PRC 1

Research in Cognitive Neuroscience and Information Technology

Detection of temporal-lobe epilepsy with the physiological responses to fear and anxiety

FEAREPILEPSY

Marta Perich Pallaruelo

martaperich@uoc.edu

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Professor Consultor: Antoni Valero-Cabré

avaleroc@uoc.edu

1. Title, acronym and scientific summary of the proposal

Epilepsy is a group of neurological diseases commonly characterized by the activation of groups of neurons which are simultaneously activated, and which cause a high-frequency activity in the brain. In these diseases, due to an excess of Glutamate or an inhibition of GABA, a group of neurons are activated in a non-controlled discharge. The symptoms of epilepsy are normally seizures or the loss of consciousness.

Within the types of epilepsy, we can find focal or generalized ones. In this project, we will focus on the focal ones; especially on the temporal lobe epilepsy. This epilepsy is one of the most common ones, and it is characterized because the group of neurons which are activated are placed on the temporal lobe of the brain. The temporal lobe is mostly related to visual memory, language comprehension, and emotion association -which is driven by the amygdala-. In the temporal lobe epilepsy, before the development of an onset, the brain's temporal lobe is activated. Since the amygdala is in the temporal lobe, we infer that activation of the amygdala cause the development of a seizure. Hence, by measuring the abnormal activation levels of the amygdala, we might be able to predict an onset (Engel, 1996).

Later on, in our project we will focus on the symptoms which are associated with the temporal lobe epilepsy, and which are also related to amygdala abnormality: fear and anxiety (Sánchez and Martínez, 2009). Since some patients are MRI-negative, and invasive techniques can be uncomfortable for patients, we have decided to use non-invasive techniques (Nitsche and Paulus, 2009). The project will use the non-invasive technique high density magnetoencephalography (MEG) to predict the increase of fear and anxiety in epilepsy patients and, therefore, the possibility to develop a seizure. It will, therefore, evaluate aspects such as: which are the minimum levels of fear which will surely develop into a seizure? Hence, what is the heart rate which will develop into a seizure?

After the proven investigation of which levels of fear and anxiety -manifested by the heart rate- develop seizures, we will develop a portable device which can measure the principal physiological response to fear and anxiety: heart rate. Therefore, patients will be able to carry within themselves the device, which will warn them when they are going to have a crisis. Of course, there are other reasons why patients could have a higher heart rate, which are not seizures. For example, patients could be anxious for a real reason or because they are scared. However, patients will be able to make their own choice: they will to able to distinguish if the warning of the machine is not real -and they are only experiencing fear because of the environment- or if it is real and they are going to have a seizure. Consequently, patients will be able to prevent the seizure on time -for example, by being in a safe space, stop driving or seeking for help-, and that will increase their well-being.

2. Summary for a non-specialist public of the proposal

Epilepsy is a neurological disease caused by an abnormal neuronal activity on a region of the brain, and it provokes seizures and the loss of consciousness to its patients. Epilepsy can be very disabling, since patients do not know when crisis or seizures are going to occur. If seizures happen when patients are doing a risk activity -such as driving, skiing or swimming- this can lead to serious or deadly accidents. The epilepsy we will focus on is "temporal lobe epilepsy". This epilepsy is caused because of an abnormal neuronal activity on the temporal lobe: a region of the brain which contains the amygdala. Before the development of an onset, the brain's temporal lobe is activated. Therefore, the amygdala is activated too (Engel, 1996). Measuring the abnormal levels of amygdala activation, we can probably predict an onset. Once having assured the relationship between the amygdala and an onset, we will use one parameter more. The amygdala has many functions, one of them related to emotion regulation. The emotion we will focus on is fear.

With our project, we will analyse the relationship between high levels of fear and anxiety and the development of a seizure. We will do that with a non-invasive technique -which means it will not hurt or penetrate any part of the body-: magnetoencephalography. After determining what is relationship between fear and anxiety and the start of the seizure, we will develop a device that can do that by itself. The device will detect the patients' heart rate -since it is the main reaction to fear- and, when the heart rate is high enough to develop into a seizure, it will warn the patient. Thanks to that, epilepsy patients will live less anxious, since they will know when a seizure is going to happen, and they will be able prevent themselves to the damages which might occur.

3. Context, conceptual framework and state of knowledge

Epilepsy

Epilepsy is a group of chronic neurological diseases which consist in a repetition of unprovoked seizures, which are sudden discharges of abnormal intensity and hypersynchrony of a set of brain neurones. Epilepsy is one of the most common chronic neurological illnesses in the world, with more than 60 million people diagnosed worldwide. To diagnose a patient with epilepsy, two or more spontaneous crisis must occur. However, to recognise a seizure is sometimes a bit hard: some people can simply stare blankly for some seconds during a seizure, while others may repeatedly twitch their arms or legs (Badawy et al, 2008).

It is important to briefly understand epilepsy's physiology, since it will be useful to then understand why we need to study the amygdala in our project. In a healthy brain, neurons are connected to each other by electrical signals through dendrites and axons. The neurons usually generate around 80 impulses every second. In an epileptic seizure, however, around 500 impulses every second are produced. That can happen because of four different reasons. First of all, due to a neuronal excitability of sodium channels in the neurons' axon. The sodium channels open, so that sodium enters into the neuron. When that happens, potassium channels open as well, and the potassium exits the neuron, which makes sodium channels close. A deregulation of these channels provokes sodium entering continuously, thus continuously action potentials keep happening.

A second cause may be due to the axonal terminals in the calcium channels. An alteration in these channels does not allow the proper closure of them. Therefore, calcium continues entering in the axonal terminal and stimulates the exocytosis of neurotransmitter to the synaptic space, causing continuous action potentials.

A third mechanism is an imbalance between the excitatory and the inhibitory neurotransmitters in favour of the former. An action potential transmitted along the axon reaches the axonal terminal and stimulates the openness of the calcium channels. The entry of calcium into the neuron causes exocytosis of the neurotransmitter, but this imbalance implies an overstimulation of the post-synaptic neurons.

A fourth mechanism is an alteration of the post-synaptic receptors. In normal conditions, once the neurotransmitter has joined them, they allow the entry of sodium to the neuron. After this neurotransmitter has entered, the channel closes. In this alteration, the neurotransmitter remains longer in the receptor and causes a greater entry of sodium to the neuron and a postsynaptic overexcitation (Badawy et al, 2008).

Temporal lobe epilepsy and amygdala

In our case, we will study the temporal lobe epilepsy, which is the most common epilepsy and therefore, we believe it is of great importance to deepen its study. In this type of epilepsy, there are unprovoked focal seizures which originate in the temporal lobe of the brain. The temporal lobe is the area of the brain where languages, processing, memory and emotions come from. One of the parts of the temporal lobe is the amygdala, and that is the element we will study on our project. In patients

with temporal lobe epilepsy, we infer that the amygdala will also suffer from seizures, which are susceptible to be measured by magnetoencephalography (MEG).

The amygdala is a subcortical structure which is located in the inner part of the medial temporal lobe, and its main function is to integrate emotions and provoke a physiological or a behavioural response. It is, therefore, the main control nucleus of emotions and feelings in the brain. The amygdala is known to play an important role in fear conditioning and it is also implicated in the pathophysiology of anxiety disorders. For all these reasons, measuring the physiological responses to fear -such as heartbeat or sweating- shall give us a hint of the amygdala's activation (Rauch et al, 2003).

Fear physiological components

We just stated that if we verify that when there is an onset, the amygdala is highly activated, we can ascertain the relationship between the amygdala activation and the development of a seizure. But how to measure the activation of the amygdala? One of the measurements is, as we said before, with a MEG. However, since our project needs something handier, we are willing to measure the amygdala with a physiological response. As we said, one of the main functions of the amygdala is the fear control. Hence, when the amygdala is activated, we experience fear. Fear is something which can be much easier measured tangibly.

Fear activates some specific responses: adrenaline, cortisol and glucose are released, so that the body is faster and more energetic. There is also an increase of the arterial pressure, which increases the heart rate (Reed and Tomkins 1958, p.221).

When we see a danger in the ambience, our amygdala gets activated, therefore we experience fear, and the fear response is activated: our heart rate increases to be prepared to run. In the temporal lobe epilepsy, though, the first part of this chain does not occur. Fear is manifested without the apparition of any real danger in the environment, but the fear response is still released; therefore, we will be able to measure it in our project.

Current status

There are some studies related to our project that we will summarise, in order to have a more accurate state of knowledge. The first thing we are analysing in our study is the relationship between the activation of the amygdala and the future development of a seizure. Previous studies with magnetic resonance imaging (MRI) have been made, which indicate that in MRI-positive patients -patients which have been scanned as epileptic by the MRI- do have epilepsy in the 98.1 per cent of the cases (95% confidence). However, MRI-negative patients -patients which have been scanned as non-epileptic by the MRI- have been found as non-epileptic only in the 84.2 per cent of the cases (95% confidence). Therefore, we can conclude that there is a slight percentage of false negatives (Bennett et al, 2019). For this reason, we have chosen to use magnetoencephalography (MEG), since it seems to be more accurate.

Another important aspect of our study is our hypothesis about the relation between fear and the development of a seizure. What has been found in this aspect is a study which predicts a relationship between the feeling of fear and the development of a seizure. Téllez-Zenteno and Ladino (2013) found that one of the symptoms detected by temporal lobe patients was the emotion of fear. That shows that the emotion of fear is one of the symptoms found before a temporal lobe crisis, therefore our project is in the right direction, although further analysis must be pursued.

4. General long-term and short-term objectives

The general long-term objective to improve the life quality of temporal-lobe epileptic patients, by being able to detect when they are going to suffer a seizure and get to safety before its onset

Epilepsy is a disease that stigmatizes patients leading to social exclusion. One of the causes of this stigma is the patients' inability to detect when a seizure is going to occur. As a result, epilepsy patients can have quite a hard life: they stop driving or performing risky activities, because that can lead them to serious accidents or death. That can be extremely incapacitating: since patients are unaware about when an onset of their epileptic seizure is going to occur, they are unable to lead peaceful lives and engage in certain activities.

Temporal-lobe epilepsy's seizures have been related to abnormal levels of amygdala activation, which in turn, causes abnormal levels of fear and anxiety. For this reason, this project aims to study the relationship between these three factors, in order to use such results to develop a device that can warn patients when their levels of fear and anxiety are higher than in resting state, therefore their odds to suffer a seizure increase. With this project, epilepsy patients will be able to sense when a seizure may happen and get to a safe spot to avoid the possible accidents. Thanks to our research and application, we hope epilepsy turns into a less stigmatized disease and, most of all, that we improve the life quality of patients so they can enjoy less anxious and capacitating lives.

The general short-term objective is to quantify the relationship between the potential onset of a seizure and fear and anxiety, and to use such information to develop a device that warns patients before the occurrence of one

Since temporal-lobe epilepsy seizures are related to amygdala activation, which in turn is related with high levels of fear and anxiety, the project will quantify the relationships between fear and the onset. Therefore, it will study which are the levels of fear and anxiety which might red flag the development of a seizure. In particular, the level of heart rate which will be used as warning signs for an upcoming seizure. More specifically, we will study all the pre-ictal signs related to fear and anxiety and the flow of a seizure. The study will be made with the non-invasive technique magnetoencephalography (MEG). Since it is a non-invasive technique, many patients will probably not reject it.

After the study, a device will be developed. The algorithms which explaining the relationship between body-signs of fear and anxiety and those of seizures will be inserted in a smartphone based portable device, able to warn patients when their body signs are abnormal enough to develop a seizure. Artificial intelligence (AI) has many applications in society nowadays, one of them being medicine. Hence, we believe that it is a great tool to be used, it can perceive the environment -in our case, perceive abnormal levels of fear and anxiety- and develop actions -in our case, warn patients if they may debouch into a seizure-.

5. Specific objectives of the proposal

Specific aim 1. Determine if there are abnormal levels of amygdala activation previous to the development of a seizure by means the magnetoencephalogram technique

We want to determine which heart rate levels -caused by the abnormal levels of amygdala activation- cause a seizure. To do so, we first need to ensure that abnormal levels of amygdala activation cause a seizure. We will take a group of 30 temporal-lobe epilepsy patients and 30 non-epilepsy patients, and we will monitor them for 10 months. During this time, we will use magnetoencephalogram (MEG) technique to study the relationship between seizures and the amygdala activity. Brain cells communicate through electrical impulses; and that is the activity detected by these techniques. We will compare amygdala activation levels before seizures of epileptic patients with amygdala levels under normal conditions -both of non-epileptic patients and epileptic patients-. The hypothesis is

that, before the flow of a seizure, the amygdala will display abnormal levels of activity. These levels will be abnormally high, compared to the levels of non-epilepsy patients and epilepsy patients under normal conditions.

We will perform this measurement with the unit Hertz (Hz) of the International System. Brain activation levels of the amygdala (Hz) will be measured in non-epilepsy patients and epilepsy patients under normal conditions. As the literature states, MEG patterns are measured with the same parameters at the EEG patterns. Hence, we will get the measure of four waves and we expect them to be in the following ranks: alpha waves -normal parameters: 8-13 Hz-, delta waves -normal parameters 0-4 Hz-, beta waves -normal parameters 14-60 Hz-, and theta waves -normal parameters 4-7 Hz-. In this particular case, we will take into account the alpha waves, since it is the measure taken into consideration during the waking periods (Van Mierlo et al, 2019).

After having monitored the non-epilepsy patients and epilepsy under normal conditions, this value will be compared with the activation levels of the amygdala (Hz) in epilepsy patients the moment before the development of a seizure. These Hz parameters will be compared, hence we will check if they are statistically significant ($p<0.05$). In other words, we will compare the Hz alpha waves of the three cases (epilepsy, epilepsy under normal conditions, non-epilepsy) and check out if the differences in their MEG results are significant.

Specific aim 2. Determine the levels of fear and anxiety previous to the development of a seizure through physiological heart rate responses, and to use such to alert of the development of a seizure by means of a portable artificial intelligence device

Amygdala plays an important role in the emotions' regulation. It is responsible for the integration of behavioural and physiological manifestations of defensive reactions against innate and learned threats. Therefore, an abnormal level of amygdala activation reverberates into abnormal levels of fear and anxiety (Graeff et al, 1993).

In this second aim, we will measure these levels of fear and anxiety with a physiological response related to fear and anxiety: heart rate. First of all, it is important to assure that abnormal activity in the MEG is actually correlated with an increased ECG. In order to do so, we will monitor the same patient cohort studied in specific aim 1 with a MEG as we did previously, but we will incorporate the EEG measure. Therefore, they will be both monitored with MEG measures and with a Holter monitor, which is used to measure heart rate. We will perform this monitoring for 2 months to make sure that the correlation between these two variables really takes place. Henceforth, we will make a statistical crossing between MEG activation and EEG increase to ensure that, previous to the occurrence of a seizure, MEG displays abnormal levels of activity, as well as EEG presents an increase of its levels, due to a higher heart rate.

After having assured this correlation, we will monitor the patients with a Holter Monitor for 8 months more, measuring their levels of heart rate previous to the development of the seizure, and in resting stage. The hypothesis is that, before the onset of a seizure, heart rate will display abnormal levels of activity. These levels will be abnormally high, compared to the levels of non-epilepsy patients and epilepsy patients under normal conditions. However, we need to standardize the exact levels of heart rate suggestive of an upcoming seizure.

After having standardized those measures, we will haul them into a device which patients can carry around. This device will have an electrocardiogram (ECG) embedded. An ECG is a test which can record the electrical activity of the heart. Thanks to artificial intelligence, which can perceive changes in the environment and develop actions, this device will measure the heart's electrical activity. When this activity has reached abnormal levels -studied before in the project-, the device will warn the patient of the possible development of a seizure.

6. Materials and methods

Regarding general inclusion criteria for patient recruitment, we will take a group of 30 non-epilepsy patients and a group of 30 epilepsy patients[1]. They will all be between 19 and 75 years old, with an equal representation of women and men -50 per cent of each- and the same representation in all age groups -19 to 37, 38 to 56 and 57 to 75-. The reason for this choice is because epilepsy has an estimated global incidence for all age groups of 1.3% per year, with a cumulative incidence of 3% of epilepsy under 75 age group (Perez et al, 2014). Therefore, our primary interest is to tackle under-75 people. Furthermore, since minors require permits to participate in the study and entail some ethical issues, we will address adults.

Concerning non-epilepsy patients, we will collect people who have a completely healthy neurological record. They cannot have epilepsy or any other neurological disorder antecedents nor be diagnosed of a neurological disorder. Regarding epilepsy patients, we will collect people with a diagnosis of temporal lobe epilepsy: patients must bring their medical diagnosis.

The type of sampling will be stratified sampling. That is so because the population will be separated by distinct categories or strata -non-epilepsy and epilepsy, gender and age group-, but in each category, the members will be randomly selected. That will be explained further in the following point.

With respect to the MEG, it is a non-invasive technique which measures the brain activity in tiny regions. It consists in the capture of the magnetic fields generated by the cerebral electrical activity originated by the changes of the membrane potential. The MEG measures the electrical camps which are activated when there is brain activity, and the measurement unit is Hertz. Moreover, the MEG uses a SQUID device and a computer, in order to measure the neuromagnetic activity in the brain. In our case, we will measure the activity in the temporal lobe -more specifically, in the amygdala- (González, 2011).

Concerning the Holter monitor, that is a device which, through electrodes attached to the patient's skin, measures the heart's electrical activity and displays it on a chart -an electrocardiograph-. The advantage is that it can make a registration of that activity for a long period of time. The device will record heart's activity during some days, and then study participants will bring the results back to the hospital, where we will check the results, through the electrocardiogram that is displayed by the Holter monitor.

With respect to the electrocardiogram (ECG), it will be embedded in the portable device, attached to epilepsy patients' skin. Each heartbeat produces an electric activity, and that is what the ECG detects, to indicate when there is a cardiac rhythm alteration. The ECG works with electrodes, which will be attached to the patient's skin and linked by a cable to the portable device. This device will process the information received by the electrodes, and then warn the patient when the heart activity is abnormal, following the parameters found in the previous investigations.

7. Materials and methods detailed by specific objectives

In the first objective, we want to determine if there are abnormal levels of amygdala activation previous to the development of a seizure. To do so, we first will choose our participants but, since we will use stratified sampling, we will divide our population into strata: epileptic and non-epileptic. The epileptic will be chosen from an epileptic association in Barcelona that will be chosen randomly by us. It has to be selected randomly since we want to pursue a random sampling, and if we chose it by ourselves this parameter would be biased. When the association has been chosen, we will contact them and tell them about the study, so that they can provide some epileptic patients who

[1] For space and agility reasons, up to now we will call the patients shortly "epilepsy patients". However, the reader must bear in mind that they will be patients diagnosed of "temporal lobe epilepsy", since that is the kind of epilepsy that we are studying in our project.

want to participate in it. Regarding the non-epileptic participants, we will advertise the study around Barcelona -with leaflets, advertisements on the street and on social networks-. Once we have got the participants, and still following with our stratified sampling, we will classify each participant with two strata: age and gender. After that, we will randomly choose 15 men and 15 women, and we will make sure there is an equal representation of the ages: 19-37, 38-56 and 57-75; hence, we will randomly select 10 people from each age group. The 60 participants will be paid, and they will also be covered their transportation expenses.

We have chosen to use the technique MEG instead of EEG because the former has more possibilities of being successful when it comes to analysing the temporal lobe, and especially the amygdala. The study made by Balderston et al (2013), shows that it is possible to signal deep subcortical structures, like the amygdala, using the sources of the MEG signal. Since EEG has a more superficial analysis, so MEG looks like a more effective technique to measure amygdala activation. Moreover, the study made in 2005 by Stephen(91) et al. found out that EEG had been unable to detect activity in extratemporal epilepsy, when MEG had been found successful. Knake(92) et al (2006) also compared the efficacy of MEG with respect to EEG in locating sources and they highlighted the high sensitivity of MEG locating the origin of interictal activity (Zhang et al, 2014).

With respect to the specific aim 1 of the study, the hypothesis is that, before the flow of a seizure, the amygdala will display abnormal levels of activity. To verify our hypothesis, we tasks will be, first, to pursue weekly measures to healthy patients. We will record a weekly MEG to the 30 healthy participants for 5 months. When this has been finished, we will take the average to know what the normal pattern for healthy participants is. Even though this sample will probably give us a pattern of what the normal conditions are, we do also provide here the normal conditions.

MEG patterns are measured with the same parameters at the EEG patterns: the same spikes are measured. Hence, we will get the measure of four waves and we expect them to be in the following ranks: alpha waves -normal parameters: 8-13 Hz-, delta waves -normal parameters 0-4 Hz-, beta waves -normal parameters 14-60 Hz-, and theta waves -normal parameters 4-7 Hz- (Van Mierlo et al, 2019).

The second task will be about recording epileptic patients. To do so, we will monitor them for a long period of time, until they have a seizure. They will be MEG-monitored in the hospital until the onset appears: therefore, we will be able to measure them under normal conditions and also before the appearance of the seizure.

When this has been finished, we will take the average to know what the normal pattern for epileptic patients under normal is. We expect that pattern to be the same as the healthy patients. Regarding the pattern before the appearance of the seizure, we will also take the average. Then, comparations will be made, to conclude if there is a significant difference in the amygdala activation before an onset and in normal conditions.

If our hypothesis is verified, the results displayed by the MEG will show that epileptic patients under normal conditions as well as healthy patients will show MEG normal patterns explained before. Non-epileptic patients, before the flow of a seizure, will display a MEG which is abnormal: the Hz will have a higher activity. If these are the results obtained, we will be able to ensure that the amygdala is related to the onset of a seizure, and therefore, fear and anxiety arise.

With respect to the specific aim 2 of the study, the same participants from the specific aim 1 will be used. In this aim, the hypothesis is that, before the onset of a seizure, heartbeat will display abnormal levels of activity. To verify the hypothesis, we will first record weekly the participants -epileptic and non-epileptic- with MEG as well as with an EEG (which will be embedded into a Holter monitor). In other words, we will monitor participants with a MEG as we did before, but we will introduce as well the EEG measure. This process will be done for two months, until we have assured a significant correlation between the MEG activation and the EEG increase.

After having checked this correlation, we will monitor the participants with a Holter monitor in their everyday life. The healthy participants will wear the Holter monitor one day a week for 5 months, and epileptic participants will also wear it for 5 months, but 5 days a week, to increase the possibility to be able to monitor a seizure. Measures of their electrical activity will be recorded, and the participants will bring the results to the hospital once the day has finished. Since the Holter monitor records the heart rate by time, we will have their full-day history.

The electrocardiograph from the Holter monitor results will be systematised, and we will analyse the differences between the heart rate of non-epileptic participants and epileptic participants under normal conditions, and the heart rate of epileptic patients before the onset of a seizure. The average will be taken in both cases, in order to determine what is the minimum heart rate which might develop into a seizure.

The participants will be given instructions about the Holter monitor. During the day they carry it, they will not be allowed to exercise or carry out activities which imply high levels of heart rate. Moreover, the participants will have to note down all the activities they pursue. For the epileptic ones, they will have to note at what time (in hours and minutes preferably) they had the seizure. Therefore, when we analyse the results, we will be able to compare the time of the seizure with the time that the Holter monitor indicates for each heartbeat. It is very important that participants accurately record their symptoms and activities so we will compare them to the results of the Holter monitor. The normal resting heart rate for adults is between 60 and 100 beats per minute. We will keep that in mind when analysing the results: therefore, higher heart rate will red flag the development of a seizure.

With respect to the portable device, it will be of a small size (around 5x5 centimetres) and will contain an elastic band which will be placed on the wrist, where the basilic vein goes through and the pulse is more noticeable. The device will have embedded an electrocardiogram on its core, which will monitor the patients' heart rate (as outlined before, monitored at the wrist). The portable device will also have a small screen where the patient will be able to check his or her heart rate and will also have a warning sound incorporated. This warning sound is actually extremely important, because after the device has recorded higher heart rates than the ones we systematised as normal ones, the warning sound will be activated and the patient will be notified of the problem.

8. Possible project's breakthroughs

I have identified four possible bottlenecks which might occur in this project: one methodological, one experimental and two logistic. Considering the methodological one, it might happen that sampling does not occur as random as we want it to. For instance, if we advertise the study only in certain sectors of the city, we might only get participants who work in a specific place or who live in a certain neighbourhood. To solve it, we will allocate a large part of our budget to marketing campaigns, and we will spread them throughout the city, making sure all neighbourhoods and occupational sectors are covered.

In reference to experimental difficulties, some people may not respond well to Holter monitor's measurements, so it might be difficult to quantify which heartbeat level indicates the development of a seizure. To solve it, we will have an alternative measurement as a back-up, which would be launched if a patient did not respond well to the Holter monitor. This measurement is skin sweating, which is also related to high levels of fear and anxiety. To measure sweating we will use fingerprints, which can reveal individual active sweat glands (Dabbs et al, 1968).

Finally, we find two possible logistic issues. Firstly, the relationship with the hospital where we will execute the study. It is possible, for instance, that the machines we need in a specific day are occupied, or that we are not provided with all our necessary material. For that, I believe that relationship with the hospital is crucial. From a beginning, we will set the list of our material and the hours in which we will occupy it. We will also ensure a good relationship with them by having weekly

meetings, where we can comment on issues, make demands and listen to their queries. Secondly, we might encounter a number of dropouts while the study lasts. Sometimes patients may get tired of the study, change residence or lose interest. To prevent that from happening, on the one hand we will make participants sign an agreement at the beginning of the study, and we will explain to the importance of participating during the 20 months that the study will last. However, it is possible that dropouts still occur. Therefore, on the other hand we will hold a waiting list, so we can incorporate more people in case there is a withdrawal.

9. Calendar distribution of phases and milestones by specific goals

TASK ID	TASK TITLE	START DATE	DUE DATE	DURATION	PCT OF TASK	MONTH 1-5					MONTH 5-10					MONTH 10-15					MONTH 15-20					MONTH 20-25					MONTH 25-30				
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	Prepare the study conditions																																		
1.1	Hospital where study is developed	01-01-20	01-02-20	31																															
1.2	Design of the stratified sampling methodology	01-02-20	15-02-20	14																															
1.3	Advertisements to collect participants	15-02-20	15-03-20	29																															
1.4	Participants' selection and information	15-03-20	15-05-20	61																															
1.5	Guidelines	15-05-20	30-05-20	15																															
1.6	Project initiation	30-05-20	30-06-20	31																															
2	Determine abnormal levels of amygdala activation previous to onset																																		
2.1	Preparation magnetoencephalogram machines	30-06-20	15-07-20	15																															
2.2	Measurement non-epilepsy patients	15-07-20	12-12-20	150																															
2.3	Measurement epilepsy patients normal conditions	15-07-20	12-12-20	150																															
2.4	Measurement epilepsy patients when onset	15-07-20	12-12-20	150																															
2.5	Determination whether activation causes seizure	15-12-20	30-01-21	46																															
3	Determine levels of fear (by heartbeat) previous to onset																																		
3.1	Preparation Holter monitors	01-02-21	15-02-21	14																															
3.2	Measurement non-epilepsy patients	15-02-21	15-07-21	150																															
3.3	Measurement epilepsy patients normal conditions	15-02-21	15-07-21	150																															
3.4	Measurement epilepsy patients when onset	15-02-21	15-07-21	150																															
3.5	Determination of which heartbeat causes seizure	15-07-21	30-07-21	15																															
3.6	Algorithm: heartbeat level and seizure	30-07-21	30-08-21	31																															
4	Development of a portable artificial intelligence device																																		
4.1	Design of the electrocardiogram	01-09-21	01-11-21	61																															
4.2	Embedment of ECG to portable device	01-11-21	30-12-21	59																															
4.3	Design of the algorithm correlating heartbeat-seizure	01-01-22	01-03-22	59																															
4.4	Insert of the algorithm in the device	01-03-22	01-04-22	31																															
4.5	Trials and evaluations	01-04-22	30-07-22	120																															

10. Potential scientific, clinical, social and technological impact of the proposal

This project has great scientific, clinical, social and technological potential. In reference to the scientific and clinical, the proposal will ensure the correlation between amygdala activation and epilepsy, and it will also accurately measure the heart rate values before the development of a seizure. This is of great interest, since important aspects of epilepsy will be explored, which may lead to future applications. Epilepsy is a very disabling disorder, and any progress which can be made to better understand its symptoms is beneficial.

On the other hand, it has a big impact on the social level. Epilepsy patients cannot predict when an onset will occur. Therefore, their daily activities may be reduced, as well as their possibilities to explores risky actions. The device proposed may shift the way they experience lives, since it will warn them of a possible seizure, thus prevent them for a deadly accident. Therefore, thanks to this device, epilepsy patients will be able to live easier and much more peaceful lives. First of all, they will be able to perform activities that they previously did not do, such as driving or certain risk sports. Secondly, epilepsy will be a less stigmatised disease, since its patients will be able to pursue a lifestyle which is almost the same as healthy people.

Along these lines, it is important to acknowledge that we have built a society for healthy people, which I consider as a failure. In most of our cultures, people who belong to a minority -which, in this case, epilepsy patients do belong to- have to adapt themselves to the status quo, which is built by and for normative healthy people. However, I believe that a truly successful society is one that

manages to adjust itself to all people and give them all opportunities to live well. For this reason, the proposal has a huge impact in building a society not only for standard people but for a minority which has not been taken into consideration enough.

Finally, the project can have a broad influence at a technological scale. The development of the device stated above might open a myriad of possibilities when exploring technological solutions to clinical problems.

On another basis, the project has an interesting impact because of its interdisciplinary approach, since the proposal is combining scientific, clinical social, technological disciplines to give a solution to one problem. In the 21st century, it has been claimed that knowledge and solutions will necessarily need to integrate a wide array of fields and people from different backgrounds working together. It is for this reason that this project stands as indispensable. Working with interdisciplinary teams can lead to much more creative results, hence it is possible that, when the project is developed in reality, solutions which we have not contemplated in this proposal or synergies which we have not foreseen might appear.

11. Justification of the team of researchers and institutions involved

Regarding the institutions chosen for the project, we need to take into account three different kinds of institutions: hospitals, an epilepsy association and the research team. To do so, we will follow two guidelines which will help us decide: proximity and professionalism.

Concerning the hospital chosen, after having studied some of the most important Spanish hospitals, the Clinic Hospital in Barcelona has been selected. This hospital appears as the first institution in Catalonia rankings, thanks to its seriousness, experienced personnel and great deal of machines. For this reason, we believe that a wide array of Holter monitors, EEG and ECG will be found there, large rooms to work, qualified professionals with whom to interact with as well as maturity and excellence when handling our project.

Moreover, there is a need to contact an epilepsy association, which will be chosen randomly in order to follow the stratified sampling we predicted. Therefore, a list of Spanish epilepsy associations will be made and we will randomly choose one. The list of all the Spanish epilepsy associations can be found in the Spanish Federation of Epilepsy's webpage, which is available here: http://www.fedeepilepsia.org/asociaciones/. Since our base will be in Barcelona, we will simplify the search on Barcelona and its surroundings, so that patients do not have to travel far away. The association randomly chosen will have the task to get in contact epilepsy patients and to contact them so that they participate in our study.

Regarding the research team, we will need both doctors or psychologists, statisticians and engineers. Following our first guidelines -proximity and professionalism-, we have found a strong research epilepsy team in the Hospital del Mar, Parc de Salut (Barcelona) named Epilepsy Unit of the Hospital del Mar: https://www.parcdesalutmar.cat/es/epilepsia/. The Epilepsy Unit is a centre of maximum complexity and has been distinguished in Catalonia as a reference centre for Epilepsy Surgery by the Ministry of Health as a national reference centre for Refractory Epilepsy CSUR. At an international level, the Epilepsy Unit is part of the European Network of Epilepsy Surgery Centres project. Therefore, it stands as a remarkable and professional institution. Before starting our project, we will contact their director (Dr. Rodrigo Bocamora) in order to meet, create network and expose our project. If the project sounds appealing to his team, we will be able to count on some of the researchers working in our project, which will be in charge of all the medical and clinical aspects of our project.

In reference to statisticians, we have followed the same guidelines as before, thus found the GRBIO, the Biostatistics and Bioinformatics Research Group from the University Politècnica de Catalunya (Barcelona): https://www.eio.upc.edu/en/recerca-en/research-groups/grbio-research-group-in-biostatistics-and-bioinformatics. Their main goal is to promote joint research in Biostatistics and

Bioinformatics in both applications and development of new methodologies. Therefore, they address complex interdisciplinary issues and make relevant scientific contributions on health and biology areas where closer collaboration is needed to promote future development and welfare of the society. Moreover, they also carry out clinical trials and develop statistical and computer tools for the exploitation of the results of biomedical research. The team is extremely interdisciplinary and works with the fields that we need to develop our portable device. Therefore, following the same procedure outlined before, we will contact them in order to meet, create network and expose our project. If the project sounds appealing to them, we will hire some of its statisticians to work in our project, since we will need a strong team analysing the data results obtained from the studies we have pursued with the participants.

Finally, to be in contact with engineers, we will display the advertisement of our project at the Association of Graduate Engineers and Industrial Technical Engineers of Barcelona: https://www.enginyersbcn.cat/, which stands out as the most relevant institution to gather all the graduated engineers. We will hire the most suitable engineers, which will be in charge of designing and developing the portable device.

12. Approximate budget and justification of items

List of tasks	Items and number	Price item	Number months	Total
Salaries				**720,000€**
	4 doctors	2,000€/month	30 months	240,000€
	4 statisticians	2,000€/month	30 months	240,000€
	4 engineers	2,000€/month	30 months	240,000€
Material rented from the hospital				**15,000€**
	MEG	500€/month	10 months	5,000€
	ECG	500€/month	10 months	5,000€
	Holter monitor	500€/month	10 months	5,000€
Participants				**12,500€**
	60 participants	200€/month/parti.	10 months	12,000€
	Transportation	50€/month	10 months	500€
Equipment				**50,000€**
	Computers	500€/month	30 months	15,000€
	Offices' rent	1,000€/month	30 months	30,000€
	Advertisement	500€/month	5 months	2,500€
	Material portable device	500€/month	5 months	2,500€
Others				**5,000€**
	Publications	500€/month	4 months	2,000€
	Contingencies	100€/month	30 months	3,000€

Total		**802,500€**

13. Project's ethical implications

Regarding the ethical implications, we will not find many in our project, since all the procedures used are non-invasive techniques. However, informed consent from all the participants must be obtained, which will consist of an explanation of the study and its phases, so that patients sign off in agreement. It is crucial that patients are aware of the procedures practised on them at all times and it is also important that all the professionals working in the study maintain an open mindset and availability to answer any query that a participant might have.

Concerning data protection, it is important that we follow the newest Data Protection procedures from the European Union which, without the intention of giving too detailed and tedious information, can be found on the GDPR official website: https://europa.eu/youreurope/business/dealing-with-customers/data-protection/data-protection-gdpr/index_en.htm. The GDPR sets out detailed requirements for companies and organisations on collecting, storing and managing personal data, and it applies both to European organisations that process personal data of individuals in the EU as well as to organisations outside the EU that target people living in the EU.

Taking into account the different kind of studies we will perform, there intervention where we will use the Holter monitor may rise some ethical implications. The electrodes used in the Holter monitor are normally placed on the patients' chest. Therefore, patients with hairy chests -normally men- will have to shave them so that we locate the electrodes and can monitor them correctly. That could be an ethical implication hence, we will inform the patients at the beginning of the study and note it down on the informed consent so that they can sign and agree with it.

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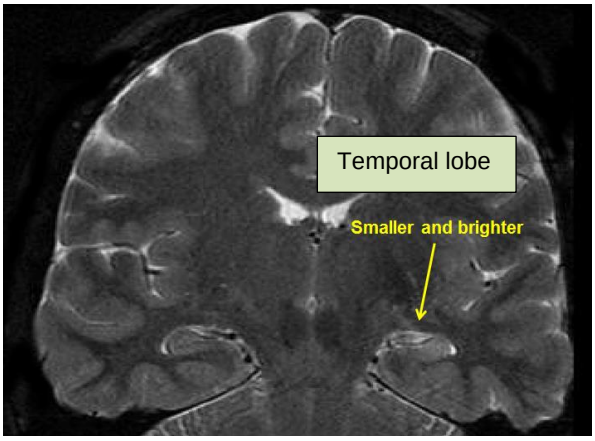
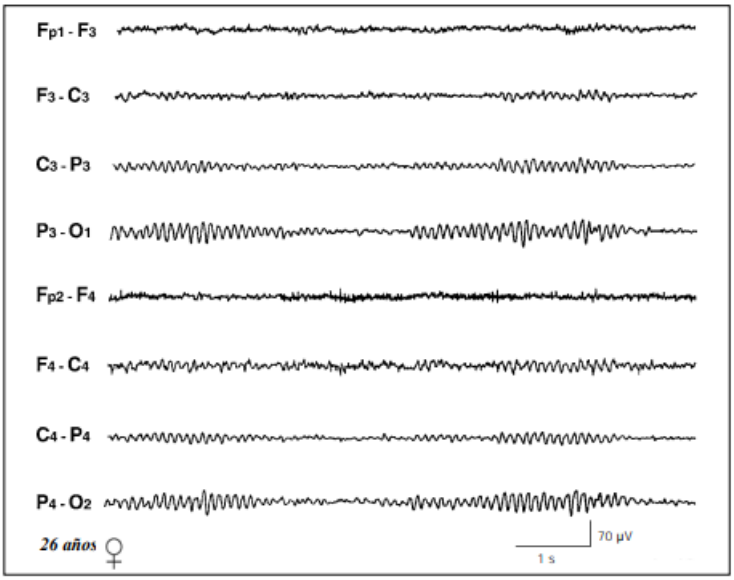
15. Annex



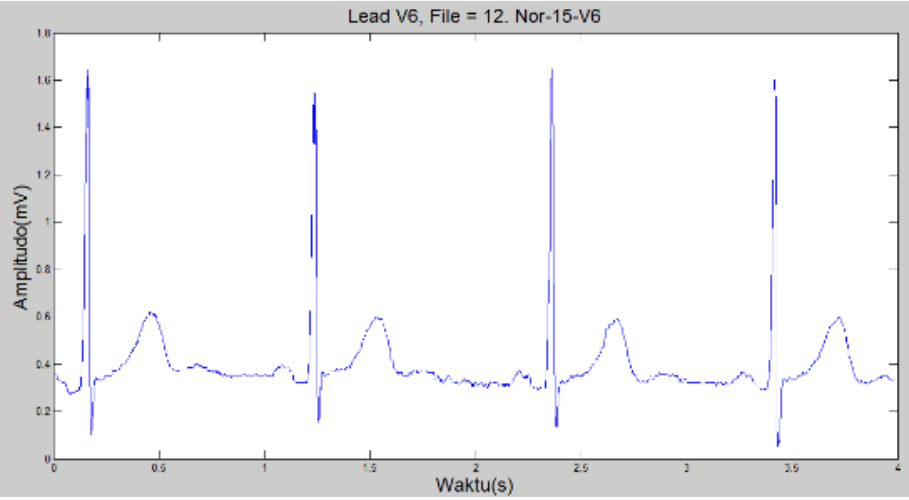
Source: Epilepsy Foundation (2019). Temporal Lobe Epilepsy

Alpha waves under normal conditions in MEG



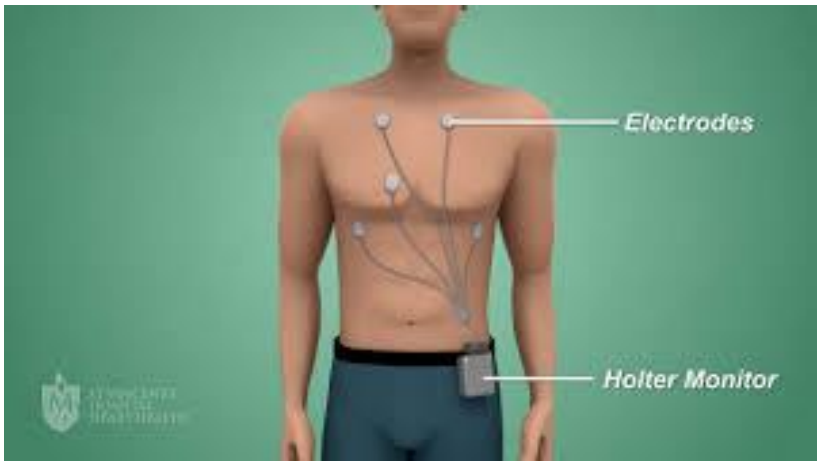
Source: Van Mierlo, P., Höller, Y., Focke, N., Vulliemoz, S. (2019). Network Perspectives on Epilepsy Using EEG/MEG Source Connectivity

ECG under normal conditions



Source: Hartati, S. (2017). The Feature Extraction to Determine the Wave's Peaks in the Electrocardiogram Graphic Image

Holter monitor attached to ECG



Source: St. Vincent's Hospital Heart Health webpage (2019)