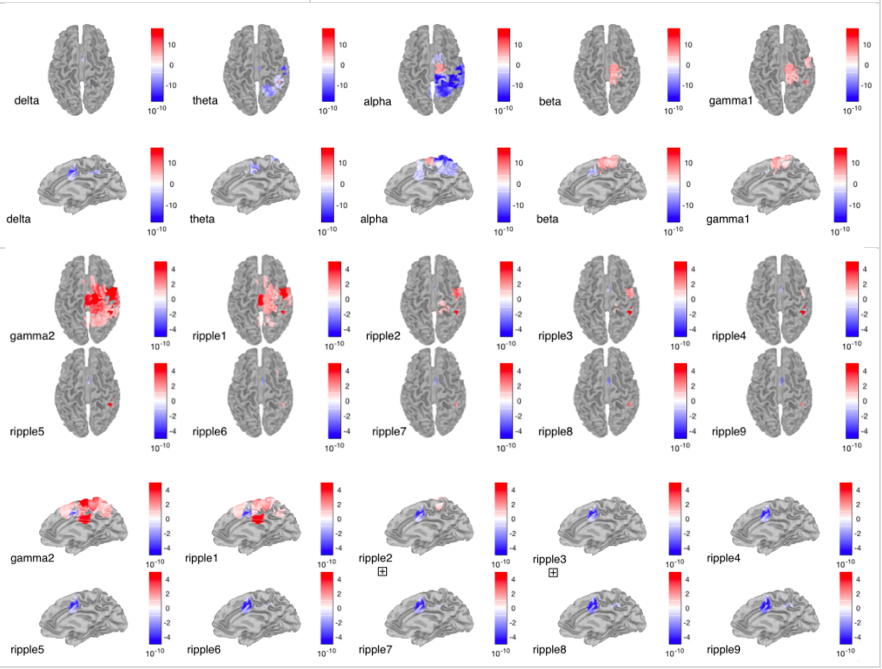
<table>
<tr><td colspan="2">Clinical observation</td><td colspan="2">Seizure almost like her usual one, but immediately tonic contraction with flexion and rotation from the inside part of the left foot and lower from her left leg. And almost simultaneously left hemibody contraction and myoclonias. She preserves her speech and consciousness.
Postictal hemiparesis that predominates in her left arm during 1-2’’.</td></tr>
<tr><td colspan="2"></td><td>Areas of the body involved</td><td>Inside part of left foot, left leg and hemibody.</td></tr>
<tr><td rowspan="2">Brain map</td><td>Low Frequencies</td><td colspan="2" rowspan="2"> 
</td></tr>
<tr><td>High Frequencies</td></tr>
<tr><td colspan="2"></td><td colspan="2">
</td></tr>
</table>

Table 5. Contacts, clinical observations and brain maps figures from the patient [24]

8.1.3. Epileptogenic zone

The EZ is a theoretical area where it is thought that seizures originate that has to be resected as a solution to fight epilepsy.

Doctors already provided us information about where all medical tests suggested that the EZ was localized.

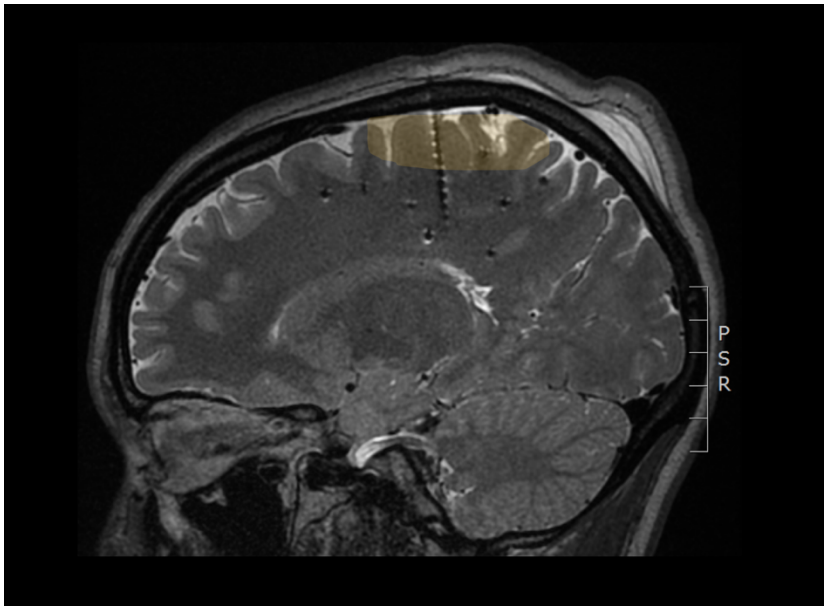


Figure 25. Computerized Tomography Image of the Epileptogenic zone provided to the research

From the conducted analysis, we could study if the previous area is really the one that is originating the seizures or if it is another one. Or maybe the area to be resected could be smaller than the medical prediction.

Depending on the analyzed frequencies, the visualization of the EZ can change. As we have commented, to study the EZ is better to focus on the signals that have caused a seizure like the patient's usual one. While low frequencies (figure 26) show more synchronized processes throughout the brain, high frequencies (figure 27) show processes that are more linked to the beginning of seizures [27]. Figure 27 shows an inhibition (decrease in power) in high frequencies, suggesting that the inhibited area may be responsible for the trigger of the seizure.

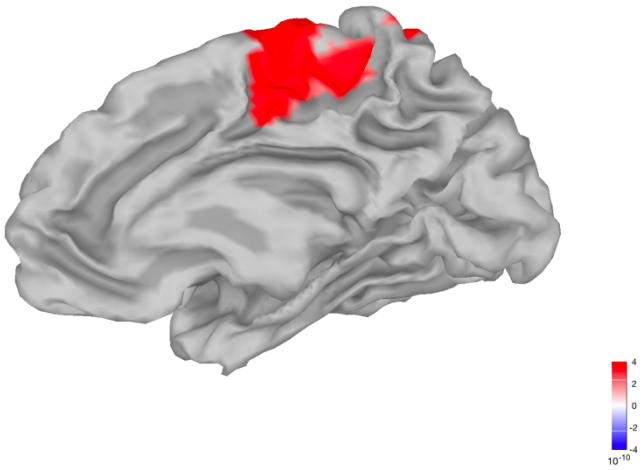


Figure 26. Epileptogenic Zone visualized in Brainstorm at low frequencies (alpha) in PO7-8

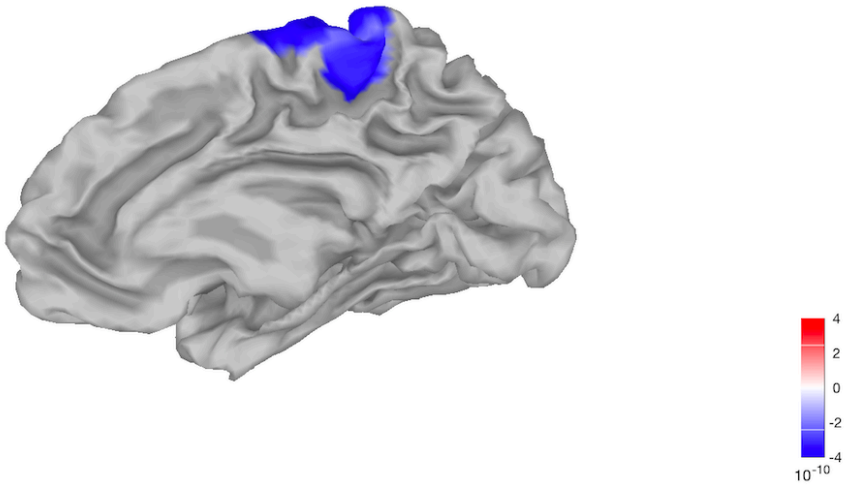


Figure 27. Epileptogenic Zone visualized in Brainstorm at high frequencies (ripple1) in PO7-8

Although mostly of the figures studied show the EZ around the previous area, in one of the pathological figures we also can visualize another area that could be causing the patient's seizures.

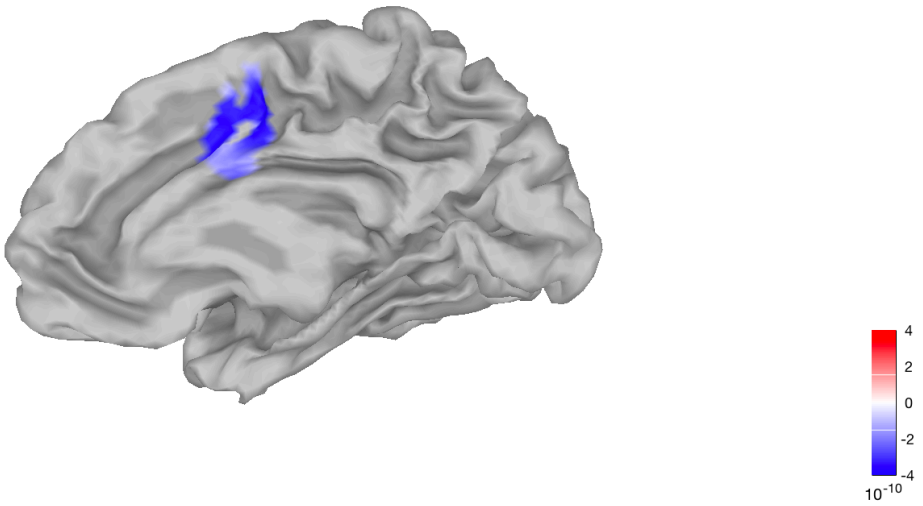


Figure 28. Pathological area in PO9-8 channel in ripple1

8.2. Overlap between functional and pathological areas

There may be some brain areas that have the same behavior at some frequencies in both functional and pathological scenarios.

For instance, left side of Figures 29 and 30, show an overlap at low frequencies, beta, from the same area. However, on the right side from Figures 29 and 30 we focus at high frequencies (ripple1) and it shows that the overlapped area has mostly disappeared.

Both figures 29 and 30, are a clear example of activations at low frequencies and inhibitions at high ones. This is due to the fact that at low frequencies the interconnection among neurons is higher than at high ones. This is the reason why we see red areas at low frequencies whereas at high ones, the areas are bluish.

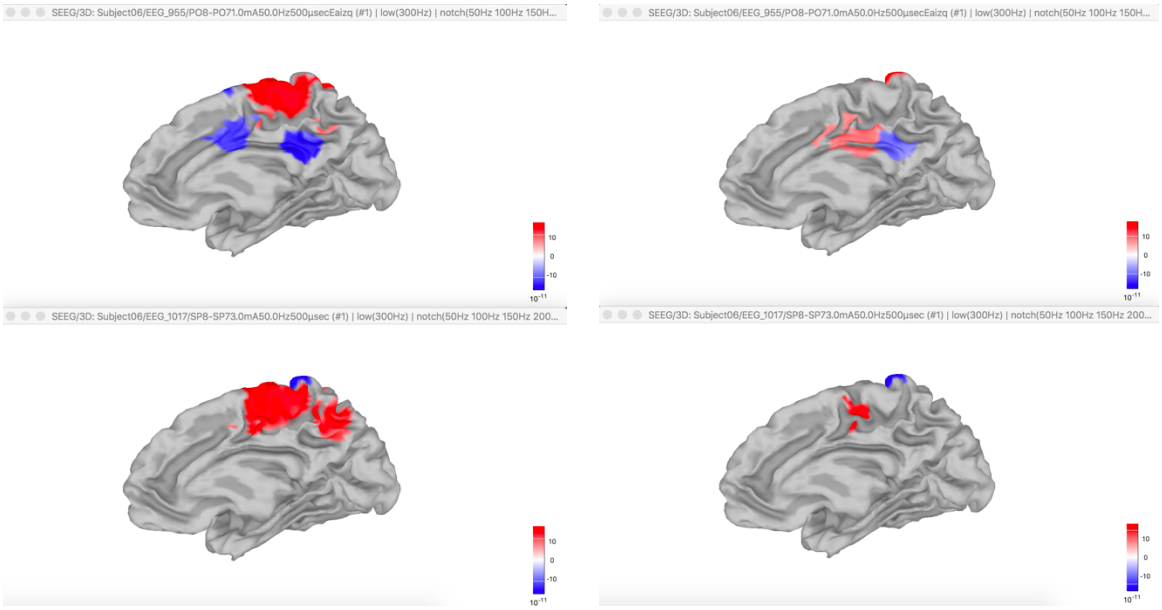


Figure 29. PO7-8 and SP7-8 at low (beta) and high frequencies (ripple1)

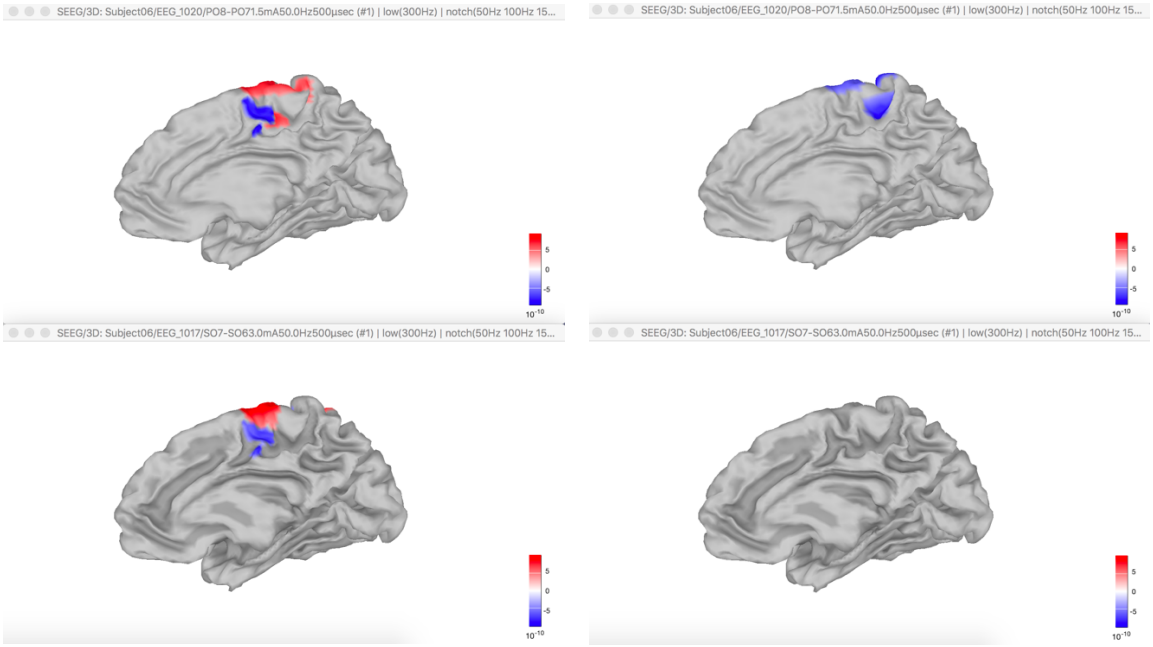


Figure 30. PO7-8 and SO6-7 at low (beta) and high frequencies (ripple1)

8.3. Interrelation with the stimulated area

Sometimes, some areas are continuously red (increase) or blue (decrease), and that could be caused for a direct relation with the stimulated area. This occurs usually around the CP contact at mostly all frequencies.

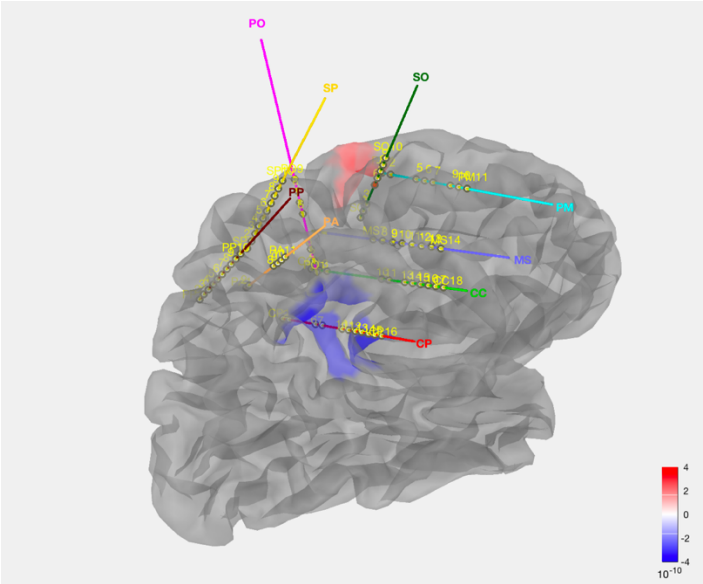


Figure 31. Area with continuously decrease around CP contact

9. Discussion

When surgery is the better option for patients who suffer from refractory epilepsy, clinicians have to thoroughly evaluate the patient conducting different medical tests. These tests will allow to determine epileptogenic zone and to see if the resection of the area could cause any damage to either healthy areas or life essential ones.

The doctors from Sant Joan the Dèu Hospital have provided us information from a 19-year-old patient who suffers from refractory epilepsy. To define the EZ and study a possible strategy to resect the area that is causing the seizures we studied the 6 days SEEG recordings where electrical stimulation was carried out during one of that days.

The provided signals were raw, for this reason, there was the need to previously conditioning the data to be able, later on, to visualize and analyze significant information. First of all, we have segmented the signals extracting thirty seconds before and thirty seconds after from each of the stimulation. We have eliminated the channel that has been stimulated to remove the stimulation artifact and then we have filtered the signals to erase the line noise.

Thanks to brainstorm, the information of the electrodes was interpolated into a three-dimensional mesh of the brain. This mesh was generated considering the anatomical points of the patients, obtained with the MRI.

After the preparation of the anatomical data, the segmentation and cleaning of the signals, we have performed the time-frequency analysis. Time-frequency is an advanced signal processing method that allow us to evaluate the stimulation through time and observe which are the changes in the brain activations at different frequency bands. This type of analysis is especially interesting in epilepsy because the neuronal activations are not the same in low than in high frequencies [27]. By being able to visualize and compare the changes of power before and after the stimulation at different frequencies, we can assess which are the areas of the brain that are involved when a specific area of the brain (one electrode) is stimulated.

For this step, we investigated two types of analysis: Multitaper and Morlet Wavelets analysis.

After visualizing the results from the time-frequency we have dismissed the Multitaper images because they did not give any relevant information. There was no pattern followed in the images and the results were inconclusive.

From the Morlet Wavelets analysis there are many observations to be commented. Firstly, from the images of the brain activity we observe that there is an hyperarousal at low frequencies. This could be caused because at low frequencies the interrelation among neurons is bigger than at high frequencies. Because at high frequencies the interrelation among neurons is lower, the effect of the ones that are still connected give better information of where the epileptogenic zone is localized. Considering that the area is more delimited at high frequencies, the resected zone should be studied there [28].

Although in a channel (PO8-9) that has originated a seizure we have noticed a possible different epileptogenic zone, there is no pattern with any other of the pathological studied.

It is noticeable that although it may be an overlap of areas at low frequencies between functional and pathological areas, it usually disappears at high ones. As previously commented, this could be caused due to the higher interrelation of neurons at low frequencies.

In Figure 31, we can observe that sometimes there is an interrelation between the area stimulated and some other area of the brain. That causes a continuously red (increase) or blue (decrease) area. Although it may have been interesting to study the brain map by erasing that area for possible noise, the Brainstorm program did not allow it.

Although it may have been useful coming up with a relation from the observed brain activations in the brain maps with the patient's symptoms, it was not obvious to find this type of relations with the available information. We have seen that the epileptogenic zone is more or less activated in every channel and that, could be related with her problems in the left arm and especially to the patient's leg. However, there is no certainty about these conclusions and would need further research.

Furthermore, as the studied area is small, and the neurons inside the brain are connected as a network, it is likely that when a stimulation is carried out in a point that is near the EZ the pathological paths activate. Even this may not be enough to trigger a seizure, the neurological network is still stimulated and we may see that the pathological areas are activated or inhibited. This effect is especially noticeable at low frequencies, where most of the hyper-synchronized activity take place. To improve these results, more channels would have to be studied with similar symptoms from the patient, in order to conclude with some sort of a brain atlas. That would allow to identify more rapidly the patient's seizure symptoms with the brain activity.

To sum up, when a signal is generated from an electrical stimulation, there is a lot of noise that may affect its interpretation. On one hand, the idea of this project was to condition the raw signals and map them three-dimensionally to improve the patients' diagnoses. The mapping allows to compere both signals and physical symptoms. In the other hand, signals have been studied in a wide range of frequencies to interpret what is happening at each frequency band. Some other studies [27] have concluded that illnesses such as epilepsy are highly recommended to be studied at high frequencies to study where the seizure is triggered. This is very much connected to our findings because as we have seen, the activation areas are smaller at high frequencies than in low ones. That allow us to reduce the damaged tissue, in other words, reduce the resected area.

Conclusions

Refractory epilepsy it is estimated to affect around 15-20% of children worldwide who suffer from epilepsy [25]. Some of them may need to undergo surgery to resect the affected area. The main objectives of this dissertation were to segment biomedical signals, to delimit and map the epileptogenic zone and to map functional areas.

The biomedical segmentation has been achieved with the usage of Brainstorm and Matlab software. The electrical stimulation signals were segmented by extracting thirty seconds before and thirty seconds after from each of the stimulations studied.

The second objective was to delimit and map the epileptogenic zone. From the previous medical tests conducted to the patient, there was already a possible epileptogenic zone provided from the doctors. From the visualizations of the signals mapping at high frequencies, we could possibly state that the epileptogenic zone, that is the area to be resected during surgery, could be smaller than previously thought.

The last objective was to map functional areas and that has been achieved using Brainstorm. Functional areas are the ones that activate while stimulating although the symptoms of the patient are not like the ones from a regular seizure. With the mapping images in the results section we have been able to see which areas activate after stimulation but it has been very difficult to observe a relationship between the patient's symptoms and the areas activated.

The study of more electrical stimulation signals would have probably provided more information of functional and pathological areas. This information would have probably allowed us to relate the patient's symptoms with the brain activity. That could be opened for further research. Also, the comparative study of the areas activated in a spontaneous seizure with the activated regions in a provoked seizure would have been interesting. Furthermore, in to validate our hypothesis of the localization of the EZ in high frequencies, the analysis of more subjects is necessary.

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Finally, although I do not know her personally, I would like to thank the patient that has been studied in this paper. I wish you all the best, and hope that some day, you will be seizure free.

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