

Abstract

Twenty-five percent of the epileptic patients today are untreatable [1]. They have to live with the (seemingly) unpredictable nature of their disorder. An epileptic seizure prediction system could make a large improvement to their lives. For almost forty years attempts have been made to find a suitable precursor in (intracranial) electroencephalogram (EEG) measurements, with no good results so far. In this study four measures are compared with respect to their capability to predict seizures for three patients with a focal epileptic disorder with a frontal origin and a γ -onset as initial morphology. The performance of a measure was defined as the area under the receiver operating characteristic (ROC)-curve for the distributions of pre- and interictal time profiles. Andrzejak's test was applied to investigate to what extent the performance of a measure was based on epilepsy related factors [2]. The measures appear to have no real predictive power. Even when they appear to be able to discriminate between pre- and interictal activity, the score on Andrzejak's test suggests that the observed differences were due to non-epileptic factors. So this study yields yet another confirmation that precursors in intracranial EEG measurements are very hard to find. Perhaps it is time to change tracks after 40 years of largely unsuccessful efforts and try other measurements, not related to EEG. A potentially fruitful alternative is the electrocardiogram (ECG) which is related to the reported clinical prodromi [3] and it adds the considerable bonus that it is far less invasive than EEG.

Keywords: • Epileptic Seizure Prediction • Intracranial EEG • ROC • Andrzejak's Test

1 Introduction

Epilepsy is one of the most common neurological disorders with 0.6-0.8% of the world population suffering from this disease [1]. Epilepsy is generally characterized by the occurrence and reoccurrence of massive synchronized high-frequency discharges of neurons. These pathological discharges are known as seizures. Although the origin of an epileptic attack (ictogenesis) is not at all clear, a seizure is thought to be triggered by the creation of a 'critical mass': a group of pathologically firing neurons that entrain an ever growing number of neurons to discharge in synchrony [4].

Different forms of epilepsy are distinguished mainly along two dimensions: the location on the cortex where the seizures are thought to start and its clinical effects. The origin of a seizure is sometimes hard to define; the entire cortex seems almost instantaneously involved so that no clear region can be found that triggers the seizure. This form of epilepsy is often referred to as *generalized* [5, 1]. In the case of *focal* epilepsy, there appears to be a region where the seizure occurs first before the pathological activity spreads¹. Instead of a sudden massive change in dynamics, the seizure tends to start in a more gradual (or cascaded) fashion [5, 1].

The clinical consequences can differ per patient and per seizure. *Clinical* seizures can cause the patient to temporally lose consciousness or to lose motor control [5, 1]. The patient can easily fall and get hurt. In contrast, *subclinical* seizures do not result in any observable behavioral changes, while brain measurements still show characteristic seizure activity. Frequent epileptic seizures can eventually lead to a slower cognitive development and in some extreme cases to a cognitive degeneration [1].

Most of the patients (63 %) can be treated with non-convulsive medication. Some patients that do not respond sufficiently to this form of treatment can resort to more drastic measures as *resective surgery*. The focal area - that part of the cortex where the epileptic seizures are assumed to start - is removed. While this operation is quite radical, only patients with a strict focal epileptic disorder are considered for treatment; generalized patients or patients with multiple focal areas are not suitable for this operation since it is unclear which area to resect. Twenty-five percent of the epileptic patients today are untreatable [1]. They have to live with the (seemingly) unpredictable nature of their disorder. To know when a seizure strikes could make a large improvement to their lives. In that case they could prepare themselves (and any medical personnel) for the oncoming seizure. Being able to lie down in time make injuries less likely. But also more sophisticated systems could be envisioned where medication or contra stimulation might reduce the impact or even stop the seizure. (See the article by Osorio et al. (2001) for more on how such a seizure intervention system could be realized).

An epileptic disorder is considered to consist of four different phases: the ictal, postictal, preictal and interictal phase. The ictal phase refers to the actual seizure; the moment where cortical neurons fire high-frequently in a synchronized fashion. The postictal phase is directly after the seizure. There is no ictal activity, but the patient recovers from his/her fit. This phase can last for a few seconds up

¹In some cases, the epileptic activity does not spread, but is contained in the focal area.

to an hour. The preictal phase is just before a seizure. This is where the seizure-initiating process is thought to start that eventually will lead to an attack. The duration (and even the existence) of this phase is under discussion (see Conclusions and Discussion) but normally it is considered to start from five minutes up to four hours before seizure onset. The interictal phase is when no seizure is about to occur or has happened. The patient functions normally and shows no epileptiform activity, except for some pathological spikes that are common for epileptic patients. See Figure 1 for the epileptic cycle.

An epileptic seizure prediction system should be able to distinguish successfully between the interictal and the preictal phase. Note that a prediction system is not the same as an early detection device which is only capable of warning the patient a few seconds in advance ([5, 1, 6]). Such a short interval will not leave the patient enough time to take the necessary preparations.

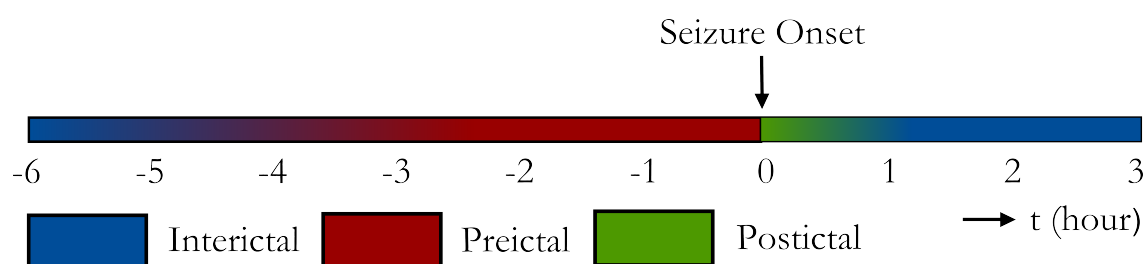


Figure 1: The epileptic cycle. A seizure occurs at time point $t = 0$. Blue represents interictal activity. Red depicts that the seizure-initiating process has started and therefore represents the preictal state. Green stands for the postictal phase, where the patient recovers from his/her seizure. While it is unclear when the preictal state starts, there is no strict distinction between the inter- and preictal phase. Due to the fact that the duration of recovery can differ per patient and per seizure, the transition between post- and interictal is not fixed as well. The postictal phase normally lasts for less than an hour. The duration of the preictal phase can range from five minutes to four hours [5, 7, 1].

Due to the neurological basis of epilepsy, the main focus in this field of research has been on changes in scalp and, especially, intracranial electroencephalogram (EEG) recordings². These imaging techniques are thought to reflect the postsynaptic activity of groups of pyramidal cells that are organized in parallel [9]. The intracranial variant is, in contrast to scalp measurements, recorded directly on the cortex of a patient. Even while the likelihood of infections and internal bleedings is high, this intracranial technique is still resorted to for two reasons. First, its high temporal and spatial resolution make it possible to accurately record the area of interest. Second, this type of data contains (almost) no artifacts (e.g., muscle contraction which typically cause γ -rhythms which normally are associated with the epileptic activity, are not (or only slightly) picked up by the electrodes) [9]. The signal-to-noise ratio in intracranial EEG is much higher than in scalp EEG-recordings.

For almost 40 years there are attempts to find a suitable precursor in (intracranial) EEG measurements for seizures that could aid in the creation of automated seizure prediction system. In the

²Other recordings, like electrocardiograms (ECG) have been tried as well, yielding fairly good results [8, 39, 40] (see Future Research).

Introduction

seventies Viglione and Walsh were the first in trying to find the right characterizing measure for absence seizures in scalp EEG-recordings [10]. Many followed their example. First simple linear features [11, 12, 13] were tried, later progressing into more complex non-linear characterizing measures [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. The results were at first encouraging. Several measures showed a strong increase or decrease from several minutes up to 24 hours in advance.

Later it became clear that many of these results were not legitimate or reproducible [1]. The *sensitivity*, the proportion of correct positives (seizures correctly predicted), was assessed correctly. The *specificity*, the proportion of correct negatives, on the other hand was neglected. The precursors that seemed suitable first, were often not unique and characteristic for an oncoming seizure, but occurred in normal interictal activity as well.

Even while it is now more common to report the specificity and the ways to assess the performance become more advanced [2, 25], the field still has to deal with some major problems. First, useful data are scarce. Because intracranial measurements are risky, the number of patients that undergo this treatment and the durations of recordings are kept to a minimum. The chance of infections or internal bleedings is simply too high. The fact that some of the recorded seizures are *highly clustered* (the postictal phase of a seizure overlaps with the preictal phase of the following seizure) decreases the number of useful data even further. The small amount of data makes the results unreliable. Second, the patients are free to move and speak during the recordings. 'Precursors' that are found could be due to natural, non-epileptic factors, e.g. the vigilance state (asleep or awake) of the patient [26]. Third, the non-convulsive medication of the patient is often changed to enhance to occurrence of seizures. The brain activity, measured in the beginning of the recordings, is therefore likely to differ from the data collected at the end of the session. The results could now also be caused by circadian fluctuations [26]. Fourth, the results are difficult to generalize over epileptic patients, while the patients who are considered for resective surgery all suffer from a rather complex form of focal epilepsy. It is questionable whether results based on their data can be generalized to patients with a generalized or another focal epileptic disorder. Because the number of electrodes and their placement are often tailored for each patient, it is even hard to compare the results between patients (See section 2.1, Data).

Many studies try to assess the predictive power of one measure at the time [13, 11, 16, 17, 18, 19, 20, 27, 22]. The study performed by Mormann et al. (2005) is unique in the sense that they were the first to systematically compare thirty different univariate and bivariate measures and that they try to generalize over five patients each recorded in a different center. Univariate measures are computed on the basis of one channel (e.g., Hjorth complexity measure, discussed in section 2.3.1), while a combination of channels is used for bivariate measures (e.g., maximized linear cross-correlation, see section 2.3.2). Both the univariate and the bivariate measures consist of linear and non-linear variants. Almost no assumptions were made about the form of the precursors: the strength and duration of the 'characteristic' increase or decrease were not specified beforehand. Parameter selections were made

afterwards and solely on the basis of the acquired intracranial EEG-data without the use of any other patient specific information. Most of the measures considered have been used before in other epileptic prediction studies.

Mormann et al. (2005) apply a moving window technique [28]; the data are divided into windows with a fixed duration. Per window, a measure is computed that results in a time profile. To assess the performance of a measure, Mormann et al. (2005) compared the distributions of the interictal and preictal time profiles. Of course, such a comparison can be made in a number of ways. In their *first scheme*, the distributions of all preictal time profiles are compared with the distribution of all interictal time profiles. Because every channel and seizure in the dataset is considered, the precursor of that particular measure must be quite strong and/or present in every channel to show a (large) difference³ in the preictal and interictal distributions. In the *second scheme*, not all channels are used, but only those channels that result in the largest difference between preictal and interictal distributions were selected. The idea is that precursors are unlikely to be found in all channels (or channel combination for bivariate measures) and that it is wise to select the most appropriate one instead of considering every channel apposed to scheme 1. This approach implies that a clinical prediction system would need training in order to select that best performing channel, before it could be put into use.

In this thesis I want to investigate to what extent the results found by Mormann et al. (2005) are reproducible. Since the parameters were selected on the basis of the data, it is questionable whether the same results can be achieved if a different dataset is used. My research question is *to what extent can several measures help to distinguish between interictal and preictal intracranial EEG data so that preparations could be made for an oncoming seizure?* I will not consider all thirty measures but will restrict myself to one linear univariate (relative power in the γ -band), one non-linear univariate (Hjorth complexity measure), one linear bivariate (maximized linear cross-correlation) and one non-linear bivariate measure (mean phase coherence). These measures performed best in their category (univariate/bivariate and linear/non-linear) in scheme 1 and 2 [7]. The results found for these measures are intended to be used as indication for the reliability of the other measures. I am not interested in early detection, but I want to find that measure that makes it possible to predict a seizure minutes or, preferably, hours before its onset, since a patient should be able to take the necessary preparations. While the term epilepsy applies to a large range of disorders, it is likely that the suitability of a measure can differ per form of epilepsy. Therefore I will first restrict myself to patients with a γ -onset as initial morphology (see Figure 2).

Besides comparing the interictal and preictal time profile distributions of all channels combined (scheme 1) and the distributions of the best performing channel or channel combination (scheme 2), but I will also look for changes over time in the time profiles that could help to predict a seizure.

³If a difference is found in scheme 1, it is likely that the performance of a measure can be increased by selecting a subset of all channels.

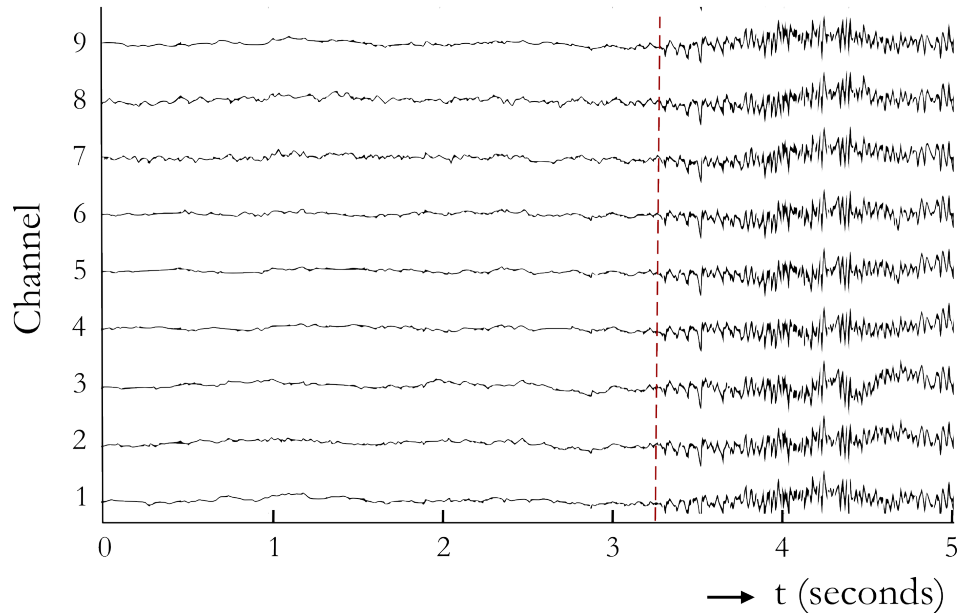


Figure 2: Five seconds of intracranial EEG-data of patient 3 (see section 2.1) recorded with nine electrodes. Seizure onset is denoted with the red vertical dashed line and determined by the EEG-specialists from the 'Universitair Medisch Centrum Utrecht' (UMC). It is a perfect example of a seizure starting with γ -oscillations. The three patients that are used in this study all have this characteristic initial morphology (see section 2.1.)

2 Method

2.1 Data

This study is done with intracranial electroencephalogram (iEEG) recordings of three patients: one female adult and two children, one boy and one girl. Each of them suffered from a focal form of epilepsy and were successfully treated with resective surgery in the 'Universitair Medisch Centrum Utrecht' (UMC). The patients have the same initial morphology; the seizures always tend to start with γ -oscillations (see Figure 2). The number of electrodes and their placement on the cortex are tailored for every patient. The measurements are made with 512 Hz precision. Seven days of (almost) continuous recordings were collected. Table 1 gives an overview of all the patient relevant information.

The procedure begins with magnetoencephalogram (MEG) measurements to try to find the location of the focal area. This imaging technique is based on the changes in magnetic field caused by neural activity and is used to decide how the intracranial electrodes should be placed on the patient's cortex. The scalp and the dura are then removed (see Figure 3). Grid electrodes with a diameter of 3 mm and an inter-distance of 0.5 or 1 cm, are placed at the regions of interest. The precise position of each electrode is documented. The yellow dots in the panels of the bottom row of Figure 3 show the electrode

Table 1: Patient Information

# Patient	Sex	Age (in Years)	Focal Area ^a	Hemisphere ^b	Initial Morphology	# Electrodes/Channels	# Channel Combinations	Data (in hours)	# Seizures	Sample Rate
1	female	18	frontal	right	γ	112	172	75	34	512
2	female	12	frontal	right	γ	104	145	26	28	512
3	male	13	frontal	left	γ	96	147	64	3	512

^a While the operation was successful, the assumed focal area appeared to be correct.

^b The electrodes are always placed unilateral in the UMC.

2.2 Data Analysis

placement for the different patients. Besides these intracranial measurements, electroencephalogram (EEG), electrocardiogram (ECG), lunge measurements and six video cameras are also used to capture all (possibly) relevant information. Patients are normally recorded for a week. During that interval, the patient is free to move and speak. The patient is often asked to perform different tasks (e.g., naming several presented object) to improve the localization of important areas. Two EEG-specialists from the UMC annotate the data; seizure onsets, offsets, other interesting epileptiform activity, changes in vigilance state and other special situations (e.g., Brain-Computer Interface tests) are noted and stored. The EEG-specialists did not know about this study while annotating the data.

The location of the focal area is determined on the basis of this data. For the reliability of their conclusions, it is necessary for the patient to have as many seizures as possible. To enhance the occurrence of seizures, the anti-convulsive medications were (often) changed. If still not enough seizures occurred, electrical stimulation directly on the cortex is sometimes resorted to.

After the focal area is determined (which normally ranges over a set of electrodes), the function of that region is determined with direct electrical stimulation. No resection is made if the region seems to be (partly) responsible for important functions. If this is not the case, the assumed focal area is removed and the scalp and dura are put back into place (see Figure 4). Most of the patients profit from this procedure: The epileptic seizures stopped or occurred less frequently.

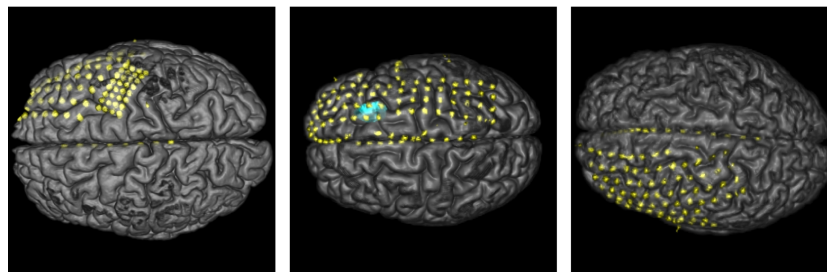
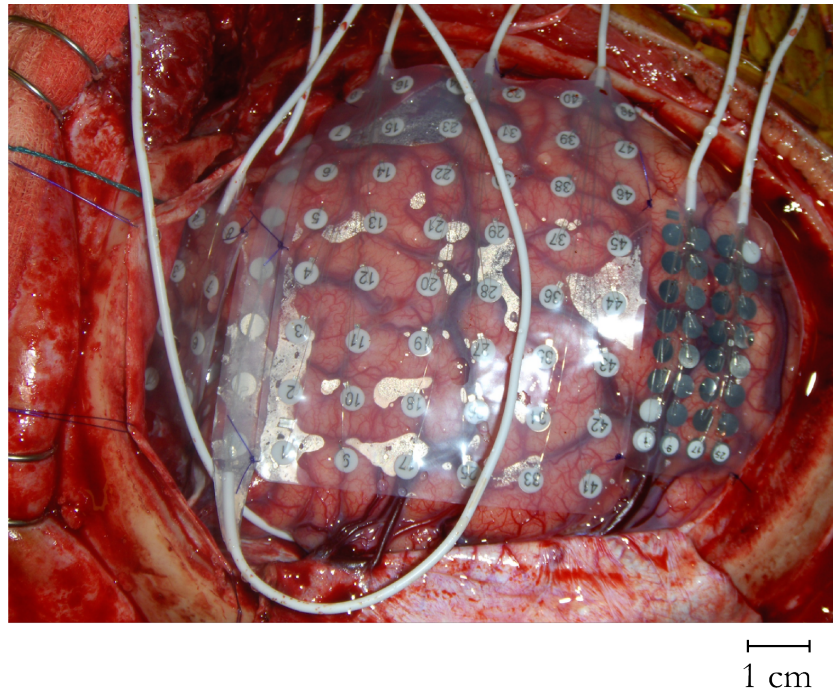
2.2 Data Analysis

Intervals of intracranial EEG data that contain 'unnatural' activity caused by e.g., electrical stimulation or Brain Computer Interfaces-tests, were discarded. Epileptiform activity as ictal spikes during the pre- and interictal phase are not removed, while these are common in epileptic patients. A clinical prediction system should be able to cope with the occurrence of these characteristic pathological activity.

The data recorded at one electrode reflects the difference between the voltage of that particular brain region and a reference point. In this study a *common reference* was used which means that the reference point for every channel is the average output of all the amplifiers [29]. A clear advantage of using this reference instead of another montage is that it makes the comparison between patients more insightful.

The data were preprocessed. Figure 5 shows every preprocessing step in chronological order. First, the data were filtered for 50 Hz line noise caused by the power supply cables (see Figure 5b). The data were then down sampled from 512 Hz to 256 Hz to make it more comparable to the data of Mormann et al. (2005). And finally, each channel was demeaned (see Figure 5b).

As Mormann et al. (2005), a standard moving window technique was used [28] (see Figure 6a). The data were divided into windows with a fixed size. Per window, the four measures (see the section 2.3) were computed which resulted in four different time profiles per channel (see Figure 6b). The



patient 1

patient 2

patient 3

Figure 3: The top row shows the electrode placement of patient 1. The scalp and dura mater have been removed and the electrodes are in place. A top view of the electrode placement of each individual patient is shown below. The grid electrodes are always placed unilateral at the UMC. You can see that the placement and number of electrodes used per patient can differ. It is therefore difficult to generalize over patients.

2.2 Data Analysis

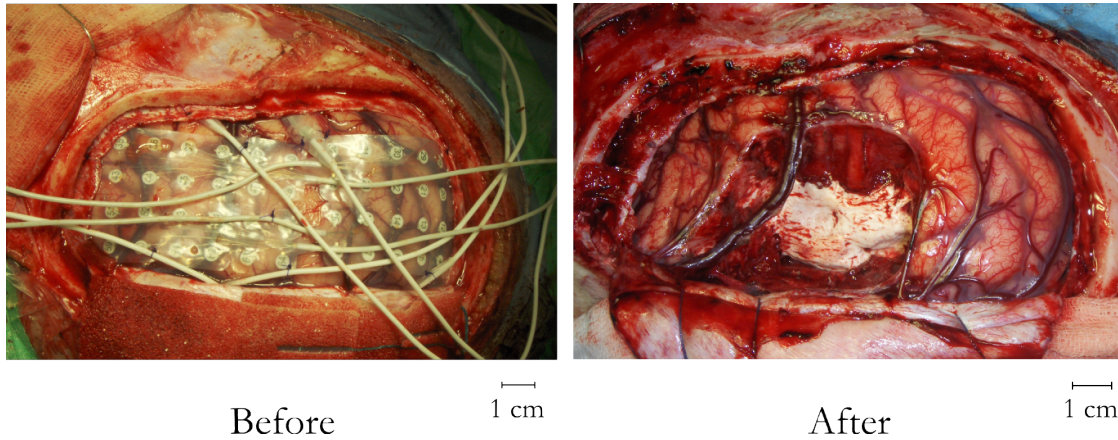


Figure 4: The left image (*before*) shows the implementation of patient 2. The scalp and dura mater have been removed and the patient is ready for recording. The right photo (*after*) is made after the focal area is decided upon. The assumed pathological part of the cortex has been explmented.

resulting time profiles would hopefully show a pattern that simplified the prediction problem at hand. The window size was set to the same size as in Mormann et al. (2005): 4096 data points, representing 16 seconds of recordings, due to the sample rate of 256 Hz.

The time profiles were then smoothed using a moving average filter with a window of 5 minutes (see Figure 6c). Every data point is replaced with the average of the last 5 minutes, which roughly corresponds with 18 windows.

The time profiles are then divided into the four epileptic phases: the ictal, postictal, preictal and interictal phase. The ictal phase was determined by the EEG-specialists at the UMC. The duration of the postictal phase was set to one hour. While most patients recover much faster, this is considered to be a safe bet. Due to the fact that precursors can differ in the moment they occur before seizure onset, it is wise to define the duration of the preictal state differently for different measures (e.g., the relative power in the γ -band is expected to increase only several minutes in advance, while the 'characteristic' decrease of the mean phase coherence measure is thought to occur in a four hour interval before seizure onset) [18, 19, 20, 7]. The duration of the preictal state will be set to 5 minutes for the relative power in the γ -band measure, while a preictal state of 240 minutes will be used for the other three measures examined here. I use these durations while they performed optimal in the study of Mormann et al. (2005). The remaining data is considered to be interictal. The ictal and postictal phases were then discarded while no seizure has to be predicted during these intervals. During the ictal phase the patient already has a fit. In the postictal phase the patient is still recovering.

First, the distributions of the interictal and preictal time profiles of the three patients will be compared. The interictal data of all channels are compared to all the preictal data. This will indicate to what extent these measures can be generalized over different patients with different forms of focal epilepsy and different electrode placements. A measure that performs well in this comparison should

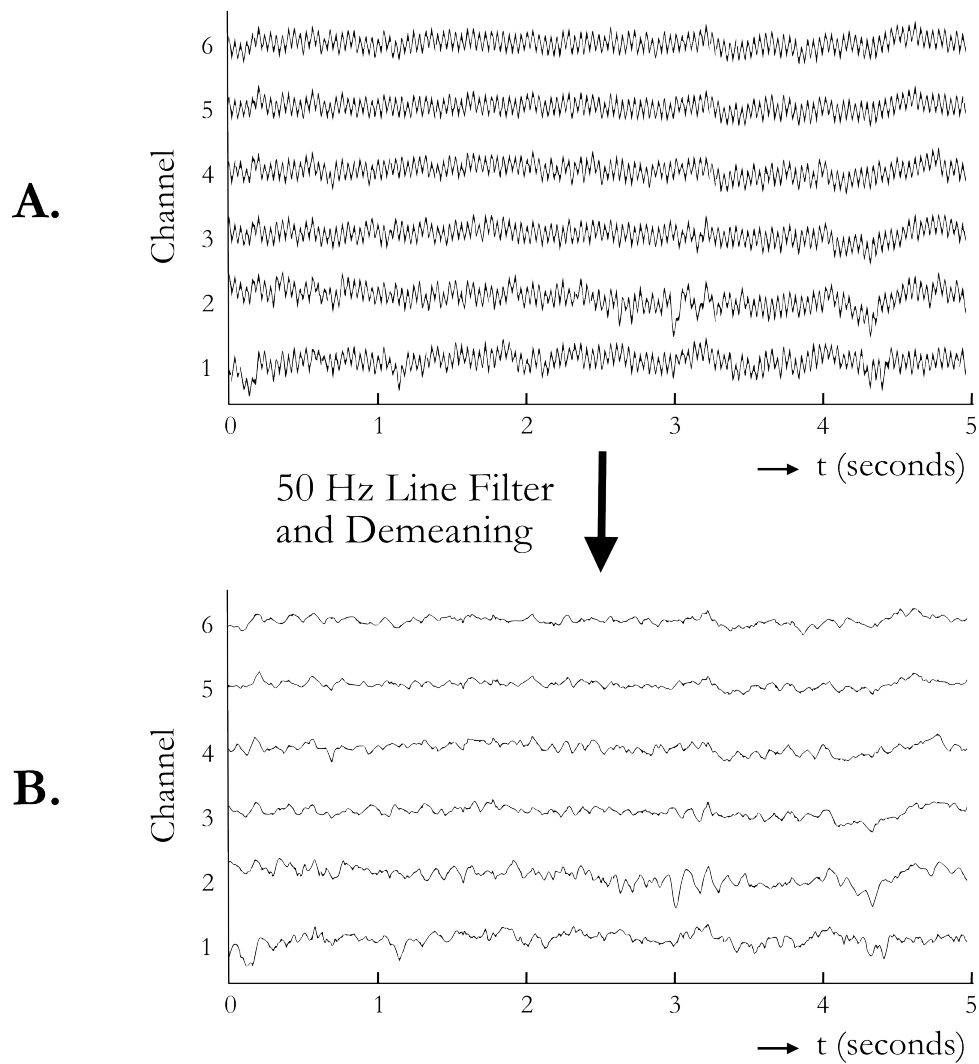


Figure 5: Preprocessing steps in chronological order. **A** Raw data of patient 1. **B** The data filtered for 50 Hz line noise caused by the power supply cables and demeaned.

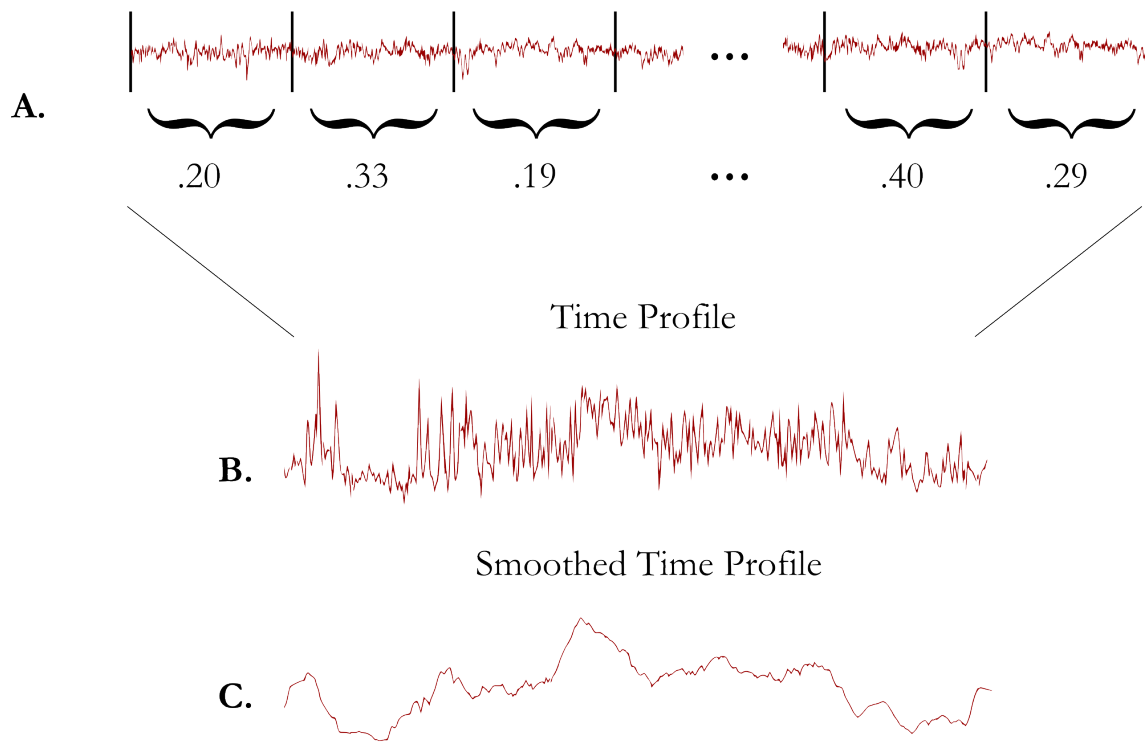


Figure 6: **A** A moving window technique was applied. The data were segmented into 16 second windows. **B** Per window and per channel (or channel combination) a measure was computed. This results in different time profiles. **C** The time profiles are then smoothed with a moving average filter with a window of five minutes.

be of interest, while the effect is strong and/or present in (almost) every channel of different patients. While not every measure is suitable to use for every patient, the distributions of the interictal and preictal time profiles of each patient will be compared separately. The performance of a measure can then be compared between patients.

Since it is known that a precursor is unlikely to appear in every channel (or channel combination for bivariate measures) it makes sense to select the most appropriate one. We will compare the interictal and preictal distributions of each patient separately, but this time, not every channel will be considered; only that channel or channel combinations that performs best (shows the largest difference between interictal and preictal data) is selected.

The downside of using distributions is that they neglect the possibility that changes over time in the time profiles may yield important information for predicting seizures. Besides comparing the distributions of the time profile, I also want to compare the distributions of the first derivative of these time profiles, to see whether there are any particular differences that could be used to forecast an epileptic seizure. The distributions of the first derivative of the time profiles will be compared in the same fashion as with the normal distributions.

2.3 Measures

In the following sections I will first discuss the univariate and then the bivariate measures. Univariate measures are computed on the basis of one channel, while a combination of channels is used for bivariate measures.

2.3.1 Univariate Measures

Relative Power in the γ -band

The recorded data of an intracranial EEG channel can be considered as a discrete time serie, $s(t)$. A time series can be expressed in amplitudes and phases over different frequencies, called the frequency domain. The time domain of the signal $s(t)$ can be mapped to its frequency domain by the Fourier Transform, $S(f)$, where f stands for the different frequencies:

$$S(f) = \sum s(t)e^{-i2\pi ft}$$

The power spectrum of a signal is then easily computed by taking the square of the amplitudes of the Fourier Transform:

$$P(f) = S^2(f) \tag{1}$$

2.3 Measures

The total power (P_{tot}) of a signal is computed by summing up the power over all the available frequencies:

$$P_{\text{tot}} = \sum_{f=0}^{f_s/2} P(f)$$

where f_s stands for the sample rate (256 Hz in our case). The relative power in the γ -band ($P_{\gamma\text{rel}}$) is determined by summing the power in the γ -band (between 30 and 48 Hz) and dividing by the total power of the signal:

$$P_{\gamma\text{rel}} = \frac{1}{P_{\text{tot}}} \sum_{f=30\text{Hz}}^{48\text{Hz}} P(f)$$

Hjorth Complexity

In the seventies, Hjorth introduced three measures for the analysis on continuous EEG data [30, 31]. His complexity measure gives an estimate of the bandwidth of a signal, $s(t)$ (i.e., peak/harmonic content) by computing the root mean square of the rate of slopes of the signal with reference to an ideal sine wave. The Hjorth Complexity (HC) is computed as follows:

$$HC = \int f^4 \cdot P(f) df = \int \left(\frac{d^2s}{dt^2} \right)^2 dt$$

where $P(f)$ stands for the power spectrum (1), f represents the different frequencies and $s(t)$ is a time serie. The Hjorth Complexity can also be computed solely on the basis of the time domain [30]:

$$HC = \frac{\frac{\sigma_{dd}}{\sigma_d}}{\frac{\sigma_d}{\sigma_s}}$$

where σ_s , σ_d and σ_{dd} are the standard deviation of respectively the time signal, the first and second derivative of the signal.

2.3.2 Bivariate Measures

While the number of electrodes ranges from 96 to 112, it is not trivial to choose the combination of channels to use for the maximized linear cross-correlation or mean phase coherence. Using every possible combination takes way too much computation time and memory capacity to be applicable in a real clinical application. Also randomly selecting combinations could result in missing important information. I only took those combinations of channels that were 'close' to each other: the bivariate measures were only computed for channels that were at most 1 cm apart [7]. The column '# Channel Combinations' in Table 1 shows how many combinations were formed per patient using this criterion.

Maximized Linear Cross Correlation

The maximized linear cross correlation is a measure of similarity between two signals, $s_1(t)$ and $s_2(t)$. The linear cross correlation (C) is defined as:

$$C(s_1, s_2, \tau) = \begin{cases} \frac{1}{T-\tau} \sum_{t=0}^{T-\tau} s_1(t+\tau) \cdot s_2(t) & \tau \geq 0 \\ C(s_2, s_1, -\tau) & \tau < 0 \end{cases}$$

where τ is time lag and T stands for the total duration of the signal s_1 and s_2 . The maximized linear cross correlation (C_{\max}) is computed as

$$C_{\max}(s_1, s_2) = \max_{\tau} \left| \frac{C(s_1, s_2, \tau)}{\sqrt{C(s_1, s_1, 0) \cdot C(s_2, s_2, 0)}} \right|$$

The cross correlation of signal s_1 and s_2 and the time lag τ is normalized with the square root of the autocorrelations of s_1 and s_2 . The normalized linear cross correlation, $C(s_1, s_2, \tau)$, is maximized for the time lag τ .

C_{\max} is naturally confined to the interval $[0, 1]$, where high values suggest a high and low values indicate a low lag synchronization [32].

Mean Phase Coherence

An important aspect of a measure is its physiological correlate: what does it mean in terms of brain activity or, in the case of intracranial EEG, in terms of postsynaptic activity in parallel pyramidal cells [9]? For many of the measure proposed until now [30, 31, 32, 1], it is not at all clear how these are related to epileptic activity. This does not apply to the mean phase coherence which makes explicit use of what is known about ictogenesis (the study of the origin of seizures). It exploits the idea that neurons tend to synchronize [4, 18, 19, 20, 1] during or just before the seizure. This synchronization can be captured by computing the phase coherence which is a measure for the difference in phase of two signals, $s_1(t)$ and $s_2(t)$. The instantaneous phase of a signal, $\phi(t)$, can be computed as follows [33, 34]:

$$\phi(t) = \arctan\left(\frac{s_H(t)}{s(t)}\right)$$

where $s_H(t)$ is the Hilbert Transform of signal $s(t)$:

$$s_H(t) = \frac{1}{\pi} \text{pv} \int_{-\infty}^{+\infty} \frac{s(t')}{t-t'} dt'$$

2.4 Classification and Validation

pv denotes the Cauchy principal value. The mean phase coherence (R) is computed by

$$R = \left| \frac{1}{N} \sum_{j=0}^{N-1} e^{i\phi_{1,2}(j\Delta t)} \right|$$

where N stands for number of data points, $\frac{1}{\Delta t}$ represents the sample rate and the phase difference $\phi_{1,2}(t)$ is computed as:

$$\phi_{1,2}(t) = \phi_1(t) - \phi_2(t)$$

where $\phi_1(t)$ and $\phi_2(t)$ are the instantaneous phases of signal s_1 and s_2 . The use of Euler's formula turns R into:

$$R = \sqrt{\left[\frac{1}{N} \sum_{j=0}^{N-1} \sin(\phi_{1,2}(j\Delta t)) \right]^2 + \left[\frac{1}{N} \sum_{j=0}^{N-1} \cos(\phi_{1,2}(j\Delta t)) \right]^2}$$

where again, N stands for number of data points and $\frac{1}{\Delta t}$ represents the sample rate of both signals.

2.4 Classification and Validation

2.4.1 ROC-areas

A good prediction system should be able to warn the patient that a seizure is approaching, but it should refrain from warning when there is nothing to worry about. The sensitivity and specificity are often used to quantify those two important aspects. The first aspect is measured by the *sensitivity* which here is defined as the percentage of preictal states that are correctly recognized as preictal. The *specificity*, the second aspect, is defined as the percentage of correctly classified interictal states. It shows wherever the measure really shows a change characteristic for an approaching seizure or that this 'characteristic' change is also common in interictal periods time when there is nothing to worry. The performance of a measure heavily depends on its sensitivity and its specificity.

The discrimination between a preictal and interictal distribution is determined by the area under the *receiver operating characteristic (ROC) curve*. The threshold value that distinguishes between preictal and interictal data is varied continuously. Per threshold, the sensitivity and specificity of the measure is computed. The ROC-curve is then created by plotting the resulting sensitivity-values on the y-axis and '1 - the resulting specificity' on the x-axis (see Figure 7). The area under this ROC curve can be used as a performance measure. The larger the area, the better the performance of this particular measure. Is the area equal to 0.5, then the measure was unable to distinguish successfully between inter- and preictal activity⁴. An area of 1 is perfect: every phase is correctly classified as being inter- or preictal.

⁴Note that the measure was unable to show differences between inter- and preictal activity when a *simple* threshold was

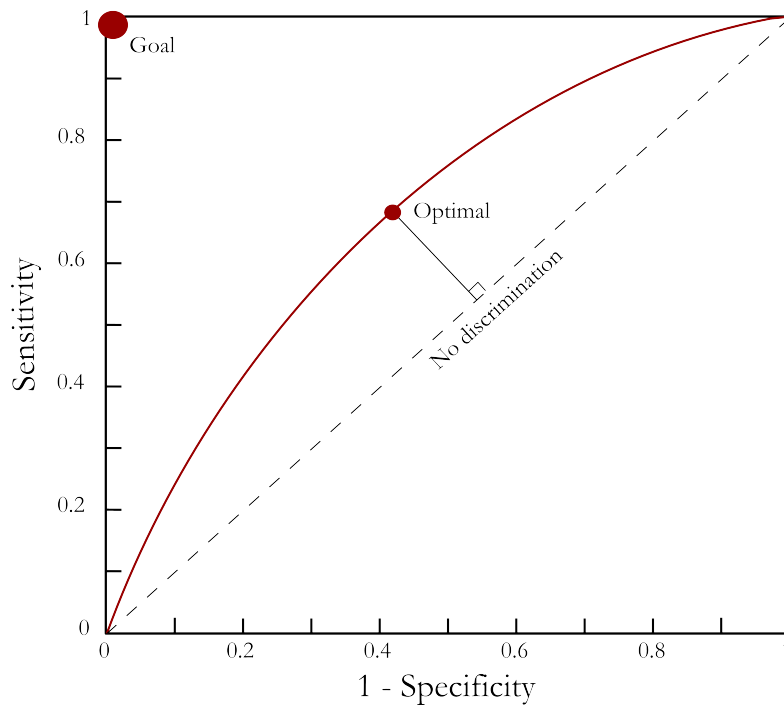


Figure 7: A receiver operating characteristic (ROC) curve. The sensitivity of a measure is plotted on the y-axis. '1 - its specificity' is plotted on the x-axis. The dashed line denotes the situation where no discrimination between two classes (in our case, pre- and interictal) is possible. The red dot in the upper left corner of the graph marks the goal: a sensitivity of one (perfect prediction) and a specificity of one (no false alarms). The threshold that resulted in best trade-off between the measure's sensitivity and specificity can be determined by selecting that point on the ROC-curve with the largest distance to the 'no discrimination'-line (dashed line) and is denoted with 'optimal'. The area under the ROC-curve is often considered to be a good indication of how well measures can help to distinguish between two classes.

2.4.2 Andrzejak's test

To test whether the observed performance of the measures (see the previous section) is reliable and is not caused by non-epileptic factors as the vigilance state (sleep/awake) or changes in medication over the week, I used a test proposed by Andrzejak et al. (2003). The entire dataset is kept intact, but the real seizure-onsets, as determined by the EEG-specialists of the UMC, are replaced by new random onsets. The ROC-areas are then determined again but this time with these *surrogate seizures*. This process of randomly selecting seizure onsets and computing the ROC-areas, is repeated 79 times. The ROC-areas found with the real seizures are then compared with surrogate ROC-areas with a z -test: one-tailed significance level is computed by estimating the probability that the real ROC-areas would occur under the null hypothesis. A significant result suggests that the differences found in the preictal and interictal time profiles are due to epilepsy related factors and are not caused by e.g., the vigilance state or circadian fluctuations [26]. There are two advantages of this form of testing [2]. First, the data is kept exactly the same; only the onsets of seizures are randomly shifted. Second, it is not necessary to divide the dataset into a test and train set, but it is still possible to get a feel to what extent the results found are trustworthy. This is a very welcome property in a field where data is scarce.

3 Results

3.1 Time Profiles

According to the moving window technique [28], the preprocessed data were divided into time windows of 16 seconds each. The four measures (see section 2.3) were computed per window, resulting in four different time profiles for every channel or, in the case of bivariate measures, every channel combination. Four characteristic time profiles of six hours of data of patient 1 are shown in the left column of Figure 8. The time profiles of the univariate measures are based on data recorded from a channel placed near the sensory cortex. The bivariate time profiles were collected by a combination of channels located at the sensory cortex as well. The data were recorded from 9 o' clock in the evening to 3 o' clock in the morning. The patient suffered from an epileptic seizure at 2:30 AM which is represented in the Figure by a dotted line.

The time profiles were then smoothed with a moving average filter with a window size of 5 minutes, which roughly corresponds with 18 windows. The middle column in Figure 8 shows the filtered time profiles. Exactly the same data were used and the seizure onset is again represented by a dotted line.

While we are also interested in changes over time in the time profiles, the first derivative of the smoothed time profiles were determined and are shown in the right column of Figure 8. Again, these

used. More complex decision methods could yield better performances (see section 4).

time profiles are based on the same data as the time profiles in the other columns.

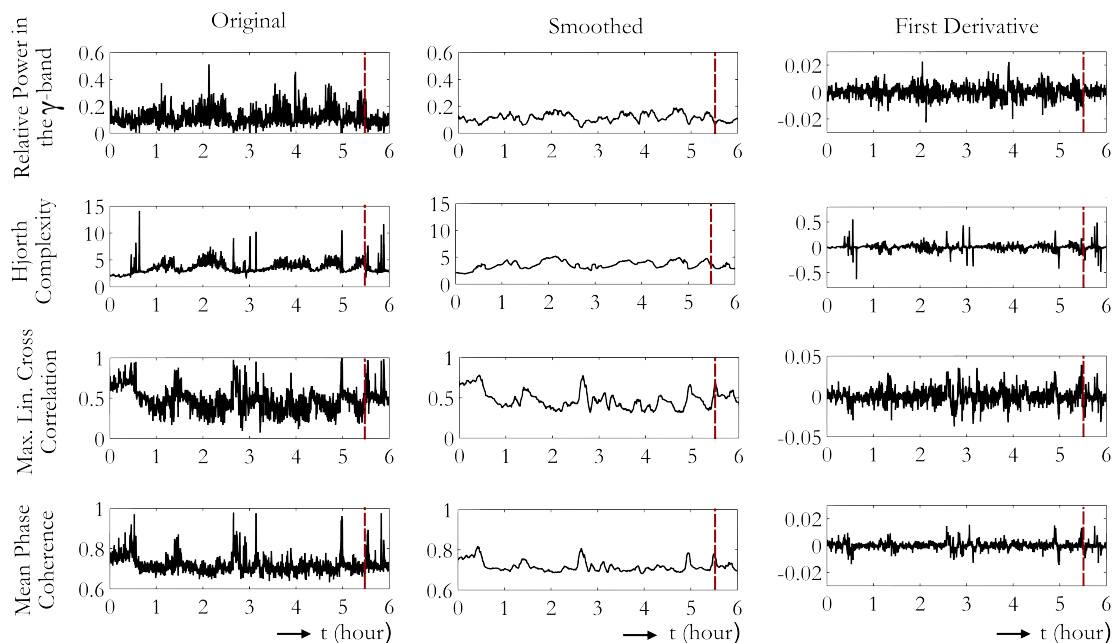


Figure 8: Different time profiles based on six hours of data of patient 1. The data were recorded from 9 o'clock in the evening to 3 o'clock in the morning. The patient suffered from an epileptic seizure at 2:30 AM, which is represented by a dotted line. Each row shows three time profiles of a particular measure. The time profiles of the univariate measures are based on the data of one electrode placed near the sensory cortex. The bivariate time profiles used a combination of channels instead, both placed around the same area. The left column shows the *original* time profiles. These are then smoothed with a moving average filter which results in the middle column (*smoothed*). The first derivative of these smoothed time profiles are shown in the right column.

The original, smoothed and first derivate of the time profiles do not seem to yield very helpful information for predicting a seizure.

3.2 Comparing Pre- and Interictal Distributions and Andrzejak's Test

The data were divided into the four epileptic phases (see Figure 1). Table 2 gives an overview of the amount of pre- and interictal data (postictal and ictal were discarded) per patient and per predefined duration of the preictal state (5 or 240 minutes).

First, the distribution of the preictal time profiles and the distribution of the interictal time profiles of all patients were compared. The performance of a measure was defined as the area under the ROC-curve [35] (see section 2.4.1). The left column in Figure 9 shows these distributions per measure. The vertical dashed lines in these distributions represent the threshold that resulted in the optimal discrimination of the pre- and interictal data. As one can see, there is no major difference between pre- and interictal for any measure. The ROC-areas reported in the top row of table 3, confirm this; the

3.2 Comparing Pre- and Interictal Distributions and Andrzejak's Test

Table 2: Pre- and Interictal Data

Patient	Duration Preictal Phase (in minutes)	Preictal (hh : mm)	Interictal (hh : mm)
1	5	1:20	63:01
	240	16:46	47:35
2	5	1:48	14:48
	240	12:06	4:30
3	5	00:15	61:02
	240	7:03	54:14
Total	5	3:23	138:51
	240	35:56	106:19

largest area equals 0.64 for the relative power in the γ -band.

Andrzejak's test was applied to assess to what extent the observed ROC-areas were caused by non-epileptic factors, e.g., change in vigilance state (sleep/awake). The resulting p -values are reported in the fourth column of table 3. Significant results ($p < .05$) are printed in bold.

Table 3: Scheme 1

Patient(s)	Measure	ROC-area	p
1, 2 and 3 (see Figure 9)	Relative Power in the γ-band	.64	.00
	Hjorth Complexity	.60	.00
	Max. Lin. Cross Correlation	.55	.08
	Mean Phase Coherence	.54	.08
1 (see Figure 9)	Relative Power in the γ-band	.64	.01
	Hjorth Complexity	.58	.44
	Max. Lin. Cross Correlation	.50	.53
	Mean Phase Coherence	.50	.58
2	Relative Power in the γ -band	.53	.62
	Hjorth Complexity	.57	.22
	Max. Lin. Cross Correlation	.52	.82
	Mean Phase Coherence	.52	.75
3	Relative Power in the γ -band	.51	.91
	Hjorth Complexity	.58	.27
	Max. Lin. Cross Correlation	.52	.59
	Mean Phase Coherence	.50	.79

It is possible that a measure is 'patient specific'; that is works for some but not for all patients. Therefore, the pre- and interictal distributions were compared per patient. The distributions for patient 1 are shown in the second column of Figure 9 and are similar to the distributions observed for patient 2 and 3. The last two columns of Table 3 show the observed ROC-areas and the p -values resulting

3.2 Comparing Pre- and Interictal Distributions and Andrzejak's Test

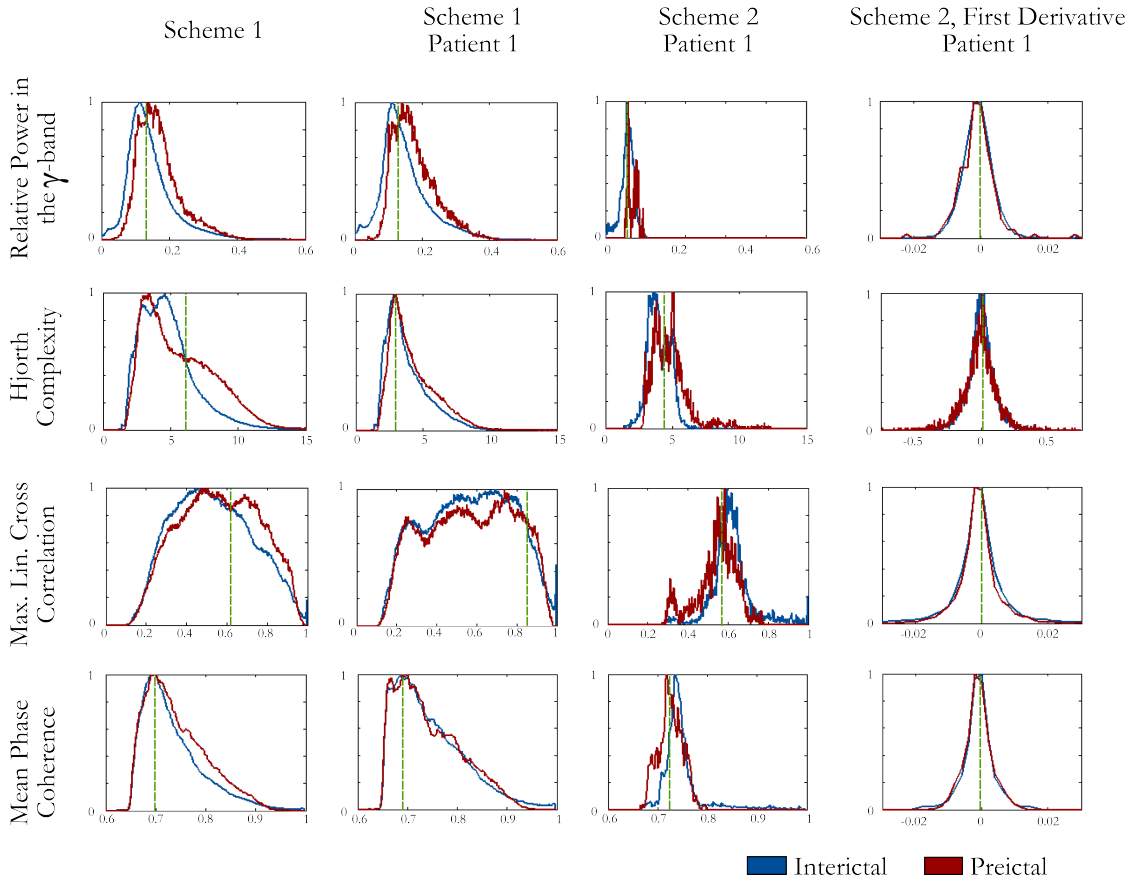


Figure 9: The preictal and interictal distributions. Red depicts preictal data. Blue represents interictal activity. The vertical dashed green line denotes the optimal threshold for discriminating between pre- and interictal. Each row shows the results of one particular measure. The left column, *Scheme 1*, contains the pre- and interictal distributions observed when scheme 1 was applied to the data of all the patients. Data of all channels were taken into account. *Scheme 1, Patient 1* shows the resulting distributions when scheme 1 was only applied to data the patient 1. The column *Scheme 2, Patient 1* shows larger differences between preictal and interictal activity since the best performing channel (or channel combination for bivariate measures) is selected for this comparison (scheme 2). The distributions of the first derivative of the time profiles are depicted in the last column, *Scheme 2, First Derivate, Patient 1*. Taking the first derivative of time profiles yield almost no information that could help in distinguishing between pre- and interictal data.

from Andrzejak's test for every patient. Notice that the performance does not increase when only one patient is evaluated compared to the situation that all patients are considered; the largest area under the ROC-curve stays 0.64.

Because it is likely that precursors do not appear in every channel (or channel combination), it makes sense to select a (subset of) channel(s) that are known to show a (preferably large) difference between the interictal and preictal phase. This idea is used in scheme 2, where not every channel is considered; only the best performing channel/channel combination is selected. This way, it becomes

3.2 Comparing Pre- and Interictal Distributions and Andrzejak's Test

much easier to distinguish between pre- and interictal activity (see the third column of Figure 9 for the pre- and interictal distributions of patient 1 when scheme 2 is applied). Table 4 shows the observed results for this scheme. At first, the ROC-areas seem to be more promising than in scheme 1. Especially the bivariate measures seem to perform well for patient 2. But results from Andrzejak's test (p -values shown in the last column of Table 4) suggest that the observed differences are based on non-epileptic factors. The measures perform not significantly better with the real seizure onsets than when the seizures are randomly shifted and the differences could be due to the changes in medication of the week, activity or the mental condition of the patient.

Table 4: Scheme 2

Patient	Measure	ROC-area	p
1 (see Figure 9)	Relative Power in the γ -band	.74	.33
	Hjorth Complexity	.69	.19
	Max. Lin. Cross Correlation	.70	.83
	Mean Phase Coherence	.68	.67
2	Relative Power in the γ -band	.65	.94
	Hjorth Complexity	.81	.43
	Max. Lin. Cross Correlation	.86	.60
	Mean Phase Coherence	.86	.63
3	Relative Power in the γ -band	.82	.51
	Hjorth Complexity	.77	.54
	Max. Lin. Cross Correlation	.69	.42
	Mean Phase Coherence	.73	.79

A problematic aspect of comparing distributions of preictal and interictal time profiles is that possible precursors in the form of changes over time stay unnoticed. To account for this, I compared the distributions of the first derivative of the preictal and interictal time profiles (see Figure 8). The last column in Figure 9 shows the pre- and interictal distributions of patient 1 for those channels (or channel combinations) that resulted in the largest difference between pre- and interictal (scheme 2). The results were not significantly better for scheme 1 performed for one and all patients. Table 5 shows the observed results when scheme 1 was applied (the data of all channels is considered). The results for scheme 2 (only the data of the best performing channel/channel combination is used) are reported in Table 6.

Table 5: Scheme 1 using the first derivate of the time profiles

Patient(s)	Measure	ROC-area	<i>p</i>
1, 2 and 3	Relative Power in the γ -band	.50	.92
	Hjorth Complexity	.50	.29
	Max. Lin. Cross Correlation	.50	.10
	Mean Phase Coherence	.50	.00
1	Relative Power in the γ-band	.51	.00
	Hjorth Complexity	.50	.24
	Max. Lin. Cross Correlation	.50	.05
	Mean Phase Coherence	.50	.17
2	Relative Power in the γ -band	.50	.43
	Hjorth Complexity	.50	.07
	Max. Lin. Cross Correlation	.50	.44
	Mean Phase Coherence	.50	.54
3	Relative Power in the γ -band	.50	.86
	Hjorth Complexity	.51	.24
	Max. Lin. Cross Correlation	.50	.45
	Mean Phase Coherence	.50	.30

Table 6: Scheme 2 using the first derivate of the time profiles

Patient	Measure	ROC-area	<i>p</i>
1 (see Figure 9)	Relative Power in the γ -band	.52	.73
	Hjorth Complexity	.51	.54
	Max. Lin. Cross Correlation	.50	.67
	Mean Phase Coherence	.51	.84
2	Relative Power in the γ -band	.56	.78
	Hjorth Complexity	.51	.81
	Max. Lin. Cross Correlation	.51	.50
	Mean Phase Coherence	.51	.54
3	Relative Power in the γ -band	.55	.33
	Hjorth Complexity	.51	.14
	Max. Lin. Cross Correlation	.52	.23
	Mean Phase Coherence	.51	.33

4 Conclusions and Discussion

Two univariate and two bivariate measures were compared with respect to their capability to discriminate between pre- and interictal intracranial EEG data of three different patients each suffering from a focal epileptic disorder. The patients were similar in the sense that the epileptic origin was determined to be on the frontal cortex and that they had a γ -onset as initial morphology (see Figure 2). Time pro-

files were computed according to a moving window technique [28] and were then compared in two schemes. In scheme 1, all the channels were taken into account. In scheme 2, we focused solely on the best performing channel or channel combination. To assess the performance of a measure, we used the area under the receiver operating characteristic (ROC)-curve. Andrzejak's test was used to get an idea to what extent these performances were based on epileptic factors and that they were not due by other factors like changes in medication or vigilance state of the patient etc. [26].

The four measures appear somewhat helpful in discriminating between pre- and interictal activity, but they are not suitable for a reliable epileptic seizure prediction system. The observed ROC-areas (see section 3) are small and often close to the 'no discrimination'-line (see Figure 7), that indicates low sensitivity and high false alarm rates. Even when the performance of a measure is more promising, the results of Andrzejak's test suggest that the differences between the pre- and interictal distributions are not epilepsy related, but more likely to be caused by changes in medication or differences in activity of the patient [26].

These results differ from the more promising performances observed in the study of Mormann et al. (2005), where these four measures clearly outperformed others in both their ROC-areas and score on Andrzejak's test. How is it possible that their results were so promising, while for our patients, these measures seem to fail?

One possible explanation is that the patients in our study are not suitable for epileptic seizure prediction. It might be that the effects of a seizure initiating process are not visible in intracranial EEG-recordings of patients with a γ -onset as initial morphology. A frontal epileptic disorder could be simply more difficult to predict than when the focus is located elsewhere.

Another explanation is that the parameter values used in the study of Mormann et al. (2005) were fitted on the data; the duration of the preictal phase (5, 30, 120 or 240 minutes), the window size used for the moving average filter (0 or 5 minutes) and the best performing channel or channel combination in scheme 2 were all selected afterwards. It is therefore very likely that the observations of Mormann et al. (2005) are the result of *capitalization on chance*.

The standard approach to correct for capitalization on chance is to divide the dataset into a training and test set. The training set is used to select the parameter values. The test set is used solely to assess the performance. But, as mentioned before, this field has to deal with small amounts of data. Most datasets only contain up to 50 seizures [15, 18, 19, 20, 27, 7, 22, 1]. Splitting the data into a training and test set would mean that there is even less left for selecting the right parameters. Andrzejak's test tries to use all data for training as well as for assessing to what extent the results can be generalized to 'new' intracranial EEG-measurements. A major disadvantage to this form of testing is that it does not correct for capitalization on chance as well as the standard approach. While the parameters were set in this study for scheme 1, it is safe to say that these results are not (heavily) influenced by overfitting for at least patient 1 and 2. The results for patient 3 are based on three seizures and it is therefore not

clear whether they generalize to new data.

A problematic aspect of the dataset used is the extent to which it is representative for the patient's daily life. The measurements are made during a very stressful week. The patients must perform different tasks and are not able to follow their daily routine. Even when a measure does perform well, success is not guaranteed when applied in an online clinical application.

The receiver operating characteristic (ROC) curve was used to assess the performance of a measure. A downside to this approach is that the ROC-curve is determined with a simple threshold that distinguishes between the pre- and interictal distributions. As shown in Figure 9, this leaves a lot of useful information untouched. It might make sense to use more sophisticated classifiers to assess the performance of a measure (see section 5).

The patients are equipped with 96 to 112 electrodes. It is not trivial to choose the combinations of channels for computing any bivariate measure. Using every possible channel combination would of course guarantee that you would use all the available information. However, it is impossible to work with such a real online application since the computations would just take too much time and memory. I took those channels that were 'close' to each other (where close is specified as being maximally 1 cm apart). It is assumed that by doing so, most of the important information is captured in these channel combinations [18, 7]. Another advantage is that no patient specific information has to be used in advance. In an earlier paper where Mormann et al. [20] assessed the performance of the mean phase coherence measure (see section 2.3.2), they compared the results of all channel combinations and using only combination of channels that are close to each other. The prediction performance did not seem to increase when more channel combinations were used.

The existence of the ictal, postictal and interictal phases are generally acknowledged, but the existence of a preictal state is rather controversial. There are some reports of observed clinical prodromi [3]. Some patients show an increase in heart rate minutes before most of the temporal lobe seizures [36]. Wienand et al. (1997) noticed an increase in cerebral blood flow as for Adelson et al. (1999) reported a rising oxygen level. These clinical findings suggest that at least in the case of focal epilepsy, we can talk about a preictal state.

After forty years of intensive search [10, 13, 11, 12, 16, 15, 18, 19, 20, 7, 1, 21, 27, 22] no successful precursor has been found in intracranial EEG-recordings. Given the facts that these measurements are invasive and that there are only weak results obtained after decades of research, it might be about time to change tracks and try other physiological and less invasive techniques.

5 Future Research

Given the reported clinical prodromi (an increase in heart rate [36], cerebral blood flow [37] and a rising oxygen level [38]), it might be interesting to focus on measurements related to these observations. Some papers on predicting epileptic seizures with electrocardiograms (ECG) report quite good

References

results [8, 39, 40]. Interestingly, it appears that ECG-measurements could not only aid in anticipating a seizure for focal epileptic patients, but could also be used for the prediction of generalized disorders [40]. Of course, being able to avoid the very invasive operations needed for intracranial studies is a considerable bonus.

The physiological correlate of many measures is vague and it is unclear how they are related to epileptic activity. It appears to make sense to investigate what is known about ictogenesis and take this into account when searching for a precursor [41].

The receiver operating characteristic (ROC) curve was used in this study to quantify the difference between pre- and interictal activity. As noted before, the ROC-curve is based on a simple threshold that distinguishes between two distributions. Figure 9 suggests that a lot of useful information remains untouched in this way. It might be interesting to investigate how the measures perform when more complex classification methods are applied.

Most studies in this field struggle with a small number of seizures, which makes it almost impossible to get robust results. This field is therefore in desperate need for a study where multiple measures are compared on a large dataset.

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