# CZECH TECHNICAL UNIVERSITY IN PRAGUE

## Faculty of Electrical Engineering


**Bachelor Thesis**

# High Frequency Oscillations Analysis in Scalp EEG of Focal Cortical Dysplasia patients


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**Department of Electrical Power Engineering**

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**Declaration**

I hereby declare that this bachelor thesis is the product of my own independent work and that I have clearly stated all information sources used in the thesis according to Methodological Instruction No.1/2009 – “On maintaining ethical principles when working on a university final project, CTU in Prague“.

Date: Signature:

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## II. Bachelor’s thesis details

Bachelor’s thesis title in English:

**High Frequency Oscillations analysis in scalp EEG in Focal Cortical Dysplasia patients.**

Bachelor’s thesis title in Czech:

**Analýza vysokofrekvenčních oscilací ve skalpovém EEG pacientů s fokální kortikální dysplázií**

Guidelines:

Perform the qualitative and quantitative analysis of the High Frequency Oscillations phenomenon on the results of scalp electroencephalograms of patients diagnosed with Focal Cortical Dysplasia. Test the hypothesis that the oscillations quantification and classification could stratify the sub-types of the focal cortical dysplasia.

Bibliography / sources:

[1] Park CJ, Hong SB. High Frequency Oscillations in Epilepsy: Detection Methods and Considerations in Clinical Application. J Epilepsy Res. 2019 Jun 30;9(1):1-13.
[2] Shibata T, Kobayashi K. Epileptic High-frequency Oscillations in Scalp Electroencephalography. Acta Med Okayama. 2018 Aug;72(4):325-329.
[3] Thomschewski A, Hincapié A-S and Frauscher B (2019) Localization of the Epileptogenic Zone Using High Frequency Oscillations. Front. Neurol. 10:94.
[4] Jacobs J, Staba R, Asano E, et al. High-frequency oscillations (HFOs) in clinical epilepsy. Prog Neurobiol. 2012;98(3):302-315.

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## Abstract

High Frequency Oscillations (HFO) is currently a promising biomarker for epileptogenicity. The research and assessment to properly define and describe its characteristics is still ongoing. In this thesis the state of the art regarding the HFO is presented and the HDEEG scalp recordings of Focal Cortical Dysplasia (FCD) patients being treated at FN Motol Hospital is evaluated. The HFO occurring simultaneously with Interictal Epileptiform discharges (IED) are analyzed with the help of signal visualization tools in the time and the time-frequency domains, and an attempt to connect FCD types to detected HFOs took place. In addition, the comparison of the HFO-based visual analysis and MELD results is performed.



**Keywords:** HFO, HDEEG, scalp EEG, epilepsy, FCD, signal processing



## Abstrakt

Vysokofrekvenční oscilace (HFO) jsou v současnosti slibným biomarkerem epileptogenity. Výzkum a hodnocení za účelem správného definování a popisu jeho charakteristik stále pokračuje. V této práci je prezentován stav techniky týkající se HFO a jsou vyhodnoceny záznamy HDEEG skalpu pacientů s fokální kortikální dysplazií (FCD) léčených ve FN Motol. HFO vyskytující se současně s interiktálními epileptiformními výboji (IED) jsou analyzovány pomocí nástrojů pro vizualizaci signálu v časové a časově-frekvenční doméně a proběhl pokus o připojení typů FCD k detekovaným HFO. Kromě toho je provedeno srovnání vizuální analýzy založené na HFO a výsledků MELD.



**Klíčová slova:** HFO, HDEEG, skalpové EEG, epilepsie, FCD, zpracování signálu

# Contents

## List of Abbreviations

| | |
|---|---|
| ECoG | Electrocorticography |
| EEG | Electroencephalography |
| EMG | Electromyography |
| ECG | Electrocardiogram |
| FCD | Focal cortical dysplasia |
| HD-EEG | High-density EEG |
| HFO | High frequency oscillation |
| IED | Interictal epileptiform discharge |
| iEEG | Intracranial EEG |
| MCD | Malformations of cortical development |
| MEG | Magnetoencephalography |
| MELD | Multi-center Epilepsy Lesion Detection |
| MRI | Magnetic Resonance Imaging |
| SEEG | Stereo electroencephalography |
| SNR | Signal to noise ratio |
| SOZ | Seizure onset zone |

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# 1. Introduction.

Epilepsy is a common neurological disorder affecting individuals of all ages characterized by persisting, unprovoked, and unpredictable seizures, which reflect brain dysfunction. About one-third of patients with epilepsy suffer from refractory epilepsy, which means antiepileptic medications are not able to effectively control the seizures [1]. Thus, an optimal treatment comprises a surgical procedure which involves a rigorous analysis of many pieces of information regarding the seizure provoking area of the brain (SOZ), and the outcome — giving the patient seizure freedom — depends on its correct delineation [2].

Electroencephalogram (EEG) is one of the crucial tools for correct diagnosis of epilepsy and localization of the SOZ. Even though the intracranial EEG is nowadays still the preferred way to obtain the signal which provides useful pre-operative information regarding the SOZ, scalp EEG needs to be studied as a non-invasive, simpler alternative procedure, covering wider area of the brain and as useful for pre-operative as for post-operative analysis [3].

One of the new biomarkers of epileptogenesis researchers have been describing for over two decades are high frequency oscillations (HFOs). This brain activity can be seen in both invasive and non-invasive EEG signal. Researchers claim that HFOs better delineate the SOZ, and some clinical studies showed that the HFO analysis helped to noticeably increase the rate of positive surgical outcome [4] [5].

Focal cortical dysplasia (FCD) is a type of cortical development malformation of the brain and one of the sources of drug resistant epilepsy. The SOZ of such patients may be better determined by EEG analysis than seen on MRI [6]. Moreover, recent studies show that FCD had higher rates of HFOs occurrence in comparison with other pathologies [4].

The goals of this project are to perform the qualitative and quantitative analysis of the HFOs phenomenon on the results of scalp EEGs of patients diagnosed with Focal Cortical Dysplasia and, based on the occurrence of HFO events and their characteristics, try to estimate the sub-types of the FCD of the given dataset.

# 1. Theoretical background

## 2.1. Electroencephalography (EEG)

Electroencephalography (EEG) is a neuroimaging technique providing macroscopic measurements of the brain electrical activity and enabling the assessment of brain functionality. The procedure consists of placing electrodes on the person's scalp and records transient signals generated by the electrical activity of groups of neurons. The electrical fields propagation takes place thanks to the conductive properties of brain and head tissues. EEG records the differential measurements between an electrode and a referential position. The amplifier connected to the electrodes boosts the signal. [7]

There are several important parameters which affect the sensitivity of the EEG signal. Signal-to-noise ratio (SNR) is a ratio of the power spectral density of a signal to the power of the background noise. In order to detect spikes when recording the signal, it is best to achieve the acceptable SNR, especially in scalp recordings.

Another important parameter is the bandwidth. According to the Nyquist theorem, the sampling frequency must be double the frequencies which we want to observe.

Electrode sizes, quality and positioning also play a great role in acquiring a valid EEG signal. Luckily, the fast technological developments improve this issue day by day. The layered and spiraled structure of the brain impedes the even distribution of the potentials and this may also affect the correct measurement [8].

It is important to mention that EEG is not the only procedure which can provide information about brain activity. Depending on the complexity of the disease, the patient may also undergo MRI scan, MEG, PET and even intracranial procedures such as SEEG or iEEG for the correct diagnosis and localization of the lesioned brain tissue. In most cases, the combination of multiple techniques is necessary.

Among the advantages of scalp recording over intracranial recording are the noninvasiveness, ease of application and the possibility of covering a much wider area of the cortex. The main disadvantage of scalp recording is the fast decay of the signal from the cortex to the electrodes due to poorly conductive tissue, which makes it difficult to

detect low-amplitude signals. Moreover, the electromyograms and other artifacts can also contaminate the scalp EEG and need to be excluded from analyses [3].

### 2.1.1. Classical 10-20 montage

The 10-20 montage is an internationally recognized system of placing the electrodes for the EEG. Figure 1 indicates the exact position and identifier of each electrode in this setup. The naming of each electrode is based on the lobe it is situated on: pre-frontal (Fp), frontal (F), temporal (T), parietal (P), occipital (O), and central (C). Subindex “z” indicates that the electrode is on the midline between the right and the left sides. The odd numbers next to the area letter denomination correspond to the left side of the head, while the even numbers correspond to the right side of the head. The numbers 10 and 20 refer to the percentage distance between electrodes.

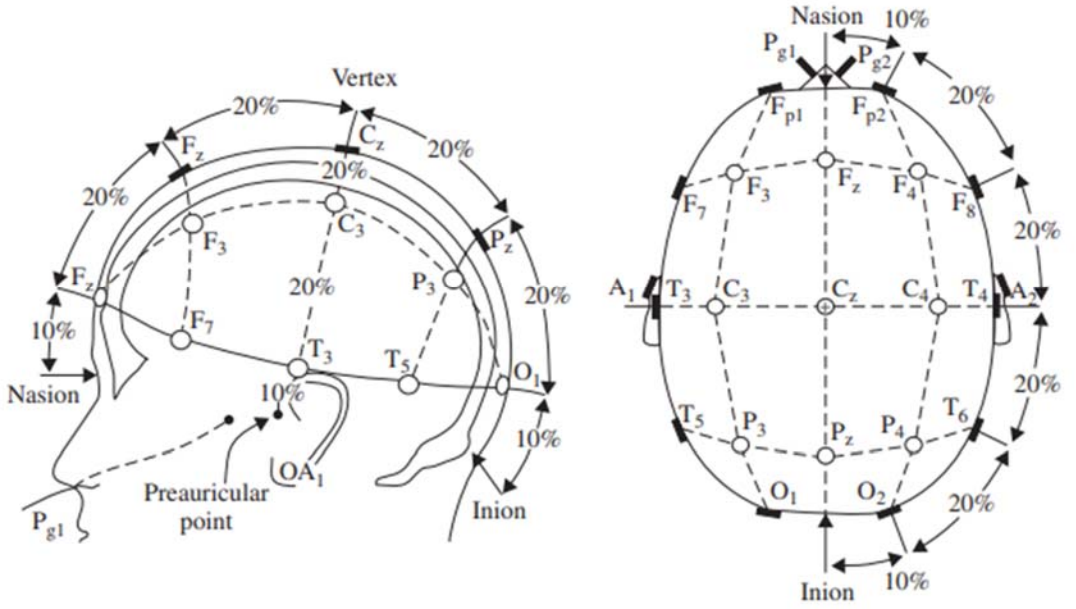


Figure 1. Classical 10-20 montage *[8]*

### 2.1.2. High-density EEG (HD-EEG)

High-density EEG (HD-EEG) is an expansion of the 10-20 system.

*Figure 2* shows the layout of the HD-EGG montage. The total number of electrodes used in the HD-EEG increases to between 64 and 256, with the additional ones spatially distributed in between the electrodes placed in the classical montage. Studies have shown the great utility of the HD-EEG montage, where increased spatial resolution permitted acquiring better information in comparison with the traditional low-density EEG. In those studies, scientists demonstrated that HD-EEG can improve the lateralization of epileptogenic lesions, the correct localization of ictal and interictal events not seen on other recordings, and the reevaluation of the resection zone for surgery [9]. Also, in the case of favorable signal-to-noise ratio, it is possible to detect high frequency oscillations [10] [9].

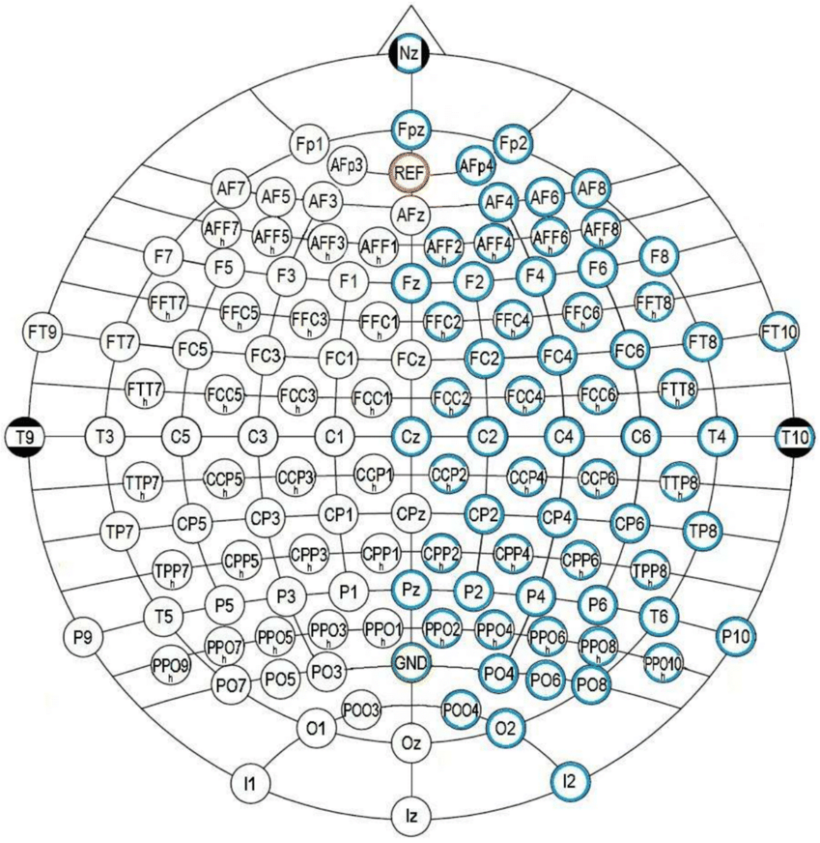

Figure 2. HD-EEG montage with 128 electrodes *[11]*

In order to achieve adequate sensitivity and accuracy in adults, the minimum number of electrodes needed is 128, whereas in the pediatric population 64 are sufficient due to the dimension of the head [12].

Even though artifacts which mimic HFOs are a major problem, a great advantage of recording interictal scalp HFOs as a biomarker of SOZ is the lack of need to record the seizures, which are potentially dangerous for the patient [5].

In an era of technological advancements, the availability of HD-EEG for clinicians and a clear procedure on how to identify the characteristics of epileptogenic markers could greatly improve the use of EEG as a tool and revolutionize the management of epilepsy [13].

## 2.2. Epileptic waveforms

The human brain has the ability to produce a variety of different waveforms which can be characteristic of some particular physiologic activity, such as sleep or reaction to some stimuli, or be pathologic and serve to medical professionals as an indication for certain diseases. When discussing epilepsy, one of the most important waveforms which has helped to diagnose patients for many decades is the interictal epileptiform discharge (IED), also referred as spikes. There are also different types of IEDs depending on the type of epilepsy. This project focuses on the spikes typically observed in patients diagnosed with Focal Cortical Dysplasia (FCD).

### 2.2.1 Interictal epileptiform discharges (IEDs)

Interictal epileptiform discharges (IEDs), known as epileptic spikes, have been a gold standard for epileptogenesis and ictogenesis. They can be recorded interictally, i.e., between seizures, and both in awake or asleep state of a patient.

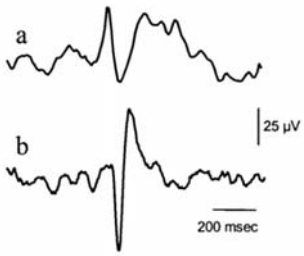


Figure 3. Examples of IED recorded in scalp EEG *[14]*

### 2.2.2 High Frequency Oscillations (HFOs)

*High-frequency oscillations (HFOs)* are described as oscillatory brain signals with a frequency higher than 80 Hz, recorded by electroencephalography (EEG) due to the transient local-field potential oscillations. Although there is no standardized definition, researchers agree that an HFO may be defined as the presence of at least 4 sinusoidal-like oscillations which stand out from the background brain activity in the filtered signal [15].

It is a relatively new biomarker, as the first human clinical data appeared in research in the early 2000s. Since then, it has been proved that some relationship between HFOs and seizure activity in both intracranial and scalp recordings exists [4].

Initially, it was believed that the skull filters away high frequencies and researchers did not expect to find epileptic HFOs in scalp EEGs. However, it was proved that the human skull does not have low-pass filter capabilities, and that it only diminishes the signal amplitude. Therefore, as long as the signal amplitude is greater than noise, high frequencies are detectable on scalp procedures [13].

Advancements in digital EEG techniques have enable expanding its range. Based on the peak frequency, duration, and amplitude, HFOs can be classified into the gamma (40-80 Hz), ripple (80-250 Hz), and fast ripple (250-500Hz) bands. In the last decade, even very-high frequency oscillations (>500 Hz) have been reported in patients with epilepsy [3] [4].

Starting from the ripple frequency range, oscillations are strongly related to epileptogenicity. In affected pediatric patients, a significant number of oscillations in the gamma and ripple ranges can be detected over the scalp EEG [3].

It is true that some normal physiological high-frequency activity exists in the human brain. Researchers describe physiological HFO as continuous high frequency activity, especially in the hippocampus and in the occipital lobe. In contrast, the pathologic activity occurs in the form of fast and very fast ripples on flat background and is often coupled with epileptiform discharges [5]. Some researchers discuss the fact that HFOs co-existing with IEDs are easier to spot and possibly have greater pathological significance [13].

Recent studies show that not only higher ripple rates can be seen with HD-EEG, but also those ripples localize the same brain regions as intracranial EEG. In contrast, 10-20 montage ripples might be confusing and not specify SOZ correctly enough [16]. The accuracy of localizing SOZ grows linearly with the number of electrodes used in HD-EEG, from 64 to 256 [17].

Research also tries to find the dependence between HFO rates and sleep cycles. The muscle, eye movement artifacts are reduced significantly during sleep. The highest number of IEDs are also typically recorded during sleep, so it is crucial to continue the evaluation of their occurrence during different stages of sleep. The differences could be explained by the variety of discharge synchronicities throughout the states. Kang & Boly found that IEDs during REM sleep are shorter in time and are concentrated in a smaller area, which they believe might coincide with the clinical ictal onset zone [17].

However, there is no consistency up to now in the findings regarding HFOs connection to sleep stages and the relation might be more complicated than expected. Some researchers have found that HFO rates are higher in NREM sleep [10] [5] and noted that HFOs appearing in phasic REM sleep are predominantly of a physiologic origin [5]. Others, in contrast, claim that, as with IEDs, the restriction of the observed HFOs in REM sleep might more accurately delineate SOZ [17]. There are various types of sleep waveforms which characterize the NREM and REM human sleep and by themselves present a topic for separate research. Therefore, they are considered out of the scope of this project.

Some studies also tried to understand the relationship between age and HFO occurrence. HFOs found in scalp EEG of pediatric patients with different epilepsy syndromes have been linked by various professionals to the severity of the disease. Moreover, the younger the patients, the more reliable the HFO findings in the scalp EEG [10].

It has also been found that one of the problems that might occur during the analysis of HD-EEG in children is that sometimes the IEDs are multifocal and diffuse even in cases of focal epilepsy. Therefore, non-epileptiform abnormalities may be more useful in localizing the affected areas [12]. However, the clinical research that would clearly describe the relationship between patient age and HFO in order to use it in the present analysis is still ongoing.

### 2.2.3. Relationship between IEDs and HFOs

Numerous scientists claim HFOs have a stronger connection to epileptogenicity than interictal spikes and that precisely, the pathological HFOs tend to couple up with the IEDs [3] [5]. A case study made by Algethami et al. showed that the presence of generalized IEDs does not exclude a focal lesion and FCD epilepsy type [18]. Thus, we might suspect that the presence of HFOs on certain channels might be indeed helpful to differentiate the SOZ.

Recent studies show that it is not compulsory for HFOs to occur simultaneously with epileptic spikes (IEDs). HFOs, together with seizures, increase when antiepileptic medication is reduced. On the other hand, the interictal spikes rate is usually higher often after seizures. This correlation was observed in both intracranial and scalp EEG recordings. This could imply that HFOs and seizures are more tightly related and have similar pathophysiologic mechanisms [4].

If we compare the HFOs and IEDs, on the contrary, researchers suggest they are of distinct morphologies: spikes appear as postsynaptic potentials, while HFOs are presumed to reflect synchronized co-firing of small clusters of principal cells.

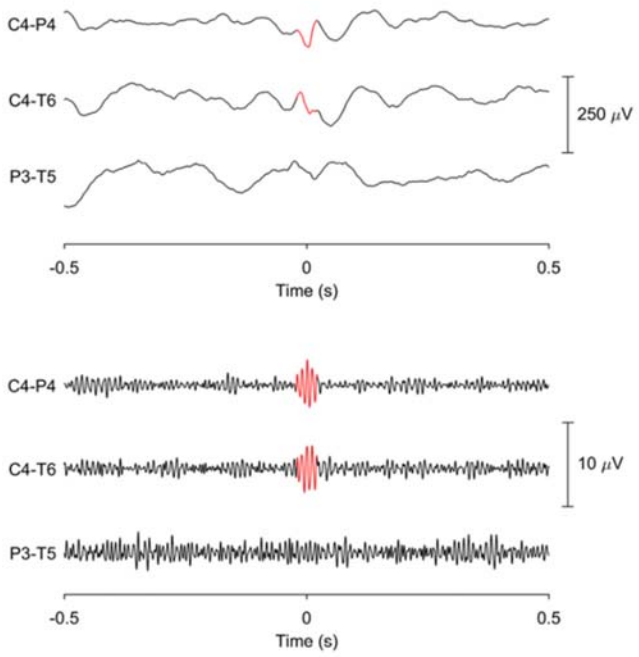


Figure 4. Example of IEDs with HFOs *[10]*

Independently of the type of the brain lesion, both HFOs which coincide with spikes and HFOs alone proved to better delineate the SOZ than IEDs alone [16] [19]. A study by Urrestarazu et al. even showed that in intracranial procedure, about 64% of HFOs occurred together with spikes and were visible on top of the spike in the unfiltered signal [20].

Figure 5 illustrates the possible types of artifacts which researchers point out when analyzing HFOs in epilepsy. In the figure, the first row is raw data, the second row represents the scalogram of the same time interval, and the third row is the power band ratio plot. The type B and C represent non-sinusoidal signals and transient events with amplitudes above global background, respectively. We are most interested in type A artifact, as it shows the high frequency components due to sharp IEDs without visible HFOs in the raw signal and therefore they are continuously stretched from the spike energy and do not form a separate blob on spectrogram [4].

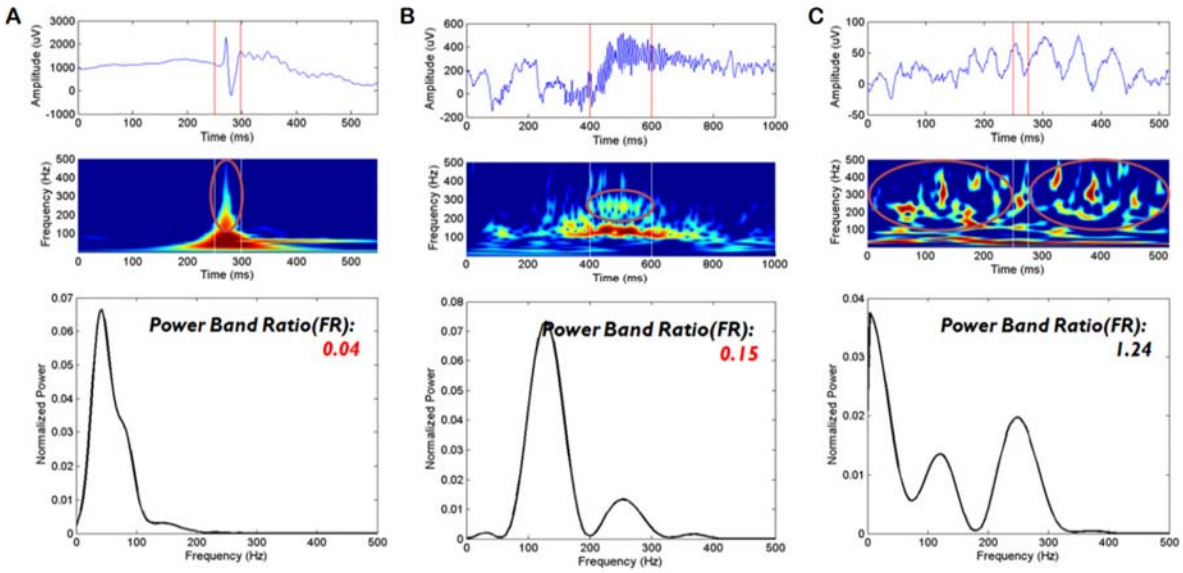


Figure 5. Possible types of artifacts *[4]*

## 2.3. Focal Cortical Dysplasia (FCD)

### 2.3.1. Definition and types

*Focal cortical dysplasia (FCD)* is a type of cortical development malformation of the brain and one of the sources of drug resistant epilepsy. It was first described in 1971 by Taylor et al. who discovered cortical disorganization, bizarre neurons, and balloon cells in 10 refractory epilepsy patients. In 2011, the classification of FCD was updated, as per which the condition may involve any part of the brain, vary in size and location, be focal or multifocal [18].

There are three general types of FCD:

- Type I is more common in adults. It is connected with temporal lobe changes, is mild symptomatic, and is often not seen on MRI.
- Type II is more common in children, more severe symptomatic, and the lesions are better observed on MRI. In it, changes in brain tissue occur also outside the temporal lobe more extensively, most likely in the frontal lobes.

- Type III is characterized as a combination of the first two types with interference of some other brain lesion [6] [21].

Seizures in this type of epilepsy commonly begin in childhood [22]. Most frequently surgical treatment is offered to children younger than 4 years old who were diagnosed with FCD [21].

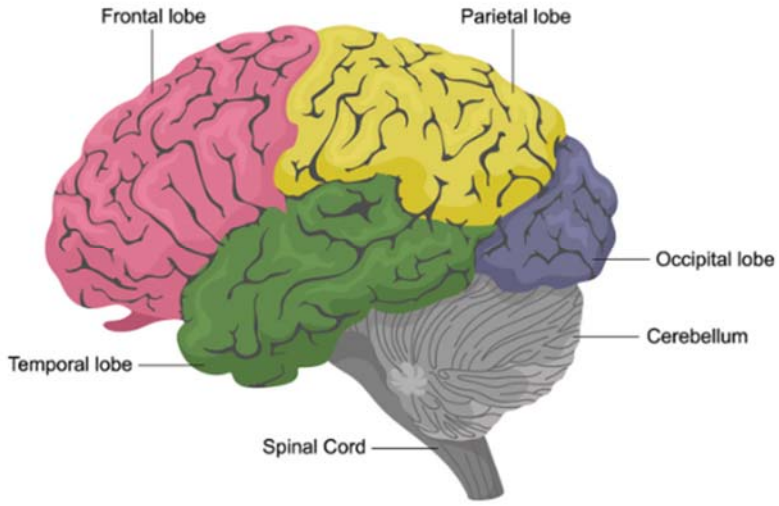


Figure 6. Human brain lobes *[27]*

There is some brain activity characterizing interictal scalp EEG of a FCD patient, such as rhythmic epileptiform discharges (REDs), polyspikes, repetitive fast waves (brushes). Moreover, they all tend to correlate with respective features in invasive procedures, for example, SEEG or ECoG [21].

Scalp EEG interictal findings could properly localize the SOZ in about 50% of the affected patients. However, SOZ is often not well defined even with intracranial electrodes [22].

The epileptogenic zone in FCD often is greater than the lesion visualized on MRI. Thus, additional information from EEG proves useful [22] [21]. About 60% of the affected patients which undergo the resection surgery are seizure free following the procedure [22].

### 2.3.2. HFOs in FCD

Generally, a MRI scan is sufficient to differentiate between type I and II of cortical dysplasia. The majority of FCD type II abnormalities can be seen on brain MRI, while only some of the FCD type I lesions can be detected using that method. However, in all types of FCD, the lesion detected by MRI may be smaller than the real SOZ which is seen in EEG. Therefore, other diagnostics are needed to establish the resection area and check if vital brain parts are not involved [6].

HFO patterns seem to be similar in various lesion types, although the HFO rates vary with different pathologies. FCD shows more HFOs per unit time. In FCD, the recording rates are the highest inside the lesion and decrease gradually further away from it [4].

The researchers of FCD have also been comparing the HFO rates in type I and type II. The results are consistent in that the seizures are significantly more frequent in type II and the HFO rates seem to mirror that disease activity. Even though HFO analysis in scalp EEG is a relatively new field and reports vary in patient population and main focus, research seem to conclude that it is helpful to localize the affected lobe or hemisphere [13].

# 2. Methods and data

## 3.1. Available datasets

The datasets contain scalp HD-EEG recordings of 40 patients suffering from refractory epilepsy. Each recording was generated from 128 electrodes as part of their pre-surgical examination and contains approximately 8 hours of signals. The EEG signals were recorded at night during patients´ sleep therefore, the physiological artifacts such as eyeball movement or muscle activity is minimal and, if present, they can be clearly identified.

The data regarding the patients' diagnosis on exact FCD type, as well as patients´ age, were blinded until after the analysis of HFOs has been completed.

## 3.2. Methodology

A recent study conducted by El Shakankiry et al. (2021), which involved 100 children diagnosed with epilepsy, investigated the presence of HFOs on IEDs on routine scalp EEG with 21 channels and sample frequency of 500 Hz. This study revealed that the patients with a higher risk of seizure occurrence, and so with spikes with high-frequency activity, could be visually identified in 19% of cases [13].

In this project, the number of electrodes is higher (128) and the signal was initially recorded at 2048 Hz and then resampled to 512 Hz. Thus, we are expecting to find some amount of HFOs at least in some patients.

Even though there have been some advancements on automatic HFO detection, visual analysis still remains the gold standard. The important limitations of the visual review are the subjectivity of the rater and the time-consuming process of detection. In some recent studies, various automatic detectors have been used. However, their sensitivity and specificity depend on the training set and thus, may not be fully applicable to another patient population. In many cases, human visual validation is still presumed important [23]. As further thorough studies are needed to establish an efficient criterion

for automatic HFO detection, this project uses visual analysis as the detection method in the applicable dataset of EEG data of FCD patients.

The steps to follow were:

1. Identify patients with clear HFO presence combined with IEDs by using the Alenka visual viewer software and group the patients into HFO-active and HFO-inactive.
2. Using the Brainstorm application, perform the visual analysis of the HFOs combined with IEDs of each patient, i.e. detect spikes with visible HFOs and mark such events at the peak of the spike and extract the signal 500ms around the peak for further processing.
3. Determine the HFO rate for each patient by analyzing the detected events.
4. Using the Brainstorm application, create scalograms in the time-frequency domain for the detected events and average the results to observe the most HFO active channels.
5. Based on the HFO findings, determine the type of FCD in each HFO-active patient and then compare the results with the confirmed FCD diagnosis and compute the statistics.
6. Compare the visual analysis of the HFOs with the diagnosis made by the automatic MELD FCD detector based on the MRI tests of the patients and compute the statistics.

### 3.2.1 Alenka signal viewer.

As mentioned earlier, there is still some discrepancy in the definition of HFOs and their relation to IEDs. Although they have some common features, IEDs and HFOs vary from patient to patient and the rate of events is not constant throughout the EEG recording.

Visualization of the signal plays an important role in determining if the patient is HFO active, i.e. if HFOs are visible in the time domain and in the Alenka viewer it is possible to approximate what frequencies they might contain. As the datasets are

resampled to 512Hz, per Nyquist theorem, we can expect 2 ranges to be observable: gamma activity (60-80Hz) and ripples (80-200Hz).

Alenka signal viewer is an EEG analysis software developed in the Intracranial Signal Analysis Research Group in the Faculty of Electrical Engineering, CTU [24]. Alenka viewer functionality enables the pre-processing of the raw signal by applying a notch filter at 50 Hz as pre-processing step before the initial analysis. The signal can also be filtered with appropriate high-pass and low-lass thresholds to detect the presence of IEDs and HFOs.

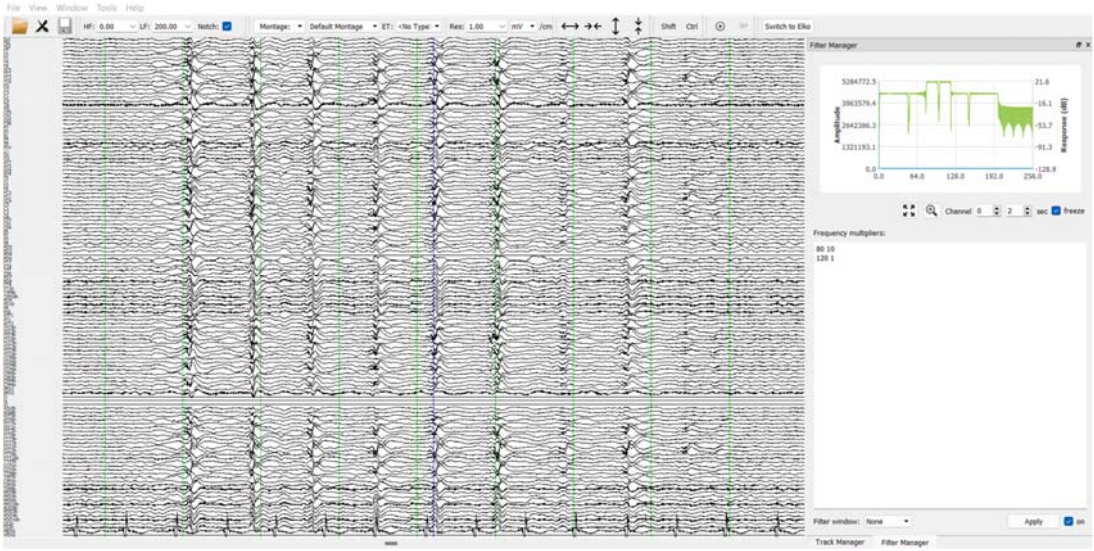

Figure 7. Alenka signal viewer interface; observed IEDs with HFOs.

Figure 7 shows the interface of the Alenka signal viewer and the presence of HFO activity co-occurring with spikes. The spike frequencies usually are in the 10-40 Hz range, the band-pass filter application confirms their presence. Following that, the same part of the signal is processed using a high-pass filter at 80Hz to confirm the HFO activity.

Some patients have HFO activity around the spikes that can even be seen with a naked eye without the filtering, as shown in Figure 7. However, in some cases, filtering the same part of the signal is necessary to confirm or discard the HFO activity.

Based on the analysis in the Alenka software, the list of HFO-active patients is created.

### 3.2.1. Brainstorm application visual analysis

Brainstorm is an open-source application used to analyze brain recordings. Its graphic interface allows to visualize various types of signals, such as EEG, MEG and ECoG, among others. This application also allows to implement different approaches and signal processing techniques based on the researcher´s needs [25].

In this project, Brainstorm is used to visualize the HD-EEG recordings of HFO-active patients, mark and group the IED combined with HFO events.

The following steps are included in the procedure:

- The recordings of the HFO-active patients are loaded and the protocol for each patient is created in the database.
- Each patient´s recordings are reviewed again with filters to confirm the HFO activity, i.e. the simultaneous occurrence of IED (10-40 Hz) and HFO (>80Hz) with more than 4 oscillations in at least one of the channels.
- Each event is marked, centered at the peak of the spike, and the signal in the range -500ms and 500ms around the spike is extracted and stored in the database.
- Finally, the events are analyzed in the time-frequency domain. The Morlet wavelet transform is applied to each event to create a scalogram. The averaged scalogram results for each of the channels are further visually analyzed.

### 3.2.2. Time-frequency analysis

In order to decompose the EEG signals into the time-frequency domain and observe the power which each frequency has at each point in time, the most valuable method is to use the Morlet wavelet transform. Wavelet is a short-lived oscillation localized in time. Figure 8 shows the general look of the mother wavelet of Morlet wavelet type. The transform is the convolution of the signal with the Morlet wavelet. The result can be visualized as a scalogram.

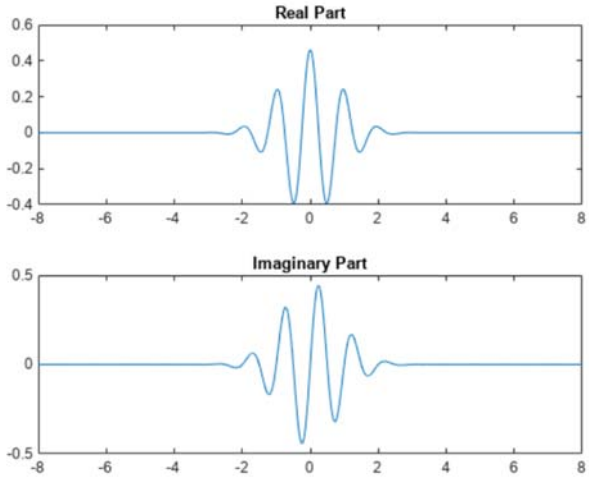


Figure 8.The Morlet wavelet.

The wavelet transform offers an optimal compromise between frequency and time resolution on the scalogram plot. For low frequencies, the time resolution is poor and improves as frequencies increase, whereas the frequency resolution decreases. At higher frequencies, there is better time resolution but poorer frequency resolution.

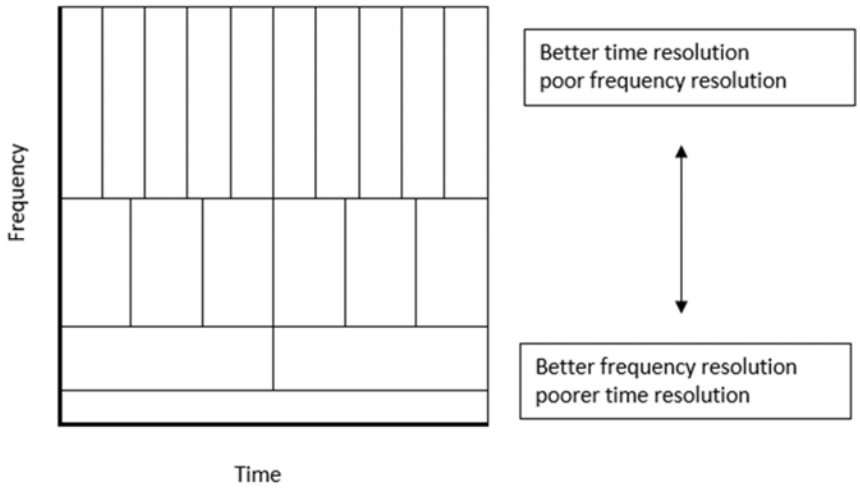


Figure 9. Scalogram resolution

### 3.2.3. MELD automated classifier

As previously discussed, patients who suffer from MCD often have ambiguous MRI scans, which make detection of abnormalities complicated. Moreover, the level of neuroradiological expertise, technical characteristics of the MRI scanner and the conditions when sequences are acquired may vary from one clinical center to another.

The Multi-center Epilepsy Lesion Detection (MELD) FCD classifier is an open-access, fully automated surface-based software which may be applied to any FCD-suspected patient who underwent 1.5 or 3 T $T_1$ scan with or without FLAIR data. The goal of the MELD classifier is to help with the detection of challenging lesions in drug-resistant epilepsies and the identification of epileptic abnormalities [26].

The MELD framework was created to enable the prediction of lesioned brain tissue based on the analysis of a variety of patient cohorts, several MRI scanners, different protocols and cooperation of a big group of professionals.

# 3. Results

In this part of the project, we present the results of the described methodology applied on the subject dataset and the findings are discussed.

## 4.1. EEG data processing

In order to determine if the patient was HFO active, the raw EEG recordings were reviewed. As we know, the HFOs may also appear as an artifact of the filtering process. The interictal recordings were made during patients sleep to minimize the present of such artifacts. The recordings were reviewed using the Alenka viewer and only the patients with clear visible spikes and co-occurring HFOs were chosen. This initial HFO analysis showed that 11 patients out of the 40 were potentially HFO active.

Table 1 shows the list of patients which were identified as having simultaneous occurrences of IEDs and HFOs. The full table of patients is included in Appendix A.

Table 1.Initially detected HFO-active patients.

| **Patient #** | **HFO rate per minute** | **HFO most active channels** |
|---|---|---|
| P_84 | 7.9 | C4, F4, P4 |
| P_133 | 0.53 | CP1, Cz, C1, P1 |
| P_143 | 1.45 | PO9, P9, TPP9h |
| P_150 | 0.94 | C2, FC2, F4, P4 |
| P_166 | 5.93 | P8, PO8, P10 |
| P_204 | 0.31 | C4, FC2, FC4, F2 |
| P_225 | 2.13 | P8, PO8, PO10 |
| P_239 | 0.09 | F1, F3 |
| P_246 | 2.5 | P7, T7, TP7 |
| P_249 | 0.73 | C4, Fp1, F4, AF7 |
| P_252 | 19.4 | C4, FC2, F4, P2 |

Later on, the recordings of HFO-active patients´ were analyzed using Brainstorm and classified according to the HFO rates. The advantage of the Brainstorm tool is that it allows to mark the central point of the IED+HFO events in the recordings and extract 500ms of the signal around it for further analysis.

One of the challenges when marking the events manually is that IED + HFO events throughout the channels differ in amplitude and phase. The goal is to set the central point at the peak of the spike as precisely as possible on the most HFO-prominent channel, i.e. where the HFO is observed at the same resolution in the program at which we can clearly see the spike and with the highest possible IED amplitude. Figure 10 shows an example of an IED with HFO.

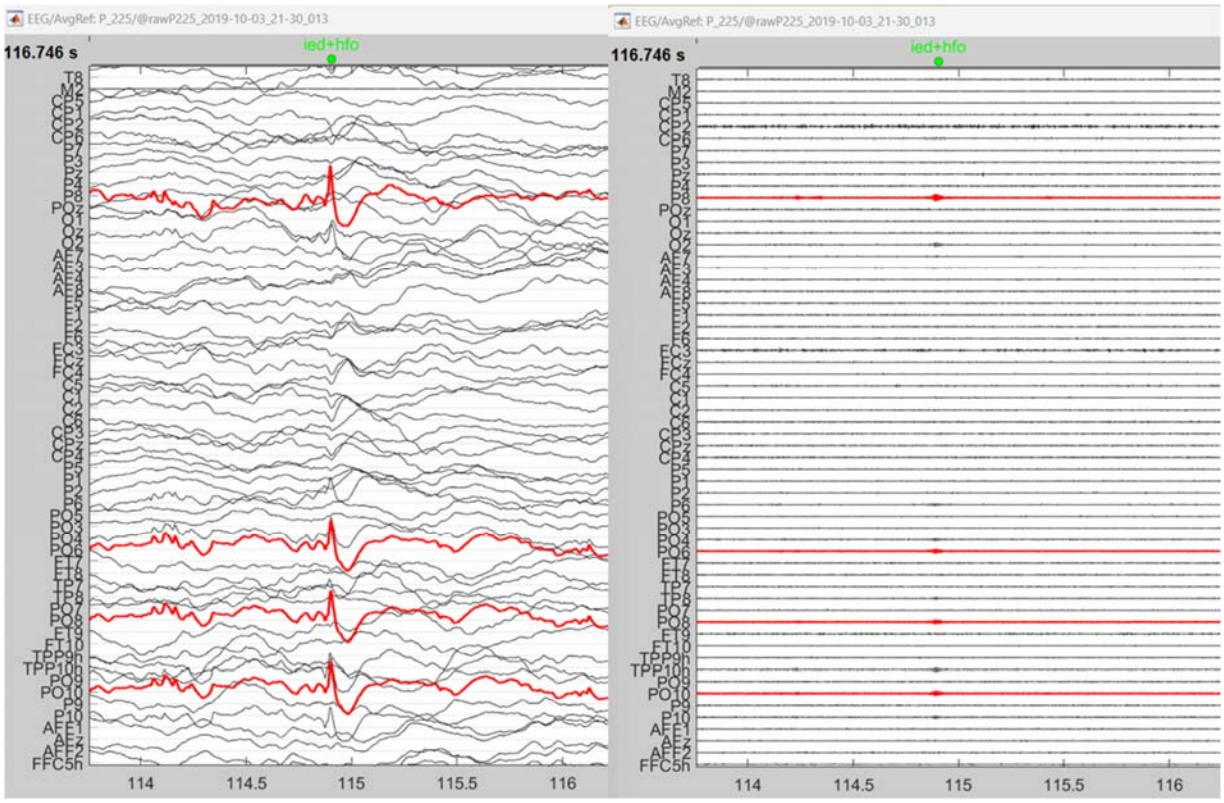


Figure 10. Example of IED with HFO.

Right: Spike filtered 10-40 Hz. Left: HFO filtered >80Hz.

The HFO rate was calculated using periods of 2 hours of signal with active IED+HFO events in the first half of the EEG recordings. Only recordings that were clear

of significant distortions, high frequency noise, and muscle activity noise were used. The marking was checked at least 3 times to minimize personal bias.

The confirmation of the presence of HFOs was made by averaging the events in the time-frequency domain by means of the Morlet wavelet transform. As a result, the scalograms of the averaged IED+HFO events for each HFO-active patient were analyzed. For patients with high HFO rates per minute (>>1), the number of events averaged were 100. For patients with an HFO rate << 1, 10-50 events were used. As the averaging in the time-frequency domain depends strongly on the central point of the marked event, the previous strategy of marking the channel with the clearest spike and HFO seems appropriate and is expected to confirm the existence of HFO both in the time and in the frequency domains.

## 4.2. Important findings

As a result of the analysis, it can be observed that a correlation exists between the HFOs observed in the channels of the EEG signal and the frequencies on the averaged scalograms. It can be observed that the same channels which were the most HFO active and had high amplitude IEDs were confirmed as having HFOs on the scalogram.

The frequencies which are expected to be detectable using a 512-Hz sampling rate in a scalp HDEEG are the ones in the ripples range (80-200 Hz).

Despite the possibility of some of the HFOs being artifacts, since the oscillations are clearly observable on the software in the time domain and are strongly related to the spike blob on the scalogram, we can deduce that those HFOs are most likely pathologic. One of the problems that may be discussed here is that the amplitude of the HFOs is much lower than the one of the IEDs and therefore affects their power. Despite this, a separate burst of high-frequency activity is observed in the majority of the patients defined as HFO-active. This high-frequency activity in the signal is related to the spike and is not homogeneously continuous, which would be the case in the case of an artifact. The complete description of the scalogram results is found in Appendix B. Figure 11 provides a sample of the scalograms for three of the analyzed patients.

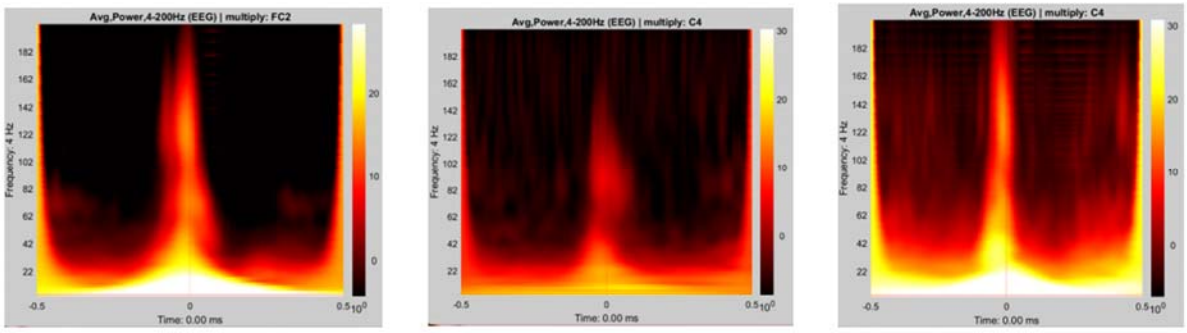


Figure 11. Scalograms. Left to right: P_252. P_249, P_84

Based on the theoretical knowledge regarding FCD types I and II, the expected HFO rates and the expected lobes of the brain affected by each type, the HFO-based diagnosis was proposed by the author of the project. The data with the true confirmed diagnosis made by medical professionals was blinded and accessed only when the visual analysis of HFO-active patients was complete. On Table *2*, we can observe that out of total 11 HFO-active patients, 3 were correctly diagnosed as FCD type I and 3 were correctly diagnosed as FCD type II. A sensitivity of 60% and specificity of 50% are not enough to make a statistically meaningful statement. It is clear that using only an HFO-based approach is not sufficient given the high number of false positives and false negatives observed, and other medical tests still need to be considered in order to obtain results closer to the correct diagnosis.

Table 2. Contingency table of confirmed FCD type diagnosis vs HFO-based diagnosis.

| Author's analysis / Medical diagnosis | HFO-based diagnosis FCD I | HFO-based diagnosis FCD II |
|---|---|---|
| Confirmed FCD I | 3 | 3 |
| Confirmed FCD II | 2 | 3 |

After receiving the correct diagnosis data, it is of interest to identify whether or not the HFOs were detected via HDEEG for each FCD type. Application of the Fisher exact test on that contingency table on Table 3, unfortunately, does not yield any statistically significant results–the Fisher´s test statistic value 0.1468 is not significant at $p<0.05$. As

the total cohort of patients is relatively small and also the group of not detected HFOs by the visual method is quite large, this prevents us from concluding that FCD type I and FCD type II are somehow differently affected by HFOs. In fact, the under-detection of HFOs by visual procedure is a big issue of the research–some HFOs of small amplitude might have been left undetected or might have been misinterpreted as artifacts. This problem highlights the need for a clear scientific definition of the HFO event and also a generalized tool for its automatic detection among FCD patients.

Table 3. Contingency table of confirmed FCD types and HFO detected.

| | Confirmed FCD I | Confirmed FCD II |
|---|---|---|
| Visually detected HFO | 6 | 5 |
| No visually detected HFO | 8 | 21 |

## 4.3. Visual analysis vs MELD results

Further on, the comparison between the visual analysis results and the MELD results was made. There were 21 available MELD analyses which provided information regarding the predicted number of lesion clusters and their locations visualized on the brain surfaces. The aim of the comparison was to observe whether the HFO active channels detected by the visual analysis coincided with the lesioned tissue predicted by the MELD classifier.

It was noted that MELD analyses detected significantly more clusters of lesioned tissue than the visual analysis of HFO co-occurring with spikes. Unfortunately, the available MELD data only contains reports for 21 of the 40 patients. The analysis of the patients' data showed that the MELD detected 19 of the 21 cases of FCD, whereas visual analyses yielded only 5 out of 21 positive detections. In one of the cases, neither of two methods detected the pathology, and in another case, while the clear IEDs with HFOs were detected by visual analysis (P_143), there was no pathologic cluster found by the MELD tool.

However, in the case of 4 patients, the visually detected active HFO regions on the scalp HD-EEG at least partially overlapped with the affected regions predicted by the MELD classifier. These are patients P_150, P_204, P_239 and P_246. It is worth taking into account that the morphology of the two methods is completely different as they focus on features of distinct physiological origin, i.e. the MELD classifier uses MRI data which describes the characteristics of the brain tissue, whereas the visual analysis of HD-EEG recordings explore the local field potentials generated by groups of neurons. Given this fact, we might say that the overlap may be quite meaningful and gives promising ideas for future research.

Table 4. Comparison of MELD and HFO analyses.

| | MELD detected clusters | MELD no clusters |
|---|---|---|
| Visually detected HFOs | 4 | 1 |
| No visually detected HFOs | 15 | 1 |

When Fisher´s exact test is applied to determine the correlation between the visual HFO analysis findings and the MELD results, p-value turns out to be 0.4286. Therefore, at $p < 0.05$. the $H_0$ hypothesis that the results of the two procedures are independent is confirmed. This was expected as it was previously also explained that HFOs and MRIs test events of distinct origin.

## 4.4. Limitations of the research

There are several important limitations of the visual analysis of EEG signal and spike detection.

The first challenge of the visual analysis is that the spikes are not distributed homogeneously along the recording, which makes the marking of the events and the calculation of the HFO rate time-consuming and possibly biased due to the limited experience of the author of the project.

Another problem is that there is no consensus on the proper definition of an HFO event. In this project, we chose to analyze the HFOs which co-occur with interictal spikes

because, as up to date research shows, they have higher probability of being related to epileptogenesis. However, according to the literature, solo HFO events could also be pathologic and need to be subject to further analysis.

Lack of a significant amount of data on how the HFOs is related to patient age is impeding to make any scientifically meaningful statement regarding this relation. Similarly, the relation between HFOs and sleep waveforms is not properly studied yet. As some experienced neuroscientists suggest, there might also be a relation of HFOs to certain stages of sleep and even some sleep waveforms not related to IEDs. This topic still requires further research.

In this project, the aim was to observe the properties of HFOs that coincide with spikes, thus the amount of HFOs detected was limited. The visual analysis process is extremely time-consuming and requires hours of practice.

It is important to note that automatic detection of HFOs needs to be developed to create automation tools which are helpful for medical professionals and make the diagnosis process more reliable and faster. For this, it will be necessary to combine different methods, equipment and patients' cohorts, as well as to achieve cooperation between various clinical centers.

# 4. Conclusion.

In accordance with this thesis assignment, the analysis of the High Frequency Oscillations (HFOs) of patients affected by Focal Cortical Dysplasia (FCD) was performed.

The latest research of high-frequency oscillations and clinical cases from a variety of medical centers that was reviewed shows the importance of these complicated phenomena and that scientists are trying to reach consensus on the definition of an HFO event.

Regarding the conditions in which the HFOs are detected, the studies vary greatly in terms of methods, wakefulness, ictal stage and age of patients.

In this project, the focus was placed on scalp HD-EEGs recorded in sleep stage so that the muscle artifacts are minimized. As the cohort of patients data was limited to 40, the visual analysis was chosen based on the current consensus definition of an HFO. The chosen events coincide with interictal spikes, as the possibility of those HFOs having a pathological nature is higher.

It was discovered that not all patients show high frequency activity at the spikes or that the amplitude of the HFOs was too low to make be directly observed in comparison with the IED. For those cases, a more in-depth approach would be required. Moreover, as we have observed in some clinical cases, the HFOs which are not visible on the spike have a higher chance of being artifacts. Thus, only the recordings with significant HFO activity (11 patients) were chosen, and the most HFO active channels were noted down.

On the scalograms of averaged events, which combined the IED with the HFO centered at the highest peak of the IED, indeed some high frequency activity was detected as well. Even though there is no clear pattern of HFOs from patient to patient, all those high frequencies do not seem to be a simple artifact. The HFOs detected are in the ripple range (80-180 Hz).

The data on the patients diagnosis made by professionals upon many medical procedures was initially blinded and another goal of this work was to determine if, based on the visual analysis of the HFOs, it is possible to differentiate between type I and type II FCDs. Out of 11 patients, 6 were correctly identified based on the HFO channels

compared to the brain lobes affected in each type of FCD. However, due to the small population, it was not possible to yield any statistically meaningful result. The dependence of HFO-active or HFO-inactive status on the FCD type I and FCD type II was also statistically not proved. The main reason for that could be that not all patients showed HFO activity visible enough for the visual analysis by the author of the project.

In addition, the results of the HFO analysis were compared to the automatic MELD FCD classifier based on the patients MRI tests. Out of 21 MELD reports available, the HFO active channels of 4 patients overlapped with their MRI lesioned brain area detected by the MELD classifier, which suggests that despite the MRI and HFO analyses focusing on different physiological phenomena, the epileptogenic area of the brain could be detected by various methods.

The conclusion of the performed analysis is that future HFO research could focus on the creation of a multi-center automatic HFO detector, which would combine various methodologies and expertise of professionals to improve the epilepsy detection and treatment.

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## Appendix A. Acquired data.

| Patient number | HFO rate per min | Visual analysis data | MELD report data | HFO-based diagnosis | Confirmed diagnosis |
|---|---|---|---|---|---|
| 75 | - | NO HFO | - | - | FCD II |
| 84 | 7.9 | C4, F4, P4 | - | FCD II | FCD I |
| 133 | 0.53 | CP1, Cz, C1, P1 | - | FCD I | FCD I |
| 143 | 1.45 | PO9, P9, TPP9h | NO HFO | FCD I | FCD I |
| 148 | - | NO HFO | - | - | FCD II |
| 149 | - | NO HFO | - | - | FCD II |
| 150 | 0.94 | C2, FC2, F4, P4 | RH: lateralorbitofrontal, parsopercularis, parsorbitalis, superiorfrontal, insula, temporalpole | FCD II | FCD II |
| 163 | - | NO HFO | - | - | FCD II |
| 166 | 5.93 | P8, PO8, P10 | - | FCD I | FCD II |
| 172 | - | NO HFO | LH: superiorfrontal<br>RH: superiorfrontal | - | FCD II |
| 174 | - | NO HFO | LH: superiorparietal, superiorfrontal | - | FCD II |
| 175 | - | NO HFO | - | - | FCD II |
| 176 | - | NO HFO | RH: inferiorparietal | - | FCD II |
| 177 | - | NO HFO | RH: postcentral | - | FCD I |
| 179 | - | NO HFO | NO HFO | - | FCD I |
| 183 | - | NO HFO | LH: inferiortemporal, middletemporal, medialorbitofrontal | - | FCD I |
| 184 | - | NO HFO | LH: caudalanteriorcingulate | - | FCD II |
| 186 | - | NO HFO | - | - | FCD II |
| 188 | - | NO HFO | - | - | FCD I |
| 194 | - | NO HFO | - | - | FCD II |
| 198 | - | NO HFO | LH: postcentral, superiorfrontal, supramarginal, superiortemporal, interiorparietal | - | FCD II |
| 204 | 0.31 | C4, FC2, FC4, F2 | RH: superiorfrontal | FCD II | FCD II |

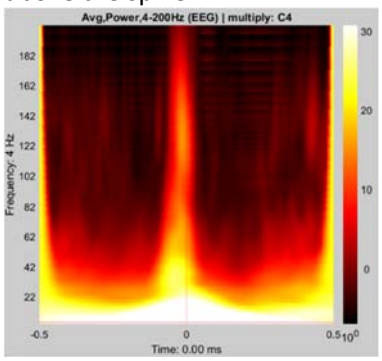
| | | | | | |
|---|---|---|---|---|---|
| 210 | - | NO HFO | RH: insula, middletemporal, superiortemporal, lingual, medialorbitofrontal, lateralorbitofrontal | - | FCD I |
| 212 | - | NO HFO | - | - | FCD II |
| 220 | - | NO HFO | - | - | FCD II |
| 223 | - | NO HFO | LH: caudalanteriorcingulate, insula | - | FCD II |
| **225** | **2.13** | **P8, PO8, PO10** | **-** | **FCD I** | **FCD II** |
| 226 | - | NO HFO | LH: rostralanteriorcingulate<br>RH: fusiform, lateralorbitofrontal | - | FCD I |
| 228 | - | NO HFO | LH:leateraloccipital<br>RH: parstriangularis | - | FCD II |
| 232 | - | NO HFO | RH: precentral, insula | - | FCD II |
| 238 | - | NO HFO | - | - | FCD I |
| **239** | **0.09** | **F1, F3** | **LH: rostralmiddlefrontal, parsorbitalis, superiorfrontal** | **FCD II** | **FCD II** |
| 241 | - | NO HFO | - | - | FCD I |
| **246** | **2.5** | **P7, T7, TP7** | **LH: parahippocampal, superiorfrontal, lateralorbitofrontal, isthmuscingulate<br>RH: parahippocampal, middletemporal, fusiform, medialorbitofrontal** | **FCD I** | **FCD I** |
| **249** | **0.73** | **C4, Fp1, F4, AF7** | **-** | **FCD II** | **FCD I** |
| **252** | **19.4** | **C4, FC2, F4, P2** | **-** | **FCD II** | **FCD I** |
| 253 | - | NO HFO | - | - | FCD II |
| 259 | - | NO HFO | - | - | FCD II |
| 261 | - | NO HFO | - | - | FCD II |
| 266 | -- | NO HFO | - | - | FCD II |

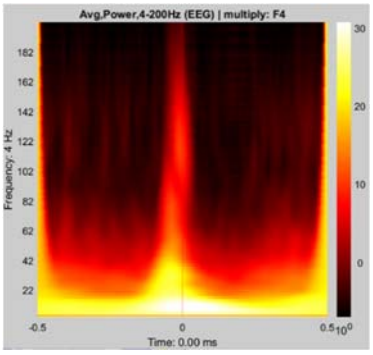
**LH – left hemisphere, RH – right hemisphere*

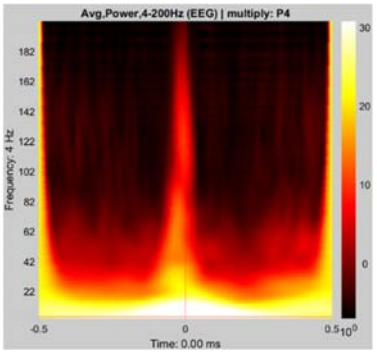
## Appendix B. Results of the HFO-active patients analysis.

| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_84 | 7.9 | C4, F4, P4 |

Comment: Here on the prominent HFO channels we observe the high frequency “blob” with high power above the spike.

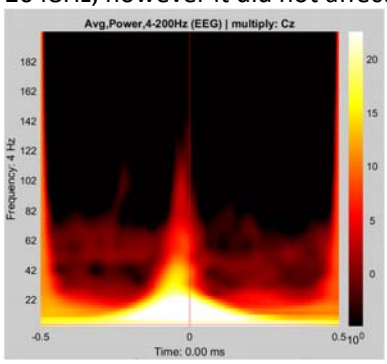


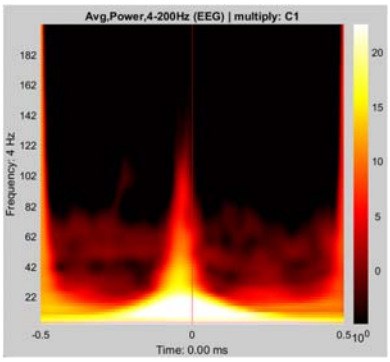



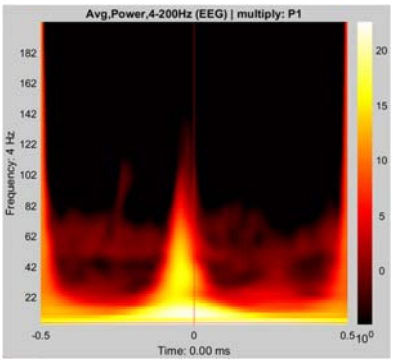




| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_133 | 0.53 | CP1, Cz, C1, P1 |

Comment: The spikes and HFOs of this patient is of very small amplitude. Here the sample rate was 2048Hz, however it did not affect the detection of the events.

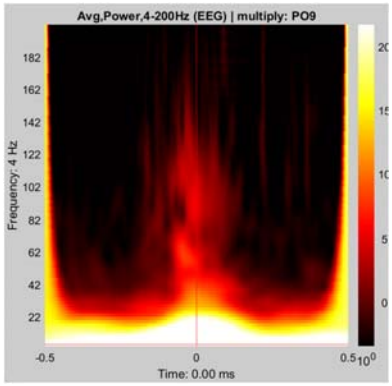


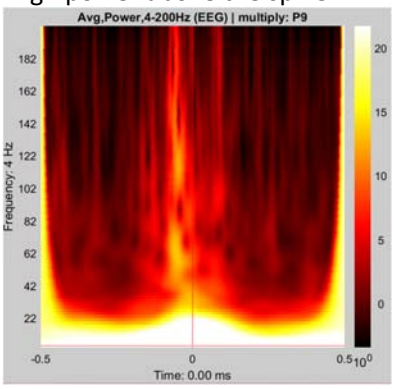



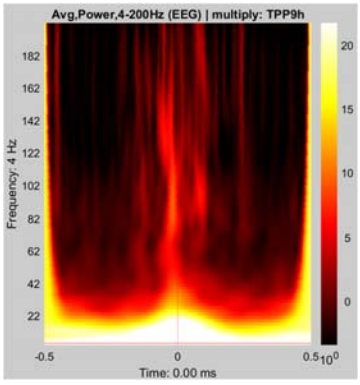




| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_143 | 1.45 | PO9, P9, TPP9h |

Comment: The spikes with HFOs observed are quite focal and do not spread to other channels. We can see on channel P9 several HFOs of high power above the spike.

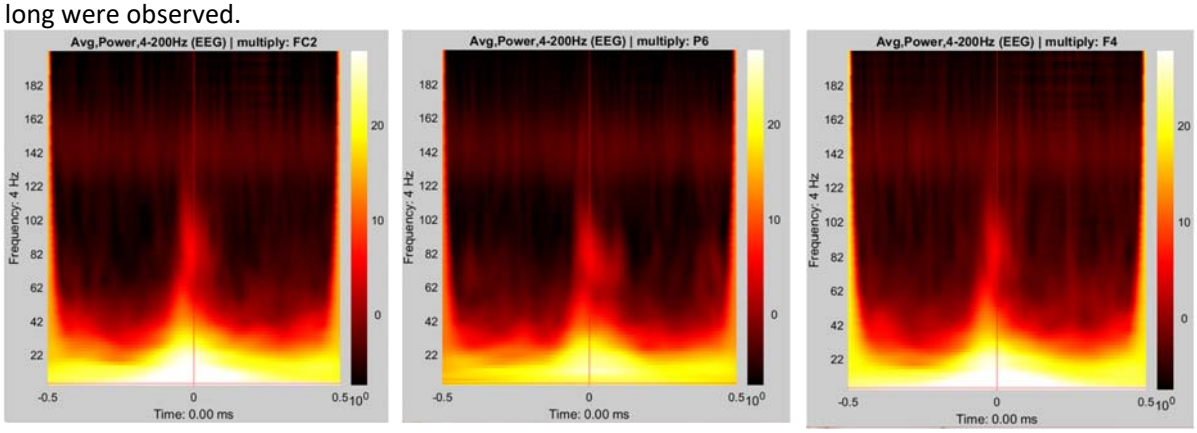


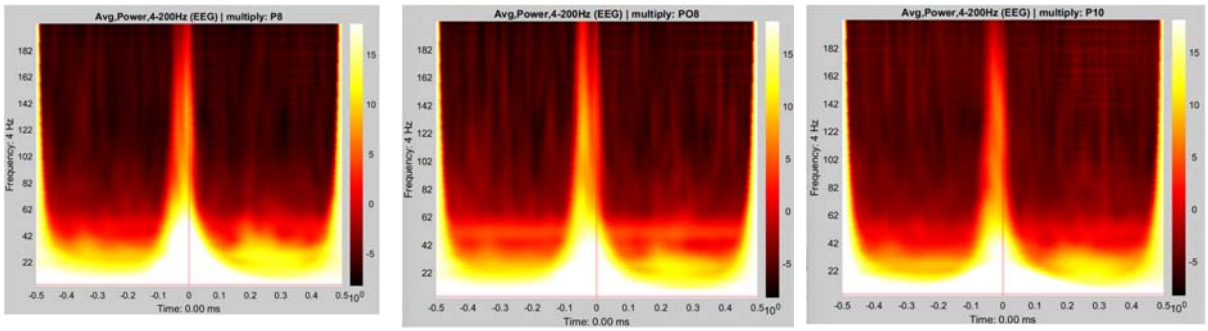
| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_150 | 0.94 | C2, FC2, F4, P4 |

Comment: This patient shows some HFOs above the spike and also multispikes with HFOs of 2-3 seconds long were observed.



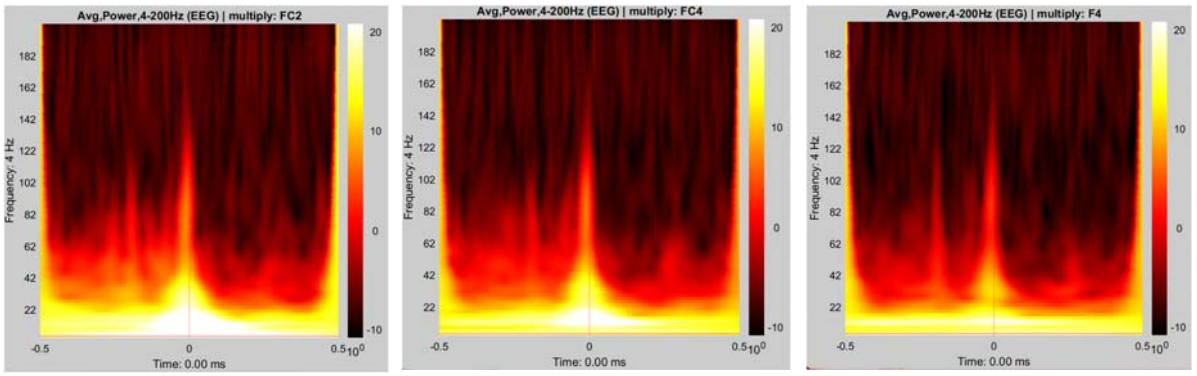

| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_166 | 5.93 | P8, PO8, P10 |

Comment: The HFOs above the spikes in parietal region is detected.



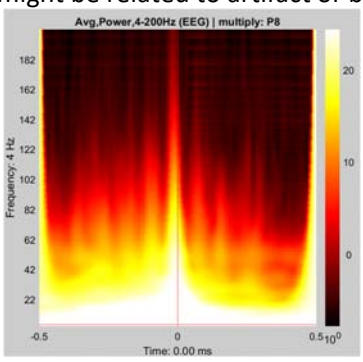

| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_204 | 0.31 | C4, FC2, FC4, F2 |

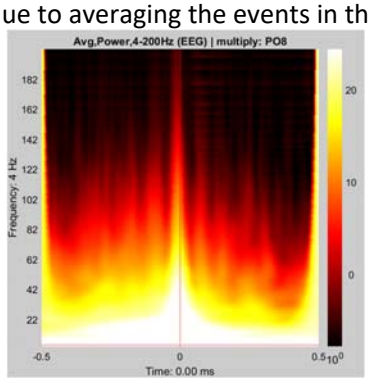
Comment: This showed multispikes and clear typical sleep waveforms around the spikes with HFOs.

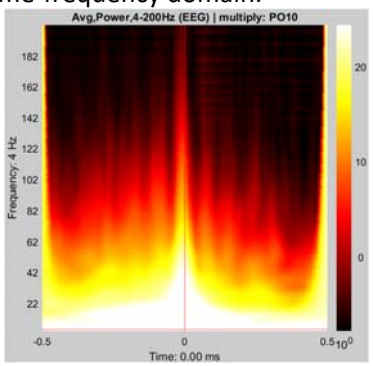


| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_225 | 2.13 | P8, PO8, PO10 |

Comment: In this patient we observe some gamma, high frequencies around the spike. This effect also might be related to artifact or be due to averaging the events in the time-frequency domain.

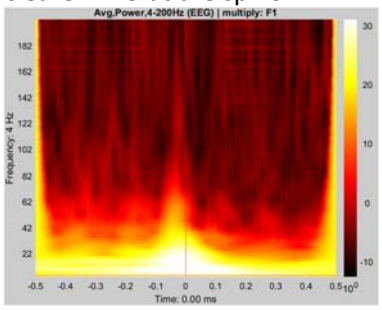


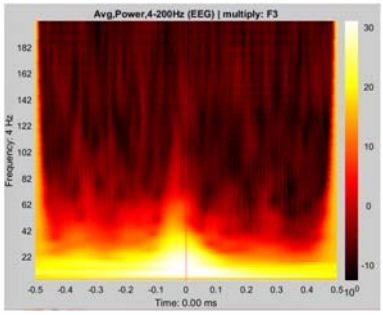





| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_239 | 0.09 | F1, F3 |

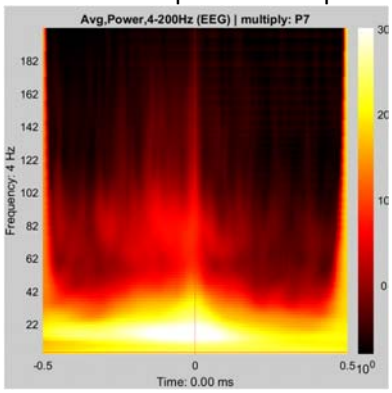
Comment: The HFO rate is quite low. Possibly if detected by some automatic detector, there would be clearer HFO at the spike.

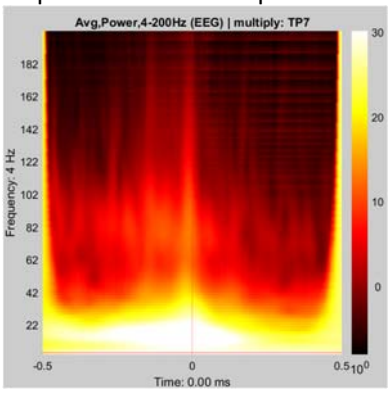


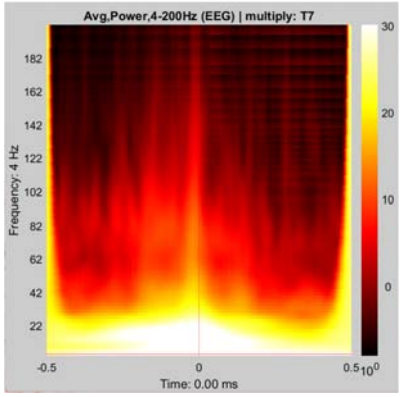



| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_246 | 2.5 | P7, T7, TP7 |

Comment: This patient has many slows, sleep waveforms and multispike activity. The HFO is not well defined at the peak of the spike but spread around the spike.

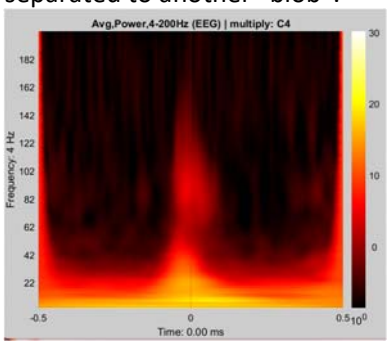


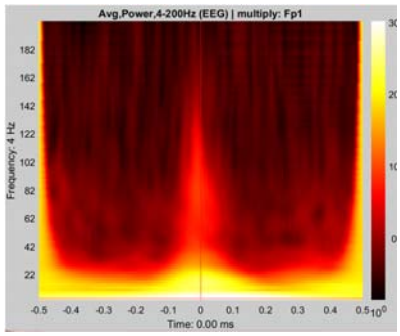


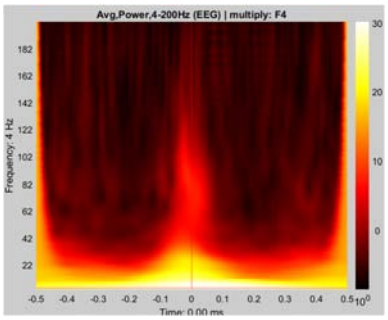


| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_249 | 0.73 | C4, Fp1, F4, AF7 |

Comment: The HFOs are located in all frontal lobes mostly. It is seen that HFOs are above the spike separated to another “blob”.




| Patient number: | HFO rate per minute: | Active HFO channels: |
|---|---|---|
| P_252 | 19.5 | C4, FC2, F4, P2 |

Comment: This patient shows very high HFO rate per minute and HFO active area seems to be broad. There are two “blobs” above the spike.