Master thesis
Medical Sensing and Stimulation
Technical Medicine

Improving the nurse response to seizures in the Epilepsy Monitoring Unit with help of EEG-based automatic seizure detection

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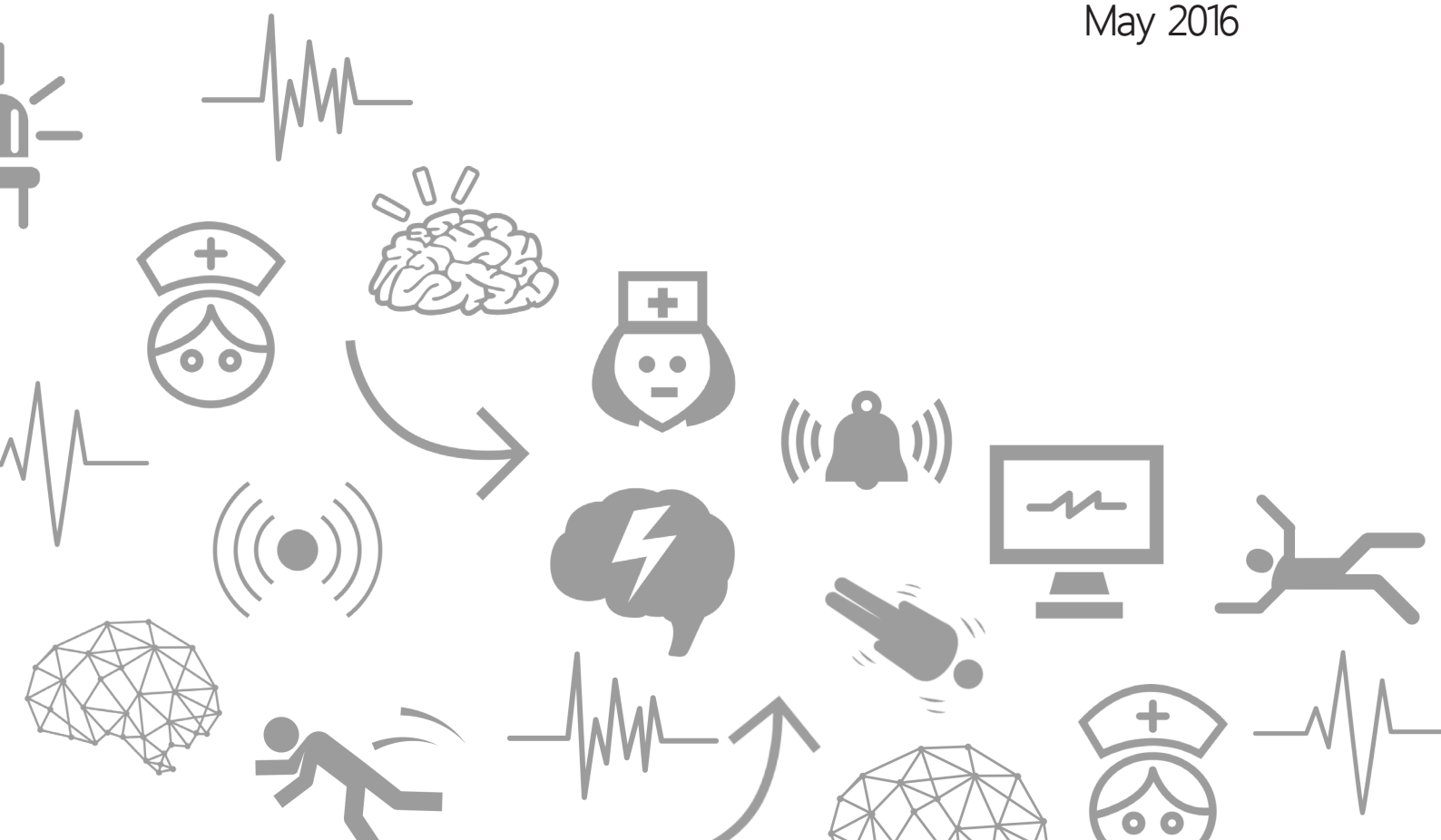

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Preface

Before you lies the result of my graduation project for the master Medical Signaling of the study Technical Medicine at the University of Twente. The subject for my graduation project was "Improving the nurse response to seizures in the Epilepsy Monitoring Unit with help of EEG-based automatic seizure detection". From May 2015 till May 2016 I undertook my graduation internship at Stichting Epilepsie Instellingen Nederland (SEIN) Heemstede.

I would like to thank my supervisors for their guidance during this project. I would like to thank Prof. Stephan van Gils for his overview on my project and for letting me think thoroughly about my project. I thank Gerhard Visser for his guidance and chances he gave me to develop myself on several different grounds. I wish to thank Evelien Geertsema for her daily guidance when needed and critical view on my work. I would like to thank Gjerrit Meinsma for his interest and view on my project. Lastly, I would like to thank Paul van Katwijk for his dedication and help during my inner search.

I like to thank Marieke Hofman for her help during my master. Lastly, I also like to thank my colleagues on the Research department for a very fun year. I loved the gardening and all the enjoyable dinners. The environment made me able to do the things I really wanted and develop myself.

Lisanne Jansen Holleboom

Heemstede, May 6, 2016

Summary

Background In an Epilepsy Monitoring Unit (EMU) it is important that seizures are recognized accurately for diagnostic and safety purposes. The online supervision of all recorded signal is labour intensive and demands skills and a lot of attention. In practice sometimes seizures are missed or recognized late.

Objective We aimed to study the current nurse response in the EMU at SEIN and investigated possible improvements with help of EEG-based seizure detection methods. Commercially available software and several promising features were studied.

Method Retrospectively EEG recordings of patients admitted to the EMU with epileptic seizures between May 2014 and April 2015 were collected. Of these seizures the nurse response and nurse response time was investigated. Further, several seizure characteristics like sounds, the use of the alarm button, and EEG characteristics were taken into account. Secondly, it was investigated how commercially available methods were able to improve the nurse response. Lastly, we studied a selection of promising features on the obtained EEG data.

Results In total, 205 seizures were included for this study. In the current EMU setting 67.0% of the seizures resulted in a nurse response with a median nurse response time of 32 seconds (p5-p95; 12 - 106 seconds). Sounds during the seizure and the use of the alarm button influenced the nurse response. The commercial software of BESA and AIT was able to detect respectively 38.7% and 66.1% of the seizures without a nurse response. In the offline setting the improvement in nurse response time was 25.6 and 18.1 seconds for respectively BESA and AIT. Lastly, for the features line length and the power over the wavelet coefficients in the majority of the seizures a significant change was observed.

Discussion The results showed that an improvement in nurse response is possible and wanted for diagnostic and safety purposes. It was shown that the commercially available software might be able to support the nurses. Additionally, some studied promising features, like line length and the power over the wavelet coefficients might be able to serve as a tool for the nurses. Additionally, the recorded ECG signal might contain promising information as well to assist the nurses. In this study mainly the sensitivity and latency is taken into account. Specificity is also a very important performance features to take into account. Further, it could be discussed what kind of output would be most applicable in an EMU setting. Further research should be performed to study the online improvement of implementation of innovative EEG-based seizure detection methods.

Abbreviations

AED = **A**nti-**e**pileptic **D**rug
AIT = **A**ustrian **I**nstitute of **T**echnology
ANN = **A**rtificial **N**eural **N**etwork
BESA = **B**rain **E**lectrical **S**ource **A**nalysis
CSE = **C**linical **S**eizure **E**nd
CSO = **C**linical **S**eizure **O**nset
CWT = **C**ontinuous **W**avelet **T**ransforms
Db4 = **D**au**b**echies **4**
DBS = **D**eep **B**rain **S**timulation
DWT = **D**iscrete **W**avelet **T**ransforms
E = **E**nergy
ECG = **E**lectro**c**ardio**g**raphy
EEG = **E**lectro**e**ncephalo**g**raphy
EMU = **E**pilepsy **M**onitoring **U**nit
ESE = **E**lectrographic **S**eizure **E**nd
ESO = **E**lectrographic **S**eizure **O**nset
EWS = **E**pileptiform **W**ave **S**equence
FWHV = **F**ast **W**eighted **H**orizontal **V**isibility
ICU = **I**ntensive **C**are **U**nit
ILAE = **I**nternational **L**eague **A**gainst **E**pilepsy
IP = **I**ntegrated **P**ower
MCC = **M**ean **C**ross **C**orrelation
MD = **M**ulti-**D**ay
PCA = **P**rincipal **C**omponent **A**nalysis
PED = **P**eriodic **E**pileptiform **D**ischarge
PLED = **P**eriodic **L**ateralized **E**pileptiform **D**ischarge
PNES = **P**sychogenic **N**on-**E**pileptic **S**eizures
PSS = **P**re-**S**urgical **S**creening
PWA = **P**eriodic **W**aveform **A**nalysis
SEIN = **S**tichting **E**pilepsie **I**nstellingen **N**ederland
VNS = **V**agus **N**erve **S**timulation

Contents

1 Introduction

Epilepsy is a chronic disease of the brain that is characterized by recurrent seizures. Seizures can vary from the briefest lapses of attention or muscle jerks, to severe and prolonged tonic clonic convulsions. The seizures are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be site of such discharges. Seizure characteristics depend on where in the brain the discharge starts and how it spreads [66, 15].

Worldwide around 50 million people currently live with epilepsy. This makes epilepsy one of the most common neurological diseases worldwide. An estimated 2.4 million people are being diagnosed with epilepsy each year. The most common type of epilepsy, which affects 6 out of 10 people with epilepsy, is called idiopathic epilepsy and has no identifiable cause. Epilepsy with a known cause is labeled as secondary epilepsy, or symptomatic epilepsy. Causes of secondary epilepsy are for example a severe head injury, a brain tumor, certain genetic syndromes, or infections of the brain [66, 45, 8, 7].

The first choice of treatment is usually prescribing anti-epileptic drugs (AEDs). Although the majority of patients is treated effectively with AEDs, in around 30% of all epilepsy patients complete seizure control cannot be achieved with medication. Other possible epilepsy treatments are for example surgery, vagus nerve stimulation (VNS), and deep brain stimulation (DBS).

Epilepsy can be diagnosed by examination of patient history, where the seizure semiology contains important information. Additionally, often electroencephalogram (EEG) findings, neuroimaging, and other diagnostic tools, can be of great value for diagnosing and classifying epilepsy. The most common differential diagnoses are cardiac or vasovagal syncope, sleep disorders, and psychogenic non-epileptic seizures (PNES).

1.1 Seizure classification

Epileptic seizure types could be divided into two main groups, namely focal and generalized seizures. Generalized seizures originate at some point, and rapidly spread across a big bilateral part of the brain. The most common generalized seizures are the absence seizure and the tonic clonic seizures. Tonic clonic seizures consist of a phase where all muscles stiffen, followed by a clonic phase where arms and legs begin to jerk. An absence seizure is characterized by abrupt changes in awareness [43, 54].

Focal seizures are defined as seizures limited to one hemisphere. They may be discretely localized or more widely spread. The semiology, or characteristics, of the seizure may reflect the involved networks. Some features of the seizure could identify which hemisphere is involved, other features allow identification of a more specific area of the brain, for example a certain lobe.

Seizures arising from the frontal lobe, generally consist of prominent motor features and are typically short ($<$ 2 minutes). Motor features are for example high energetic movements or asymmetric tonic posturing. Frontal seizures can contain vocalization, bizarre behavior,

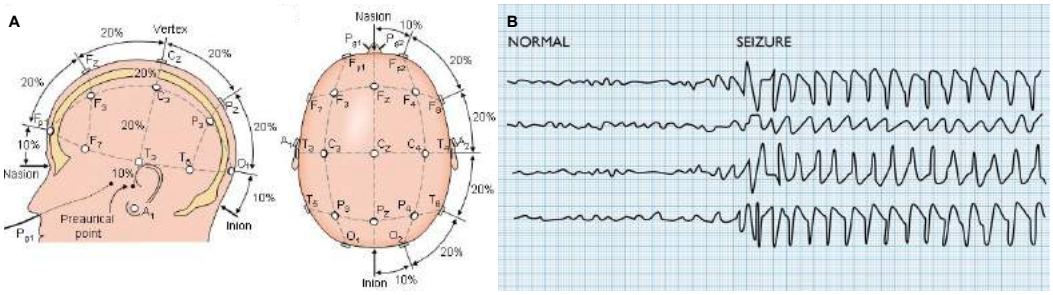


Fig. 1.1: The electrode placement *(A)* according to the international 10-20 placement system and how an EEG signal can change when a seizure occurs *(B)* is shown.

urinary incontinence, or head deviation. Frontal lobe seizure have a tendency to occur exclusively nocturnal and may begin with a brief aura.

For seizures arising from the temporal lobe behavioral arrest and automatisms are common. Automatisms can include oro-alimentary characteristics like chewing and simple gesture automatisms like fiddling. Often seizures start with an aura, which can be for example a déjà vu or an epigastric aura. Specific features like ictal speech, vomiting, and drinking suggest the seizure involvement of the non-dominant lobe. In temporal lobe seizures also autonomic features are common like pallor and palpitations.

Seizures arising from the parietal and occipital lobe are less common. Parietal seizures consist of sensory features, which are difficult due to the subjective nature. Typically sensations of tingling or tickling of a person's skin is reported but disorientation or visual illusions are also possible. Occipital seizures are characterized by visual auras and also oculomotor features could occur like eye closure, eye deviation, or nystagmus.

1.2 EEG

The EEG is one of the most used modalities in the diagnostics of epilepsy. The EEG measures the electric activity of the brain. Specialized EEG technologists and clinical neurophysiologists analyse the EEG for diagnostic purposes. The EEG can help solve the diagnostic question, like answering where the seizure activity starts and how it spreads [57].

In case of a scalp EEG, electrodes are placed along the scalp. The electrodes are systematically placed following an international positioning system. At Stichting Epilepsie Instellingen Nederland (SEIN), the epilepsy centre where this project is executed, the 10-20 system is used (see Figure 1.1A).

The electrodes capture electric potentials of neurons. The EEG activity always reflects the summation of a group of neurons, since the electric potential of one neuron is far too small to measure. In healthy adults the EEG shows a somewhat chaotic signal. Whenever a seizure occurs, neurons start to fire synchronously, resulting in spikes and other rhythmic EEG patterns (See figure 1.1B).

Certain seizure types have specific patterns. For example typical absence seizures show three per second generalized spike-wave discharges and in mesial temporal lobe epilepsy the evolving temporal theta rhythm (5-7Hz) is typical. Tonic seizures most often show high frequency discharges. Generally, the seizure patterns of one patient show similar EEG characteristics, but between patients there is a lot of variability.

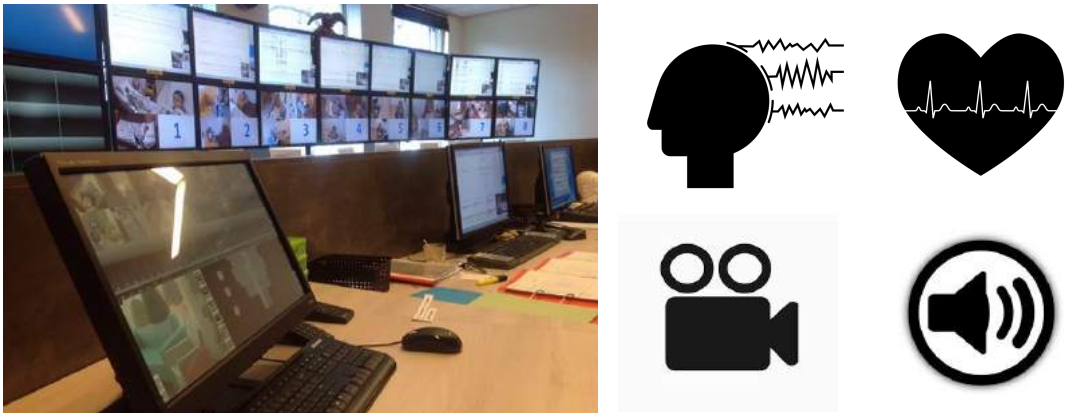


Fig. 1.2: The observation room at SEIN with all the input signals displayed on the monitors; EEG, ECG, video recordings, and sound recordings.

Sometimes, epileptic activity can be missed on the scalp EEG. Due to the skull and skin between the electrodes and the brain, the signals of the neurons are somewhat suppressed. Further, as the electrodes are situated along the scalp, the activity of deeper brain structures is often not registered. For example for frontal seizures the scalp EEG is not always helpful since the anatomical position is relative distant from the recording electrodes. Further, in partial seizures, the ictal tissue can be very small. This could result in no noticeable signal, since the EEG needs a certain amount of cortex neurons to be synchronized before it is registered. Lastly, artefacts can obscure the recorded EEG signal. These artefacts can by caused by for example muscle activity or movement for example. Nevertheless, for many diagnostic questions the EEG is very informative and useful.

1.3 Epilepsy monitoring unit

If additional diagnostics are necessary, patients can be admitted to an epilepsy monitoring unit (EMU). Registrations on the EMU are used to answer various diagnostic questions. For example patients are admitted to localize the epileptic focus or to distinguish epileptic seizures from PNES. In the EMU patients are monitored with the co-registration of an EEG, Electrocardiogram (ECG), sound, and video recordings. Specific characteristics of the epilepsy can be studied by the analysis of the recorded signals.

At SEIN in Heemstede on the EMU department eight patient rooms are available, therefore a maximum of eight patients can be monitored simultaneously. Per room three to four rotatable cameras, controlled by nurses, are installed that can capture the whole room, except for the bathroom. In each room there is an intercom system by which patients and nurses can communicate with each other. Further, the patient has an alarm button which can be used to alert the nurses.

All the signals from the eight rooms are aggregated in the observation room (see Figure 1.2). In this room, specialized nurses continuously supervise all the recordings online. When seizures occur, the nurses respond by attending to the patient and by executing standardized tests to assess amongst others, responsiveness and cognitive functions during the seizure [6]. Moreover, nurses take care of the patient's safety; they ensure patients do not get injured, and when needed they administer medication. In conclusion, accurately detecting seizures is important because of diagnostic and safety purposes.

1.4 Problem definition

The online supervision of all recorded signals is labour intensive and demands skills and a lot of attention. In practice sometimes seizures are missed or recognized late. In order to assist the nurses to detect the seizures more rapidly and accurately, this project will focus on automatic seizure detection as a tool to help the nurses recognizing seizures.

Automatic seizure detection can be achieved by using all kind of signals that change during seizures, like movement, heart rate, the EEG, blood pressure, respiration, or temperature [63, 52]. For this project we chose to study seizure detection based on the EEG signal. The EEG is already recorded on the EMU and therefore it can be used without any added measurements. Further, the EEG signal is closest to the source of the epilepsy and therefore contains a lot of informative information. Moreover, the nurses staffing the observation room are not thoroughly trained to read the EEG. Therefore, a tool that helps the nurses to read the EEG and detect seizures might assist them to recognize seizures.

Literature is filled with articles about EEG-based seizure detection methods. Even commercially available seizure detection software are produced.

1.5 Literature

In 1982 Gotman et al. [22, 23] developed one of the earliest patient non-specific EEG seizure event detectors. Their algorithm is successful in detecting seizures that evolve with a sustained rhythmic activity in the EEG. In the following decades a lot of algorithms for seizure detection appeared. The field of seizure detection has become immense, a lot of articles are published in a lot of different papers and even commercial software has been developed.

Seizure prediction and seizure detection In the field of seizure recognition we can distinguish three different goals; seizure prediction, seizure onset detection, and seizure event detection. There has been a lot of discussion about seizure prediction. Some believe that there is something called a pre-ictal state that can be detected. They state that it is possible to predict seizures minutes and sometimes even hours before the actual seizure starts. This pre-ictal state however has remained elusive. Initially there has been a lot of enthusiasm, but this has been muted when the initial reports could not be reproduced [32, 33, 42]. Seizure onset detection aims to recognize when a seizure has started with the shortest possible delay but not necessarily with the highest possible accuracy. Seizure event detection works the opposite way. With seizure event detection it is aimed to recognize the seizure with a high accuracy, so we get less false positive detections [44]. One can imagine that for reviewing several offline EEG recordings, the detection delay is less important than for online use. In this project we focus on seizure onset detection, since we want to implement the detection algorithm in an online setting.

Algorithm structure Most of the seizure detection algorithms consist of three important basic steps; pre-processing, feature extraction and classification (see Figure 1.3). For all three steps many different methods are published in literature.

For pre-processing most algorithms filter the data between certain frequencies. For artefact rejection some use simple filters and others implement more complex strategies like independent component analysis [48].

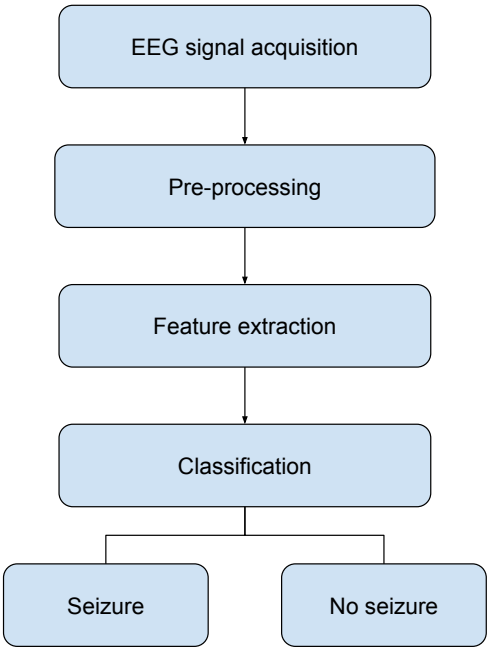


Fig. 1.3: A flowchart of algorithms construction in general. It shows the process from the EEG signal to the decision in seizure or non-seizure data.

Classification implies the process to make a decision whether the observed feature is part of a seizure or not. In literature many different approaches are chosen, from simple thresholding techniques to more advanced machine learning artificial neural networks or support vector machines [24, 49, 58, 52].

Commercially available software In short, there are three major commercial detection software packages developed for online use. These include the software of AIT, Besa, and Persyst. In chapter 3 the packages are described in more detail.

Features Many authors in seizure detection literature attempted to find the best feature for seizure detection. Features that provide the most diversity between a seizure and non-seizure EEG section and show most resemblance between different seizure epochs, are promising for seizure detection purposes. The reviews of Nasehi et al. [44], Faust et al. [13], Ramgopal et al. [52], Carney et al. [9], Jouny et al. [31], Logesparan et al. [38], Acharya et al. [2], Alotaiby et al. [4], Orosco et al. [47], Van Putten et al. [50], and Giannakakis et al. [21] studied various features.

In the time domain features like for example the mean, variance, skewness, kurtosis, and energy are used [9]. In the frequency domain power of certain spectral bands like the delta, theta, alpha, beta or gamma band are used to detect seizures [44]. Synchronicity between electrodes is measured by amongst others cross correlation and phase correlation [50, 40, 29].

In literature often methods are used to transform the time series signal before the features are extracted. For example the empirical mode decomposition or the horizontal visibility graphs are used to transform the time series signal in order to focus on aspects of the EEG that might help to detect seizures [4, 69]. In the time-frequency domain the wavelet transform technique seems promising [13, 67, 18, 20, 3, 10]. It is stated that the wavelet decomposition technique is able to capture very subtle details and sudden changes. With the

wavelet decomposition it is possible to focus on certain frequency ranges. In chapter 5 more about the wavelet decomposition technique is explained.

In the review article of Acharya et al. [2] it is mentioned that non-linear features are most promising in the detection of seizures. Non-linear measures like entropy, gabor atom density, and the Hjorth complexity are discussed in literature. In the review of Jouny et al. [31] they studied several of these nonlinear measures. Most non-linear measures, address the complexity of the EEG signal.

Obstacles Although many articles are published about EEG-based automatic seizure detection methods, still the majority of epilepsy centres have not implemented them in clinical routine.

One reason may be the high number of false-positive detections. Ictal EEG can vary greatly across patients. The ictal EEG patterns of the one patient can have different characteristics to the other patient's ictal EEG. Furthermore, some physiological changes may seem like seizure activity, for example sleep spindles, arousals, and alpha activity. Additionally, also artefacts could cause false positive alarms.

Secondly, a lot of algorithms show good results on a publicly available benchmark data set, but are not validated yet on large clinical databases. Lastly, a lot of algorithms are tested offline, but are not ready yet for a continuous monitoring setting, due to e.g. programming language for online registration.

1.6 Aim of this project

In this project we aimed to study the possible improvement of the nurse response on the EMU at SEIN. We focused on automatic seizure detection possibilities based on the EEG.

Firstly, the need of improvement in the nurse response to seizures was investigated. As a baseline measure it was aimed to investigate the nurse response and nurse response time to seizures. Additionally, the effect of certain seizure characteristics on nurse response was studied. In Chapter 2 this study is presented.

Secondly, we aimed to study commercially available seizure detection software methods in an offline setting. We examined the possible improvement of nurse response when we would implement such a seizure detection method. In Chapter 3 and Chapter 4 this study will be described.

Lastly, we examined a selection of promising features from literature. We explored whether the features could contribute in helping the nurses respond to seizures. Further, it was investigated how the performance stated in literature related to the performance in recordings from our own clinical setting. In Chapter 5 and Chapter 6 this study is presented.

2 Performance of the current nurse response to seizures in the EMU

2.1 Introduction

In the EMU it is of importance that seizures are being recognized by the nurses for safety and diagnostic reasons. In some cases, it is observed that seizures were missed, or recognized in a later phase of the seizure. In this chapter the current nurse response to seizures in the EMU at SEIN without any automatic seizure detection is studied in more detail to objectify the need of a tool to help the nurses recognize seizures.

In 2012 Atkinson et al. [5] published a study where they examined the staff response in the EMU of the Harper Hospital in Detroit. They showed that for 20 patients with a total of 170 seizures, for only 69 seizures staff responded. The overall staff response time was two minutes and 22.3 seconds. They specified that approximately half of the seizures without staff response was due to electrographic seizures without clinical semiology. Interestingly, in their study 19 of these electrographic seizures without clinical manifestation were detected by an automatic seizure detection method, nevertheless, no staff responded.

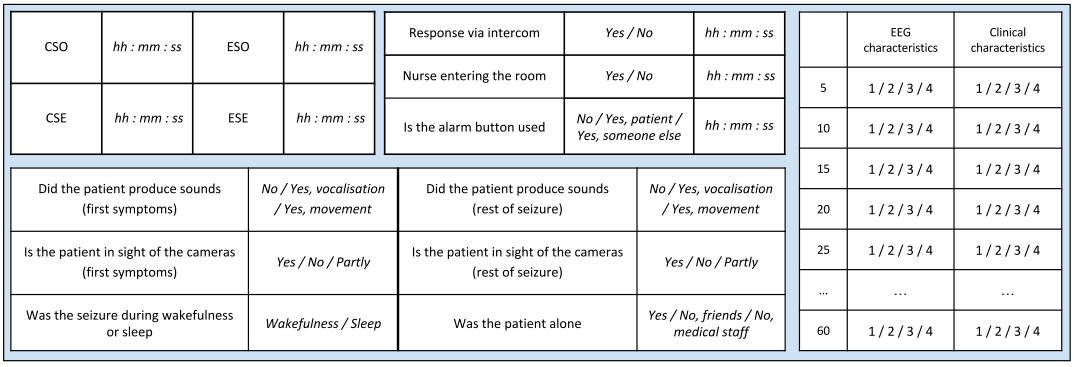
Another study that addresses the response to seizures in the EMU is the study of Shin et al. [55]. They looked into different signals that could alert the medical staff. In addition, they compared complex partial seizures to generalized tonic clonic seizures and PNES. They observed that seizures of patients with PNES were more often signaled by the alarm button. Besides, more often patients themselves pressed the button in case of PNES, compared to generalized tonic clonic and complex partial seizures where more often someone else pressed the button.

To give more insight in the current staff response in the EMU at SEIN we looked in more detail to the response to epileptic seizures over a year's time without any automatic seizure detection. The main goal was to observe whether and with how much delay nurses respond to seizures. Secondly, we obtained the video and EEG characteristics of the seizures, in order to display what kind of seizure aspects help the nurses to respond. This information could also indicate how the medical staff response could be improved and where automatic seizure detection could help in the process of responding to seizures. Lastly, the data of this study serves as a baseline measure for the following studies to investigate the improvement of possible automatic detection methods.

2.2 Methods

2.2.1 Study population

For this study retrospectively video and EEG recordings of epilepsy patients admitted to the EMU at SEIN Heemstede between May 2014 and April 2015 were collected. Patients with confirmation in the EEG report of the occurrence of epileptic seizures during the registration



CSO	*hh : mm : ss*	ESO	*hh : mm : ss*
CSE	*hh : mm : ss*	ESE	*hh : mm : ss*

Response via intercom	*Yes / No*	*hh : mm : ss*
Nurse entering the room	*Yes / No*	*hh : mm : ss*
Is the alarm button used	*No / Yes, patient / Yes, someone else*	*hh : mm : ss*

Did the patient produce sounds (first symptoms)	*No / Yes, vocalisation / Yes, movement*	Did the patient produce sounds (rest of seizure)	*No / Yes, vocalisation / Yes, movement*
Is the patient in sight of the cameras (first symptoms)	*Yes / No / Partly*	Is the patient in sight of the cameras (rest of seizure)	*Yes / No / Partly*
Was the seizure during wakefulness or sleep	*Wakefulness / Sleep*	Was the patient alone	*Yes / No, friends / No, medical staff*

	EEG characteristics	Clinical characteristics
5	1 / 2 / 3 / 4	1 / 2 / 3 / 4
10	1 / 2 / 3 / 4	1 / 2 / 3 / 4
15	1 / 2 / 3 / 4	1 / 2 / 3 / 4
20	1 / 2 / 3 / 4	1 / 2 / 3 / 4
25	1 / 2 / 3 / 4	1 / 2 / 3 / 4
...	...	...
60	1 / 2 / 3 / 4	1 / 2 / 3 / 4

Fig. 2.1: This form shows all the aspects that were scored per seizure. For a detailed explanation of the scoring of EEG and clinical characteristics, see table 2.1. *CSO = Clinical seizure onset, CSE = Clinical seizure end, ESO = Electrographic seizure onset, ESE = Electrographic seizure end, hh:mm:ss = hours:minutes:seconds*

were included. These seizures could range from the most subtle to the most severe tonic clonic seizures. Recordings with the occurrence of PNES were not included. The EEG reports are routinely written by EEG technologists and supervised by clinical neurophysiologists.

Where possible, the first five seizures listed in the EEG report that did not occur during the routine diagnostic EEG and lasted longer than five seconds were collected. During the diagnostic EEG standardized tests are executed like opening and closure of the eyes, hyperventilation, and light flashing. Out of the first five seizures two seizures were randomly selected for scoring.

2.2.2 Scoring of seizures

The selected seizures were scored by three reviewers(*FvB, EG, LJH*) on aspects that might signal or help the nurse to respond to the seizure. The scoring was performed using the video images and the EEG recording. Similar to the nurses in the observation room, the EEG recordings were reviewed using the common average reference montage. In this montage the average of all electrodes is used as the reference input for each electrode.

Figure 4.1 shows all the aspects of a seizure that were scored. Firstly, the boundaries of the seizures were noted. This includes the clinical seizure onset (CSO), the clinical seizure end (CSE), the electrographic seizure onset (ESO), and the electrographic seizure end (ESE). For the CSE, the moment when the patients were able to take care of themselves independently again was selected. Up to that point, for safety reasons and to execute diagnostic tests, it is of value to respond to the seizure. Electrographically the moment where the postictal phase started was chosen as the end of the seizure activity. This most often shows a clear change in the EEG. In some seizures it occurred that there is an absence of clinical or electrographic features. Then, no boundaries of respectively the clinic or electrographic were reported. See Figure 2.2 for a visual explanation of the CSO, CSE, ESO, and ESE in time.

Secondly, the nurse response was considered. Nurses can respond to a seizure by using the intercom or by entering the room of the patient. In this study a nurse response is defined as the use of the intercom or entering the room either during the seizure or within ten seconds after the last end of the seizure.

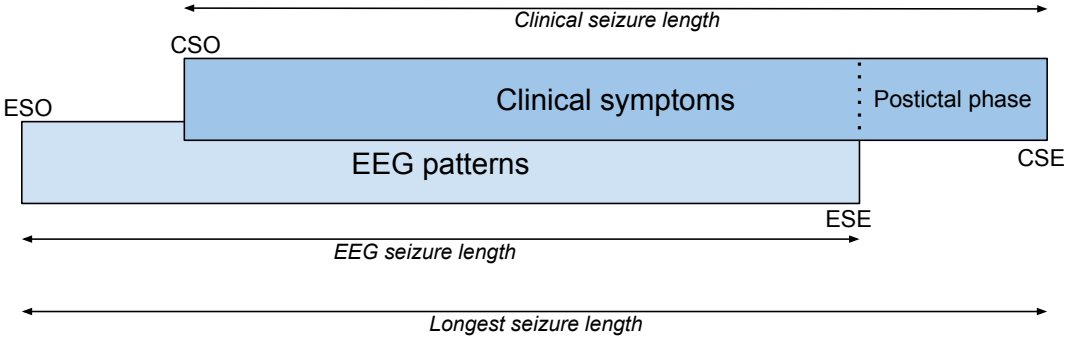


Fig. 2.2: A visualisation of how we chose the begin and end of the clinical symptoms and electrographical seizure patterns is shown. This is an example of how the different boundaries could be situated relative to each other. It also possible that the boundaries are situated differently, for example that the CSO is situated prior to the ESO. Another possibility is the absence of the CSO/CSE or the ESO/ESE. *CSO = Clinical seizure onset, CSE = Clinical seizure end, ESO = Electrographic seizure onset, ESE = Electrographic seizure end.*

Further, it was noted; whether the alarm button was used, whether the patient was in sight of the cameras, whether the seizure produced sounds, whether the seizure occurred during wakefulness or sleep, and whether the patient was alone in the room.

Lastly, the electrographic and clinical characteristics were scored during every 5 consecutive seconds until the medical staff responded, up to a maximum of 60 seconds. We classified these characteristics with a score between 1 and 4, resembling respectively no visible changes up to very clear changes. See Table 2.1 for a detailed explanation of the different scores.

2.2.3 Analysis

In this study the seizures where already medical staff was present in the room at the first sign of the seizure were excluded for further analysis, because the goal is to investigate the response of the nurses based on the video and EEG aspects.

There are two important outcome measures of this study. One is the response rate, meaning the amount of seizures that nurses responded to. The other is the response time, meaning the time needed to respond to the seizure with respect to the first sign of the seizure.

At last, the scored seizure aspects were evaluated. The difference in seizure aspects between the seizures with a nurses response and the seizures without a nurse response was investigated. This difference was evaluated with help of the statistical Chi-square test for categorical groups like the EEG and clinical characteristics, and the Mann-Whitney U test for seizure lengths. For the EEG and clinical characteristics, the mean rounded score of all scored five-seconds sections of the considered seizure were used to categorize every seizure in a score of one to four, from very subtle (*1*) to very clear (*4*) seizures.

2.3 Results

In total 121 patients were included in this study. Table 2.2 shows the patient characteristics. 37 patients had only one seizure, the other 84 patients had two seizures or more. This results in 205 scored seizures. For 17 seizures, medical staff was already present in the room. These seizures were excluded, resulting in 188 seizures included in this study (see Figure 2.3).

Tab. 2.1: This table shows a description of how we scored the characteristics of the EEG and clinical symptoms every 5 seconds up to the first 60 seconds of the seizure.

EEG characteristics	
1	**No visible changes**
2	**Subtle changes**; These changes are hard to notice in the background
3	**Clear focal changes**; These changes might not directly catch the attention
4	**Clear diffuse changes**; These changes immediately catch ones attention
Clinical characteristics	
1	**No visible changes**
2	**Subtle clinical symptoms**; These symptoms might be missed; for example staring, fiddling, and/or arrest
3	**Clear clinical symptoms**; These symptoms might not directly catch the attention; for example tonic movement, wandering
4	**Very clear clinical symptoms**; These symptoms immediately catch ones attention; for example tonic clonic seizure, hypermotoric seizures

Tab. 2.2: Patient characteristics

Patient characteristics *(N=121)*	
Gender	55m/66f
Mean age	29.0 (range; 2-73, SD;17.1)
Kind of registration	
PSS	50
MD	18
24 hour	53

m = male, f = female, PSS = Pre-surgical screening, MD = Multi-day

Of the 188 seizures, 67.0% (126) resulted in a nurse response. Nurses could respond by using the intercom or by entering the room of the patient. Of the 126 detected seizures, 92 times nurses entered the room of the patient as a response to the seizure. In 2 seizures only the intercom was used. For 32 seizures, both the intercom was used and the nurse entered the room of the patient. In 30 EEG recordings the intercom preceded the entering of the nurse in the room.

2.3.1 Response time

For the 126 detected seizures, the median response time with respect to the first sign of the seizure was 32 seconds (p5-p95; 12 - 106 seconds). The first sign either may be the beginning in the EEG or the beginning of clinical symptoms preceding the EEG patterns. Figure 2.4 shows the response time of the 126 detected seizures. Two outliers were observed. One had a response time of 11 minutes and 4 seconds. This was a tonic clonic seizure. The seizure was not detected because the patient was not in scope of the camera; the patient was not correctly followed across the room with the cameras. The other outlier had a response time of 27 minutes and 27 seconds. This seizure occurred during sleep and the EEG seizure patterns started 12 minutes and 2 seconds before the subtle clinical symptoms started. For

Tab. 2.3: Results of seizure characteristics per seizure group

	All (n=188)	No response (n=62)	Nurse response (n=126)	p-value
Length (seconds)(median(p5-p95))				
EEG	60 (12-310)	28 (9-107)	72 (18-377)	***<0.001***
Clinical	91.0 (12-660)	28.5 (7-168)	119.5 (21-741)	***<0.001***
Longest	88.5 (13-678)	29.5 (10-143)	125.5 (30-759)	***<0.001***
Sounds (% (*n*))				
At start of seizure				
No	85.1 (160)	88.7 (55)	83.3 (105)	*0.33*
Vocalisation	12.8 (24)	11.3 (7)	13.5 (17)	*0.67*
Movement	2.1 (4)	0.0 (0)	3.2 (4)	*0.15*
During rest of seizure				
No	73.9 (139)	90.9 (56)	65.9 (83)	***<0.001***
Vocalisation	18.1 (34)	7.3 (5)	23.0 (29)	***0.01***
Movement	8.0 (15)	1.8 (1)	11.1 (14)	***0.02***
In view of camera (% (*n*))				
At start of seizure				
Yes	98.4 (185)	96.8 (60)	99.2 (125)	*0.21*
No	1.1 (2)	1.6 (1)	0.8 (1)	*0.61*
Partly	0.5 (1)	1.6 (1)	0.0 (0)	*0.15*
During rest of seizure				
Yes	96.3 (181)	98.2 (60)	95.5 (121)	*0.80*
No	1.1 (2)	1.6 (1)	0.8 (1)	*0.61*
Partly	2.7 (5)	0.0 (1)	3.9 (4)	*0.53*
Alarm button used (% (*n*))				
Yes	26.1 (49)	0.0 (0)	38.9 (49)	***<0.001***
Wakefulness/sleep (% (*n*))				
Sleep	42.5 (80)	48.4 (30)	39.7 (50)	*0.26*
Patient alone (% (n))				
No	28.7 (54)	29.0 (18)	28.6 (36)	*0.95*
EEG characteristics (% (*n*))				
1	6.9 (13)	4.8 (3)	7.9 (10)	*0.43*
2	35.1 (66)	46.8(29)	29.4 (37)	***0.019***
3	39.4 (74)	30.6(19)	43.7 (55)	*0.086*
4	18.6 (35)	17.7 (11)	19.0 (24)	*0.83*
Clinical characteristics (% (*n*))				
1	17.0 (32)	27.4 (17)	11.9 (15)	***0.008***
2	61.7 (116)	62.9 (39)	61.1 (77)	*0.81*
3	18.1 (34)	9.7 (6)	22.2 (28)	***0.035***
4	3.2 (6)	0.0 (0)	4.8 (6)	*0.08*

The EEG length of a seizure is defined as the time between ESO and ESE, clinical length is the time between the CSO and CSE, and the longest length is defined as the time between the first sign and the last sign of the seizure. The subclinical and seizure without patterns in the EEG are not taken into account in the calculations of the seizure lengths. The p-values show the significance in the difference between the seizure with a nurse response and without a nurse response. For the EEG and clinical characteristics, 1 represents very subtle seizures, 2 subtle seizures, 3 clear seizures, and 4 respresents very clear seizures.

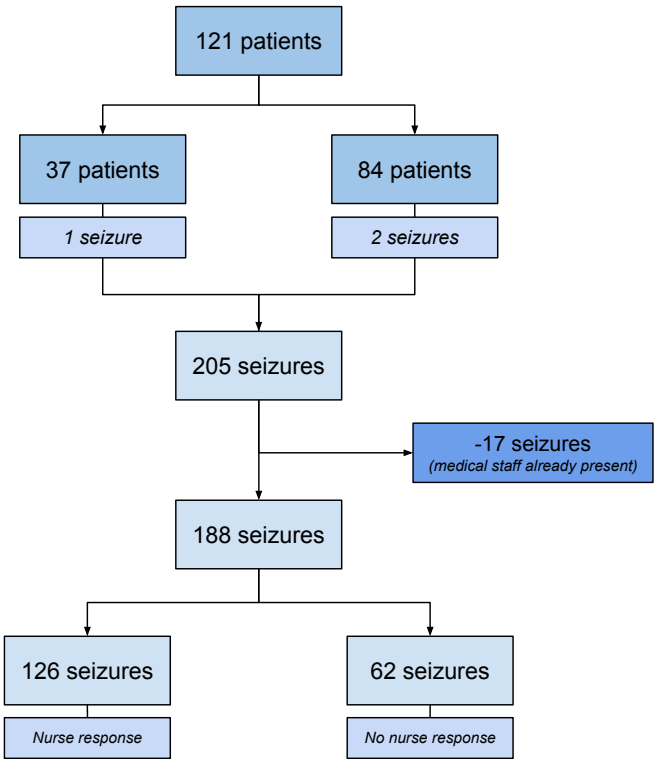


Fig. 2.3: An overview of the flow of the seizures from the amount of patients into the nurse response and no response group.

29 seizures the nurses responded within 20 seconds and for 24 seizure it took the nurses 60 seconds or more to respond to the seizure.

2.3.2 Descriptive results

All scored aspects of the seizures are listed in Table 2.3. Of the 188 seizures, in 62.8% (118) the start of EEG seizure patterns preceded the clinical symptoms. In 14 seizures (7.4%) there were no clinical symptoms at all and 3 times (1.6%) there were no EEG patterns. For 28.2% (53) of the seizures, the clinical symptoms preceded the EEG seizure patterns. For all the subclinical seizures and seizures without EEG patterns, no nurse response was noted. Seizures in the no response group showed significantly ($p < 0.001$) shorter seizure lengths compared to the group seizures with a nurse response.

Whenever the alarm button was used to inform the nurses a seizure occurred, the nurses did respond to it accurately. Further, out of the 43 times the alarm button was used, for 65.1% (28) the patient pressed the button, and for 34.9% (15) a companion in the room pressed the button.

In 28.7% (54) of the seizures, the patient had a companion with them in the room. The response rate to these seizures was comparable to seizures where the patient was alone in the room ($p = 0.95$). For seizures during wakefulness a companion seemed to improve the responder rate slightly. For 75.6% of the seizures during wakefulness with a companion in the room a nurse responded, compared to a response rate of 68.0% in seizures during wakefulness without a companion ($p = 0.416$).

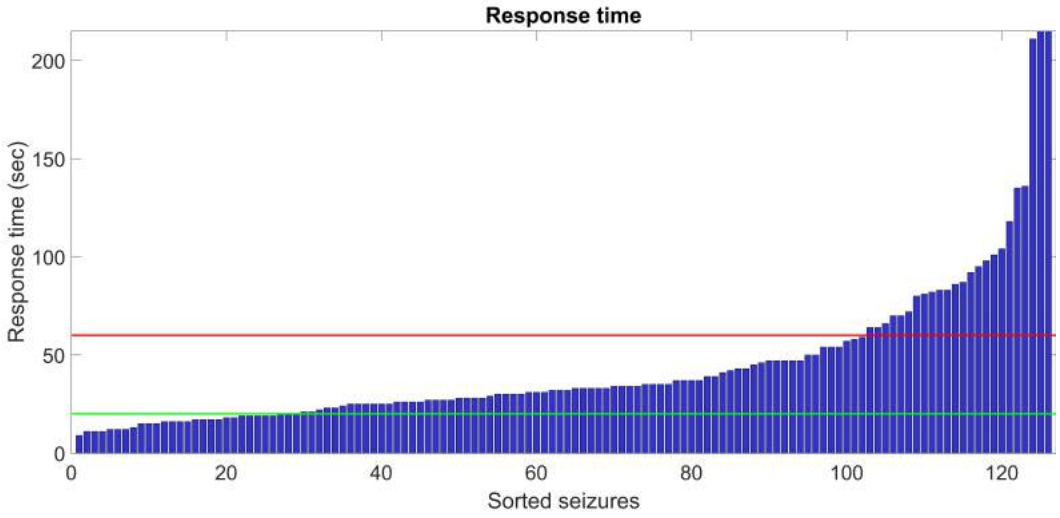


Fig. 2.4: The 126 seizures with a nurse response and their corresponding response time are shown. The seizures are sorted based on response time. Two horizontal lines represent respectively the 20 *(green)* and 60 *(red)* second line. Note that the two outliers are not displayed in total. For 29 seizures the nurses responded within 20 seconds and for 24 seizure it took the nurses 60 seconds or more to respond to the seizure.

In 80 recordings the seizure occurred during sleep. In 62.5% (50) of these seizures nurses responded, compared to 70.4% response rate for seizures during wakefulness ($p = 0.26$).

For 2 seizures, the patient was not in scope of the camera during the main part of the seizure. In both of these seizures, the patient was in the bathroom at the beginning of the EEG recording. For one of these two seizures, the nurses did not respond, for the other it took the nurses 11 minutes and 4 seconds before they entered the room of the patient. For 5 seizures the patient was partly not in scope of the camera during sections of the seizure. These patients were not followed adequately with the cameras. One of these 5 seizures did not result in a nurse response. The nurse response time of the four remaining seizures did not differ significantly to seizures where the patients were in scope of the camera.

For 24 seizures the patient made a vocal sound at the beginning of the seizure. In 70.8% (17) this resulted in a nurse response. In four seizures, the patient made sounds by movement at the beginning of the seizure, this resulted in all four cases in a nurse response. During the rest of the seizure, 49 seizures included sounds (34 vocal, 15 movement). Of those seizures 87.7% (43) resulted in a nurse response. There is a significant difference between the detection of seizures with and without sound aspects ($p < 0.001$).

The majority of seizures (61.7% (116)) was scored as clinically subtle (2). To all 6 seizures that were marked as clinically very clear, nurses responded. On the contrary, for 31.4% (11) of the very clear seizures based on the EEG, no nurse responded ($p = 0.11$). Figure 2.5 shows the distribution of the EEG and clinical characteristics combinations of the response and no response group in a table.

2.4 Discussion

In this part of our project it is studied whether and with how much delay the nurses responded to the seizures. Besides, several video and EEG aspects were taken into account. The study results indicate the necessity of a tool to help the nurses. With 62 (33.0%)

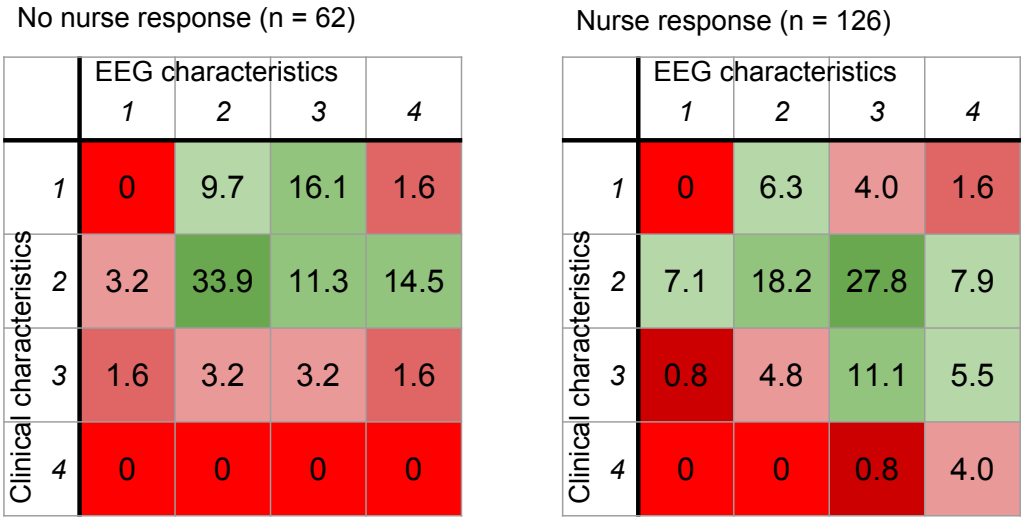


Fig. 2.5: These tables show the EEG and clinical characteristics combinations of the response and no response group. It shows the percentage of seizures that showed the considered combination in the specific group. The red areas represent areas with little amount of seizures and the green areas with more amount of seizures.

missed seizures, we can conclude that improvement in responding to seizures is possible. Additionally, for 19.0% (24) of the seizures with nurse response, the response time was over 60 seconds. For diagnostic and safety reasons it would be valuable to improve this response time.

Our results compared to those of Shin et al. [55] and Atkinson et al. [5] show different results. Based on the amount of seizure response, Shin et al. showed with 80% response rate a higher, and Atkinson with 40.6% a lower response rate compared to our response rate of 67.0%. Further, the study of Atkinson et al. presented a mean response time of 2 minutes and 22.3 seconds. In the study of Shin et al. a mean responder time is 23.5 for complex partial seizures and 20.3 for tonic clonic seizures was observed. Comparing this to our mean response rate of 32 seconds, it seems more comparable with the study Shin et al. published. The differences between our study and the studies of Shin et al. and Atkinson et al. might be explained by the difference in data selection. In our study we did not select the recordings based on seizure type, whereas the studies of Atkinson et al. and Shin et al. selected specific seizure types; Shin et al. selected complex partial seizures and generalized tonic clonic seizure and Atkinson et al. used partial onset seizures, generalized tonic clonic seizures, and myoclonic seizures.

One can question whether for all of the missed seizures a nurse response was needed. Furthermore, it could be questioned if the nurses did recognize the seizure but chose to not respond to this seizure by intercom or entering the room. We included seizures with a length of more than 5 seconds selected from the first five occurred seizures. For every such seizure a nurse response is preferred for diagnostic tests and safety reasons.

A major part of the seizures were scored as clinically subtle within the first 60 seconds. In Figure 2.5 it can be observed that the clinically subtle seizures are equally detected as not detected. This figure also showed that very clear clinical seizures were always detected. On the contrary, when observing the EEG characteristics we see that the very clear patterns are still missed sometimes. This could affirm that the nurses mainly focus on the video images.

It is shown that the alarm button is a very good tool to alert the nurses. Nurses always respond to this button. Nevertheless, this button showed some technical issues. Sometimes the button is pressed by the patient, but no signal is send to the observation room. Furthermore, sometimes patients cannot find the button quickly.

In this study it was shown that a companion in the room did not result in a higher nurse response rate. Generally, it was expected that an extra person in the room, could help to alert the nurses. Although in our study this added value of a companion is not clearly shown, we did observe a trend to a higher nurse responses in seizures with a companion during wakefulness.

In scoring the start of the EEG and the clinical and EEG characteristics every 5 seconds it is expected that there could be some difference in interpretation of the signals. Although a thorough study to inspect the inter-observer agreement was not performed due to time constraints, we did explore the possible variation. We selected ten random seizures to score the start of the EEG patterns by an experienced clinical neurophysiologist. A mean difference with respect to the original observer score of 2.8 seconds (SD = 3.8) was noted. This indicates that sometimes, choosing the start of the seizure in the EEG is somewhat subjective and fluctuates within several seconds.

We scored the EEG and clinical characteristics only for the first 60 seconds, while some seizures lasted longer and might evolved in more or less clear changes in EEG and/or clinical characteristics. That could result in seizures that progressed in very clear EEG patterns but started subtle and thus are scored as subtle EEG seizures.

Of the 62 seizures without nurse response 17.7% (11) showed very clear EEG patterns (score 4). Since many seizure detection algorithms show better results for clear seizures, we expect that a seizure detection algorithm at least is able to alert the nurses for these clear missed seizures.

2.5 Conclusion

This study provided insight in the nurse response to seizures in the EMU at SEIN. With a response rate of 67.0% we can conclude that improvement in the amount of seizures with a response is possible. For the response time, 19.0% of the seizure with a nurse response showed a response time over 60 seconds. As an epilepsy expertise centre we believe it should be aimed to improve both the response rate and response time for diagnostic and safety purposes.

We conclude that the use of the alarm button or sound aspects are seizure characteristics that influence the nurse response rate. Further, seizures without a nurse response show shorter seizure lengths compared to the seizures with a nurse response.

A notable part of the missed seizures showed clear EEG patterns. Literature shows that seizures with clear EEG patterns are easier to detect with an automatic detection than seizures with subtle EEG patterns. This indicates that a tool based on the EEG might help the nurses in the EMU at SEIN to detect seizures more accurate.

Lastly, this nurse response measurement helps us to inspect the possible improvement when automatic seizure detection methods are implemented, which is the follow-up research of this project.

3 Commercially available algorithms

3.1 Introduction

To view and analyze the EEG recordings nowadays hospitals use EEG viewers. This software displays the EEG and gives certain signal analysis possibilities. Sometimes seizure detection is already a module and thus part of such software. For example, at SEIN they use the Micromed software to view and analyze the EEG recordings. Somewhere in their software it is possible to use some kind of seizure detection. This however, is not user friendly and hardly used at SEIN.

Several companies focus on more advanced quantitative methods to analyze EEG. Some have spike detection or even include automatic observation of the background activity. Seizure detection is available in some software packages. Often they offer only offline seizure detection, but sometimes it is also presented as an online tool. Companies that offer these modules include BESA, AIT, and Persyst.

This Chapter describes the algorithms of BESA, AIT, and Persyst in more detail. Following, in Chapter 4 our study that investigated the added value and the sensitivity and latency performance of the algorithms of BESA and AIT is presented. Due to availability, the performance of the Persyst software is not investigated thoroughly, but the algorithm will be shortly described in the following sections. The following sections describe the algorithms of BESA, AIT, and Persyst, to give an overview of the available commercially available online seizure detection algorithms.

3.2 BESA

MEGIS Software GmbH was founded by Dr. Michael Scherg in 1995. They introduced digital EEG software that is easy to use. In the following years they expanded their software with amongst other things, imaging methods and source modules. In 2009 they renamed the company to BESA GmbH. BESA is an acronym for Brain Electrical Source Analysis. Nowadays they provide several software packages for EEG analysis of which some packages can be used in the field of epilepsy.

3.2.1 Seizure detection algorithm

In 2007 BESA proposed a seizure detection algorithm by an article of Hopfengärtner et al.[26]. In 2014 they improved the algorithm and performed a validation study for clinical routine [27]. The algorithm is based on change in amplitude and frequency of the EEG signal. They hypothesize that electroencephalographic seizure activity manifests itself by a sequential change in frequency and amplitude that is distinct from non-seizure or background activity.

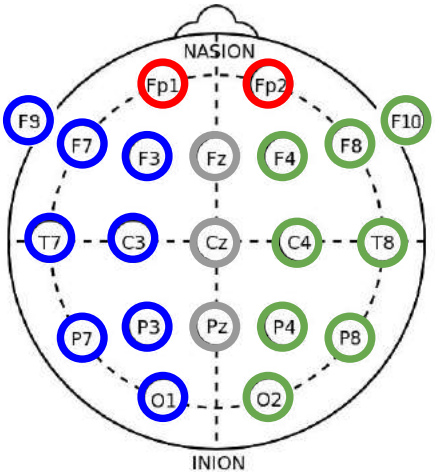


Fig. 3.1: The EEG electrodes of the 10-20 system with additional F9 and F10 electrodes. The blue electrodes represent the left subset and the green electrodes represent the right subset used in the BESA algorithm. The grey electrodes show the referenced electrodes. The red electrodes Fp1 and Fp2 are omitted due to eye blink artefacts.

Steps through the algorithm The electrodes that are selected for the algorithm are divided into a left and right subset. The left subset consists of the electrodes F7, T7, P7, O1, F3, C3, and P3. The right subset contains the electrodes F8, T8, P8, O2, F4, C4, and P4. They referenced these electrodes against the average of Fz, Cz, and Pz. Electrodes Fp1 and Fp2 are omitted due to eye blink artefacts.

Figure 3.2 shows a flowchart of how the BESA algorithm processes EEG data. First the data is segmented into epochs of 2 seconds. They use overlapping epochs with an overlap of 50%. Secondly artefact rejection is performed per channel (j) for each epoch (k). High amplitude EEG sections are omitted. This is accomplished by equation 3.1, where $\widetilde{x}_{max,min}[j,k] = max, min\{x_n[j,k] - \overline{x}[j,k]\}$ are the maximum and minimum amplitudes of the signal. When $d[j,k]$ is greater than the threshold of 600 μV, the epoch of that specific channel is omitted.

$$d[j,k] = \widetilde{x}_{max}[j,k] - \widetilde{x}_{min}[j,k] \tag{3.1}$$

As a third step, the integrated power (IP) and normalized energy (E) are calculated per channel (j) per epoch (k) according to equations 3.2 and 3.3. The used frequency band (b) for integrated power is from $2,5$ to $12Hz$. After that the IP and E are averaged per epoch following equations 3.4 and 3.5, where $Nch_i[k]$ denotes the number of artefact-free channels in epoch k. The IP and E are interpreted as an estimate for respectively characteristic frequency and amplitude changes.

$$IP[j,k,b] = \sum_{fl=f_1^b}^{f_2{}^b} P_n[j,k](f_l) \tag{3.2}$$

$$E[j,k] = \frac{1}{N}\sum_n (x_n[j,k] - \overline{x}[j,k])^2 \tag{3.3}$$

$$\overline{IP}[k,b] = \frac{1}{Nch_i[k]}\sum_j IP[j,k,b] \tag{3.4}$$

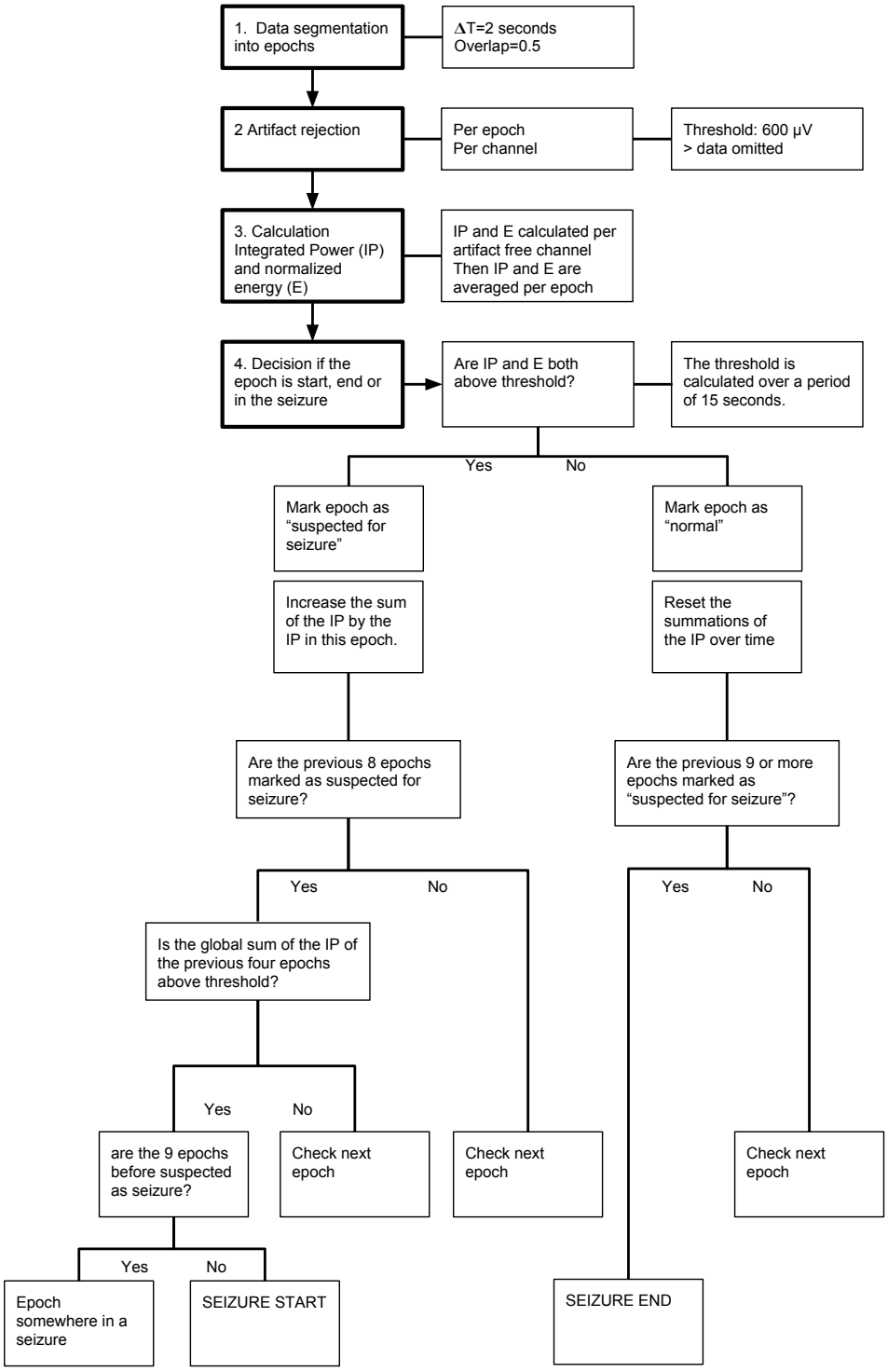


Fig. 3.2: The flowchart of the BESA algorithm. It shows the criteria and steps of how the algorithm scores the EEG on seizures.

$$\overline{E}[k] = \frac{1}{Nch_i[k]} \sum_j E[j,k] \tag{3.5}$$

Finally these calculated IP and E values are compared to certain thresholds. These thresholds are calculated over a section of 15 seconds. The precise method is unknown, as it is not described in literature. If both IP and E are above threshold, the epoch is marked as "*suspected for seizure*". If a cluster of 9 consecutive epochs, representing ten seconds, are marked as "*suspected for seizure*" and those 9 epochs together cross a certain threshold as well, this section is marked as a seizure.

Setting The patient group used in the validation study of 2014 consisted of 117 patients with temporal lobe epilepsy, 35 patients with extra-temporal lobe epilepsy, 2 patients with multifocal epilepsy, and 5 patients with undetermined seizure origin. They selected patients who were admitted to the Epilepsy Center Erlangen for non-invasive long-term video-EEG monitoring as part of presurgical evaluation.

They analyzed a total of 25,278 hours of scalp EEG recordings, including 794 clinically identified seizures. The duration of the recordings per patient varied between 46 and 310 hours (mean: 159 hours). The number of seizures per patient varied between 2 and 28 per patient (mean: 5 seizures).

They analyzed 551 complex partial seizures, 115 simple partial seizures, and 128 secondary generalized tonic clonic-seizures. They did not include subclinical seizures or clinically evident seizures without visually recognizable EEG pattern.

Performance The averaged sensitivity value was 78.8%. For 110 patients the sensitivity was perfect, 100%. In three patients the algorithm did not detect any seizure. For the temporal lobe patient recordings, consisting of 589 seizures, sensitivity reached an averaged value of 81.0%. For the recordings of patients with extra-temporal lobe epilepsy, consisting of 172 seizures, the averaged sensitivity was 71.3%, which is significantly lower than for temporal lobe epilepsy patients. This observation contains some uncertainty due to the different volumes of the two groups.

The averaged rate of false positive events per hour was 0.11/h. For temporal lobe patients the averaged false positive rate was slightly lower with 0.08 false positives per hour. For the extra-temporal lobe patients, the rate reached 0.16/h.

Strength and weaknesses The algorithm BESA proposed can be used without adaptations per patient. For all patients identical parameters are used. The performance is based on a large data set including all kinds of artefacts, different states and non-ictal pathological patterns.

The algorithm is not able to detect seizures with the following features: *a*) A seizure duration of less than 10 seconds; *b*) a seizure with a low amplitude; *c*) a seizure pattern presented in only a few electrodes; and *d*) a seizure with activity in the beta band. Besides, seizures that evolve quickly into the generalized tonic-clonic phase accompanied by artefacts are difficult to be detected as well.

They mentioned that for the lower frequencies they managed to detect more seizure patterns in the delta band due to their frequency range from $2,5$ to $12Hz$. A negative side effect of these lower frequencies is the increased false detection rate, substantially due to prolonged frontal and temporal intermittent rhythmic delta activity.

The article of 2014 did not mention anything about the detection delay. This is however also an important parameter. Looking at the criteria of the algorithm the detection delay will be at least 10 seconds in an online setting. In their previous study of 2007, with a smaller patient population they noted a delay varying between 10 and 44 seconds.

The article of 2014 mentions that the method of BESA is comparable to EpiScan from AIT 3.3 with respect to artefact rejection and a multichannel calculation.

Recent developments As mentioned before the signals of electrodes F9 and F10 were not included in the algorithm calculation. Recently BESA added these two electrodes to respectively the left and right subset. Furthermore they are in a progress of development and improvement of the algorithm. Nowadays they focus more on pediatric recordings, to see if their algorithm is able to detect seizures in EEG of children.

SEIN has a closer collaboration with BESA in comparison to the contact wit Persyst and AIT. In order to help each other SEIN and BESA work together to improve the BESA algorithm and research whether it is an option in the EMU setting of SEIN.

3.3 AIT

The Austrian Institute of Technology (AIT) is a large research institute consisting of different departments, from digital safety to health and environment. The computational Encephalography research group of AIT develops software for analyzing EEG recordings. Part of this software is a seizure detection method named 'EpiScan'.

3.3.1 Seizure detection algorithm

In 2014 Fürbass et al.[16] published a prospective multi-center study regarding the algorithm 'EpiScan'. As part of this article they also made a comparison with the Persyst algorithm.

Steps through the algorithm The EEG is analyzed in epochs of 0.25 seconds. Frequencies below 0.7 Hz and above 99 Hz are removed by finite impulse response filters. A notch filter is used to filter at 50 and 60 Hz.

Segments with excessive amplitudes are removed, resulting in some artefact removal from loose electrodes for example. After artefact removal, they use two algorithms to check the EEG for rhythmic patterns in the time and frequency domain. These algorithms are respectively Epileptiform Wave Sequence Analysis (EWS) and Periodic Waveform Analysis (PWA) [25, 17]. The PWA was designed to detect rhythmic patterns that can be found most frequently. For temporal lobe epilepsy this should work properly with the frequencies displayed during those seizures. The EWS analysis is designed to detect especially seizure patterns with a moderate irregular structure, high frequency variations, abrupt phase changes, and distortions by muscle or electrode artefacts. A third feature they use is energy. The algorithm scans the EEG for tonic and tonic-clonic seizures with strong muscle artefacts.

The extracted features are normalized by a spatio-spectral model of the brain activity. They update the model continuously by past information from the EEG. Furthermore they use classifiers to remove events with physiological origin. They state that these two steps avoid repeated detections of patterns that are not seizures.

PWA The PWA consists of a continuous wavelet transformation. It searches for rhythmic patterns. They use waveforms to detect periodic patterns in the delta-, theta-, alpha-, and beta-bands. They normalize the waveform results to the total energy in the EEG in order to only detect dominant components.

EWS The EWS analysis is a time series analysis. This is chosen because patterns with irregular structures are difficult to measure with a spectral analysis. First, the analysis searches for epileptogenic waves. The wave has to meet three criteria to be defined as a wave. It has to be within a certain frequency range, has high enough amplitude, and small high frequency noise. All waves are handled separately, this way the variations in the signal is not a problem. After defining the waves, the waves are clustered based on the three wave classification criteria. In this process some waves will be excluded as they do not fit into any cluster. Thirdly, the clustered waves are sequenced, allowing gaps that correspond to artifacts and/or distortion. At last, within the sequence, the analysis calculates a similarity value, to inspect the similarity between groups of waves. They observed that ictal sequences of epileptogenic waves look similar to each other, therefore they state that this similarity value indicates whether an EEG section is ictal.

Setting They used the EEG recordings of 205 patients older than 18 years, of which 94 recordings consists of seizures. Data were recorded at three EMUs, two in Vienna and one in Heeze. A total of 15.684 hours of EEG with 526 seizures was analyzed.

They let reviewers score the EEG on seizures. These reviewers were asked to decide whether the EEG at a defined moment represented a seizure. They could choose six different values of increasing certainty. Based on that score, data was divided into four groups; *a*) all marked seizures without opinion of reviewers, *b*) all seizures with perception value of at least 25% certainty, *c*) all seizures with perception value of at least 50% certainty, and *d*) all seizures with perception value of at least 75% certainty.

Performance They defined a seizure epoch as a three minute time range starting from the beginning of the seizure marker. An EpiScan alarm occurs at a specific moment in time, without a time duration. When this alarm appeared in a seizure epoch it was defined as a true positive detection.

They showed in the group where seizures were clearly visible according to the experts ($> 75\%$), a sensitivity of 81%. They noticed an expected lower sensitivity of 78% and 72% for the groups in which the experts were less certain, respectively the $> 50\%$ and $> 25\%$ group. When calculating the sensitivity for all seizures, regardless of whether those seizures were visible in the EEG, they achieved a sensitivity of 72%. During the study, EpiScan discovered 16 previously undetected seizures. Overall, a false alarm rate of 7.05 per day was achieved.

In the comparison with Persyst, they state that the algorithm of Persyst achieved a sensitivity of 68% compared to the 72% of EpiScan. Also for the other groups the sensitivity of EpiScan was higher. For the false alarm rate Episcan showed better results in comparison to Persyst for all the detection groups as well. The false positive rate of Persyst appeared to be 27% higher than the false positive rate of EpiScan.

In the study they also tested the algorithm on a small pediatric publicly available data set of 24 patients. A sensitivity of 67% and false positive rate of 7.7 per day was achieved.

Strength and weaknesses In their article they do not explicitly explain what kind of seizures were missed and what made the false detections. However we could reason that the more subtle seizures are more difficult, because the sensitivity gets lower when reviewers are less certain of the occurrence of a seizure. In this reasoning we assume that reviewers are less certain when seizures show subtle EEG patters.

Their algorithm is intentionally built out of two analysis methods, the PWA and EWS. This way they tend to focus with the PWA on the obvious seizures and with the EWS the more difficult seizures to detect properly.

The performance of the EpiScan algorithm is based on a large uncut dataset, for a reliable false detection rate this is important.

Lastly AIT offers another kind of software, called Neurotrend. This software takes several features and displays it in time. It is based on totally other calculations than EpiScan. It does not detect seizures yet, but in the future it might be able to.

3.4 Persyst

Persyst is an American company, founded by Scott Wilson in 1987. They develop EEG analysis products for amongst others Intensive Care Units (ICU) and EMU purposes. For the long-term monitoring on the EMU they provide software which they state is able to detect spikes and seizures. Furthermore their software is able to help in the offline reviewing of long-term EEG registrations.

3.4.1 Seizure detection algorithm

A validation study of the Persyst algorithm for seizure detection is presented in 2015 by Sierra-Marcos et al. [56]. The algorithm this study refers to is a version of June 2013. As mentioned in the article there are ongoing refinements to improve the algorithm. Thereby the steps through the algorithm and the performance discussed in the validation study might not fully correspond to the current algorithm Persyst offers.

Steps through the algorithm The algorithm is based on changes in background activity, displaying rhythmicity, evolution in amplitude and/or frequency, and asymmetry. A key input to the algorithm is the rhythmicity spectrogram. It measures the amount of rhythmicity at each frequency presented in the recording. The algorithm is built by combining the output of many small artificial neural networks, each of which were trained to recognize a particular feature. A set of various EEG recordings was used to train the algorithm. These recordings were drawn from EMU, ICU, and ambulatory settings.

They analyze the EEG per one-second epochs. Per epoch two outputs are presented. One output represents the identification of seizures and the other shows the probability curve that shows the probability that an epoch would be marked as "*seizure*". At least 11 epochs, representing 11 seconds, have to be marked as "*seizure*" to generate an identification of a discrete seizure event.

Setting They analyzed 98 recordings, which they classified in four groups:

1. Recordings with periodic lateralized epileptiform discharges (PLEDs) and/or Periodic epileptiform discharges (PEDs) with seizures. 21 patients were included in this group.

2. Recordings with PLEDS/PEDs but without seizures. 29 patients were included in this group.
3. Recordings with seizures but without PLEDs/PEDs. 17 patients were included in this group.
4. Recordings without PLEDs/PEDs and seizures. These recordings did contain some suggestive patterns for seizures. 31 patients were included in this group.

The total duration of all recordings was 82.7 hours (mean: 1 hour; range 20 minutes - 19 hours). The recordings of group A contained 170 seizures (mean 4; range 1-50) and of group C 98 seizures (mean: 3; range 1-18).

The presumed etiology of the included patients was structural-metabolic in 66, genetic in 7, and unknown in 25 patients.

Performance The sensitivity of this algorithm was 76.1%. For 29 patients, all seizures were captured. In three subjects no seizures were detected. For group C the averaged sensitivity was 100% and for group A 75%.

80 false positive events were identified, resulting in a false positive rate of 0.97 per hour. Two recordings in group B show a very high false positive rate of more than 20 per hour. False positive detections were concentrated in group A and B, both with PLEDs/PEDs

Strength and weaknesses Of the 64 undetected seizures, 30 correspond to subtle ictal patterns without clear changes in frequency and amplitude, 21 to short events, 8 to fast rhythms, and 5 to muscular artefacts.

They state that the performance is lower in patients having periodic patterns, with and/or without seizures. The strength of this study is that they took difficult EEG recordings to validate their algorithm. A weakness to these recordings is that they are relatively short and have relatively small amount of seizures, therefore this can hardly be called a validation study. Especially about the performance measure of false positive events we can not draw conclusions.

The output of probability could be a strength, because it might make it able to respond more quickly to seizures. It could make the medical staff more aware of something might happen.

3.5 Conclusion

The three considered companies have constructed very different algorithms. BESA uses a relatively simple robust algorithm with certain thresholds to discriminate between seizure and non-seizure patterns, Persyst uses more complex neuronal networks, and AIT uses different wavelet analyses to detect the seizures. With the available articles we were not able to get a total detailed insight into all the algorithms.

In the different validation studies, three different methods are noted. The main difference can be observed in the way the data recordings were divided. Where BESA and AIT used big data sets, Persyst chose a relatively small amount of recordings. BESA did not discriminate between certain recordings, whereas AIT and Persyst divided the recordings in different subgroups. Persyst indicated that they used very challenging recordings with and without PLEDs or PEDs and with and without seizures. AIT made another partition, they let reviewers

	Sensitivity	False positives per hour
BESA	78,8%	0.11
Persyst	76,1%	0.97
AIT	72%	0.29

Tab. 3.1: This table shows the sensitivity values and false positive rates of the three algorithms obtained in their own validation studies.

score the seizure events and divided the EEG sections into groups of seizure certainty based on the opinion of the reviewers.

Looking at the performance measures in the validation articles, BESA shows the best sensitivity value and false positive rate. Table 3.1 shows the different performance results. In the article of AIT, they also used the algorithm of Persyst on their data and with their method, then the sensitivity value and false positive rate of Persyst showed respectively 68% and 0,4 false positives per hour. We should be aware that the performance measures are obtained from different data and different methods.

Persyst and BESA both mentioned that the algorithm struggles with subtle seizure patterns. In the results of the AIT validation study we could also conclude that subtle seizures are more difficult to detect. AIT explicitly has a certain analysis for more difficult seizures, but still we believe they encounter problems with subtle seizures just like BESA and Persyst.

None of the validation articles studied the latency values thoroughly. We believe that latency is however very important for the EMU setting to study an improvement in response time compared to the current situation. The Persyst software includes a probability value which indicates whether it is less or more likely that a seizure is occurring. We expect that such a probability value could really help to grab the attention of nurses on the EMU to look more precisely to a certain patient and detect seizures adequately and more rapidly.

Because of several aspects described above we can not conclude which commercially available algorithm would be best suitable for SEIN without further research. We consider the probability value of the Persyst software as an added value. Their validation study though is with the little amount of data not very convincing. BESA seems to have a good algorithm because it is robust. A downside is that they probably have the most issues with subtle EEG patterns. For the more difficult EEG patterns AIT seems most applicable because they intended to implement a special waveform analysis for those seizures. Lastly we believe that the latency values are important. In all the articles they did not elaborate about latency values. We however believe that for EMU purposes the latency values could be important to decide which algorithm is more applicable.

In the following chapter we will look more closely to the added value and sensitivity and latency performance of the algorithms of BESA and AIT on our previously obtained EEG recordings.

4 Sensitivity and latency performance and seizure nurse response improvement of two commercial seizure detection algorithms

4.1 Introduction

As described in Chapter 3, commercial seizure detection methods for an online clinical setting are being developed. These EEG based algorithms for seizure detection might be able to help the nurses in responding more accurately to seizures, which is important for diagnostic and safety purposes.

In the articles of Hopfengärtner et al. [27] and Fürbass et al. [16] validation studies of respectively BESA and AIT are described. Both studies mainly focus on sensitivity and false positives, while the latency is also an important aspect for the implementation of the algorithm in a clinical online setting. Further, in order to implement a seizure detection algorithm, improvement of the current situation, both in terms of detected seizures and response time is essential.

The aim of this study is to investigate performance in terms of sensitivity and latency of BESA and AIT on our previously obtained EMU EEG recordings. Moreover, the improvement with respect to the current nurse response is of interest in order to determine the added value of implementing BESA or AIT. The improvement in number of detected seizures, and gain in response time is studied.

4.2 Methods

In this study the previously obtained EEG recordings were scored with both the BESA and the AIT algorithm. Details about the algorithms are written in Chapter 3 and information about the recordings can be found in Chapter 2.

The analysis of the data by BESA and AIT resulted in an output of time points where the algorithms stated a seizure occurred. To decide whether the algorithms made a correct detection, the boundaries (*CSO, ESO, CSE, and ESE*) of the seizure, that were scored in Chapter 2, were used. A correct detection was defined as a detection within ten seconds before the first start (*CSO or ESO*) of the seizure up to ten seconds after the last end (*ESE or CSE*) of the seizure (see Figure 4.1).

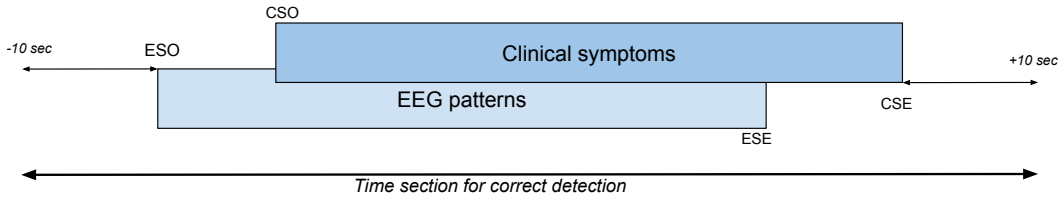


Fig. 4.1: The definition of a correct detection is illustrated. A correct detection is defined as a detection within ten seconds before the first start of the seizure till ten seconds after the last end of the seizure.

4.2.1 Analysis

Firstly, the sensitivity and latency performance of the BESA and AIT algorithms were studied. The amount of detected seizures were determined, resulting in a sensitivity score. Furthermore, the amount of seizures that were detected by both the BESA and AIT algorithm were considered. Latency was studied by comparing the detection time points of the algorithms with the ESO. For BESA it is known that in an online setting, the algorithm demands at least ten seconds of seizure data before it gives an alarm. To translate the detection moment of the offline setting to an online setting, at least 10 seconds should be added for the BESA algorithm. For AIT it is not known on forehand what the consequences in terms of response time are when translating the results to an online setting.

Secondly, the response improvement with respect to the previously inspected nurse response is studied. Both improvements in amount of detected seizures, and gain in response time were taken into account. As nurse response time point the moment the intercom is used, or the moment the nurse entered the room was used. Because the nurses need some time to walk from the observation room to the patient's room, 5 seconds were taken into account as delay time.

Lastly, subgroup analyses were executed to investigate the differences in performance between groups based on the seizure aspects EEG and clinical characteristics. In the previous study (see Chapter 2) the EEG and clinical characteristics are described in more detail. For this study we used the maximum score of the EEG and clinical characteristics scores per seizure, to divide the seizures into four different groups, from very subtle to very clear seizures (see Table 2.1 in Chapter 2). The amount of detected seizures and response time of the different groups were investigated. Since the seizures where already medical staff was present were not scored on EEG and clinical characteristics, these seizures were excluded for this part of the analysis.

4.3 Results

4.3.1 Sensitivity

Figure 4.2 shows the sensitivity performance of BESA, AIT, and the nurses. It illustrates that the BESA algorithm was able to detect 63.9% (131) of the seizures and the algorithm of AIT correctly detected 76.1% (156) of the seizures. Furthermore, the amount of the shared seizures that were both detected by BESA and AIT are illustrated. For 61.5% (126) of the seizures, both BESA and AIT showed a correct detection.

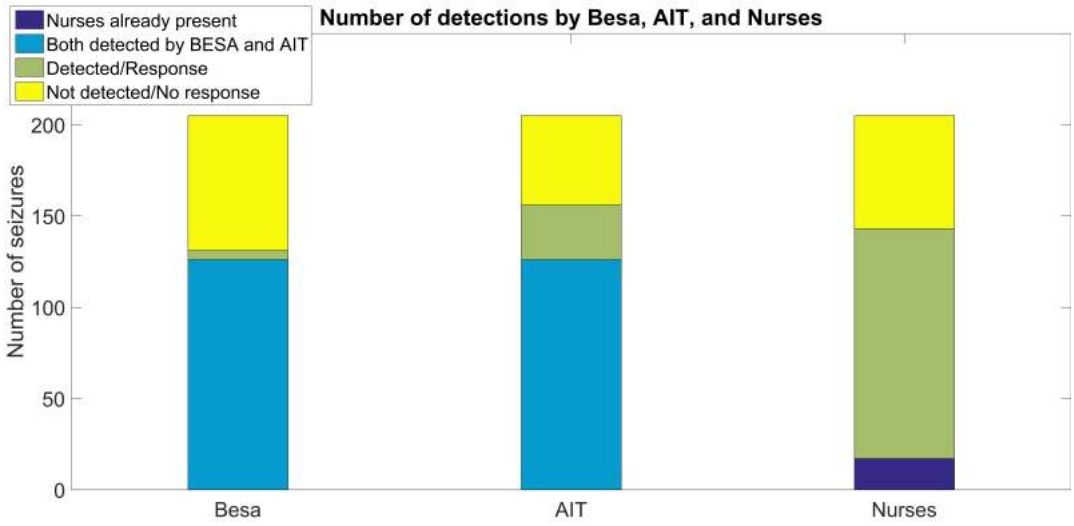


Fig. 4.2: The amount of seizures that are detected by the different groups, Besa, AIT, and the nurses. For 126 seizures, both BESA and AIT detected them. Additionally BESA detects 5 and AIT detects 30 seizures. The nurses were at 17 seizures already present, and responded to 126 seizures out of the 205.

4.3.2 Latency

For the 131 and 156 detected seizures by respectively BESA and AIT, the latency values were calculated. These values were computed by comparing the time of detection to the ESO. Figure 4.3 shows these latency results. The median latency value for BESA was 3.75 seconds (p5-p95; -4.0-41.1), in comparison with the latency of 10.15 seconds (p5-p95; -3.9-49.5) for AIT ($p < 0.001$). For BESA there is one major outlier with a latency of 33 minutes and 59 seconds. This corresponds to a seizure with a very slow build up of epileptic patterns. Of the 126 seizures where both BESA and AIT produced a correct detection, for 77.0% (97) the detection of BESA preceded the detection of AIT in the offline setting.

Online setting Considering the delay of ten seconds when implementing BESA in an online setting, for the latency results ten seconds should be added. This results in better latency results for AIT ($p < 0.001$). Taking the ten second delay in consideration, for the 126 seizures where both BESA and AIT showed a correct detection, for 35.7% (45) the detection of BESA preceded the detection of AIT, compared to 77.0% in the offline setting.

4.3.3 Improvement

Figure 4.4 shows the amount of detected seizures by BESA and AIT for the different nurse response groups. In the subgroup of seizures that were not detected by the nurses, BESA and AIT both detected 24 (38.7%) shared seizures. Additionally, AIT is able to detect 17 (27.4%) seizures that were not detected by BESA. When implementing AIT the results show an improvement of 66.1% detected seizures in the group of seizure where the nurses did not respond to.

For the seizures that were detected by the nurses as well as by BESA and/or AIT (see Figure 4.4), possible response time improvement by automated seizure detection was studied. Figure 4.5 shows detection by BESA and AIT with respect to the nurse response. The median improvement in time in the offline setting for BESA is -25.6 seconds (p5-p95; -88.7-7.6), compared to the median improvement of -18.1 seconds (p5-p95; -89.4-18.3) for AIT (p =

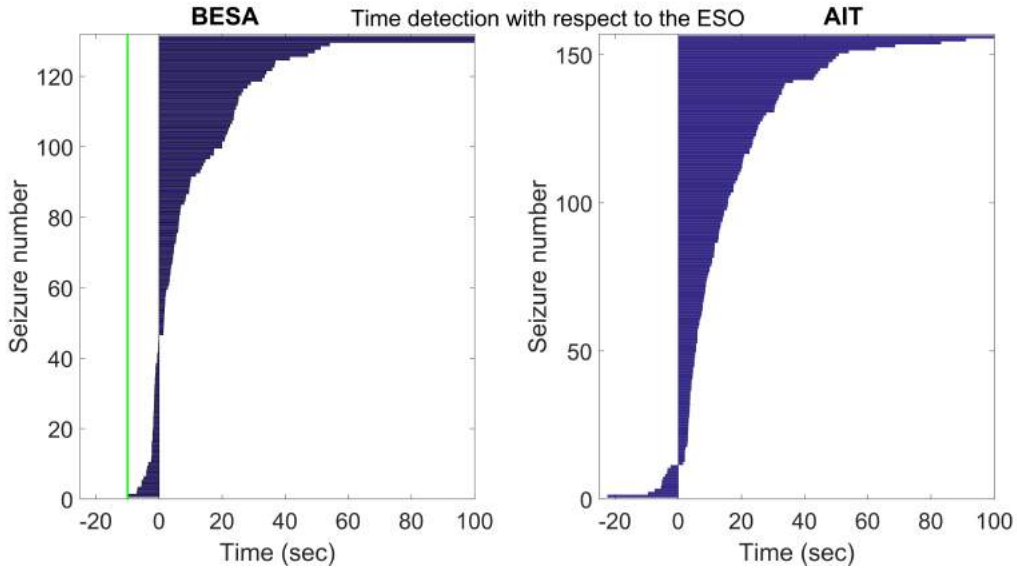


Fig. 4.3: The latency values of Besa(*left*) and AIT(*right*) with respect to the ESO. At zero the ESO is visualized. The bars represent the time point of the detection of respectively BESA and AIT. A negative value indicates that the time point of detection lies before the ESO, a positive value represents a detection of the algorithm after the ESO. For BESA it is known that the algorithm in an online setting, needs ten seconds of seizure before it gives an alarm. The green vertical line at ten seconds illustrates these ten seconds.

0.007). As discussed, the estimated delay from the nurses walking to the room and the BESA delay in online use is visualized by vertical lines in the figure. Taking the ten second delay in consideration results in a slightly better possible improvement for AIT ($p = 0.57$).

4.3.4 Subgroup analysis

EEG and clinical characteristics of seizures detected by BESA and AIT were examined. Figure 4.6 shows the results of the subgroup analysis based on clinical and EEG characteristics. It can be noticed that for the subtle seizures in the EEG, BESA and AIT present lower sensitivity values than for clear and very clear seizure patterns. For 7 out of 205 seizures, no electrographic patterns were observed. None of these seizures were detected by BESA or AIT.

Further, the response time for the different subroups based on the EEG and clinical characteristics was calculated. There was no significant difference between the subgroups regarding the response time. Figure 9.2 in supplementary materials shows the boxplots of the response time of the subgroups.

4.4 Discussion

In this part of the project the commercially available seizure detection algorithms by BESA and AIT were investigated in an offline setting with help of EEG recordings. The results of both BESA and AIT show improvements in more detected seizures as well as improvement in response time. It is observed that AIT is able to detect more seizures than BESA does. It can be concluded that for the detected seizures, BESA is able to detect them before AIT does in the offline setting. When translating the offline results to an online setting with the

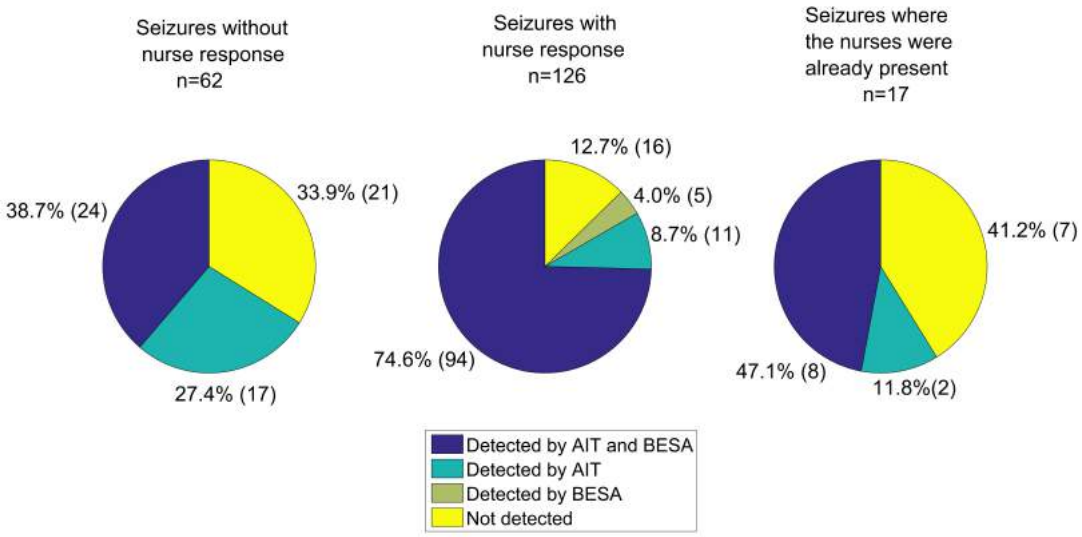


Fig. 4.4: The detection of Besa and AIT in the subgroups based on the nurse response. Additionally, it shows the amount of seizures that were both detected by Besa as well as by AIT.

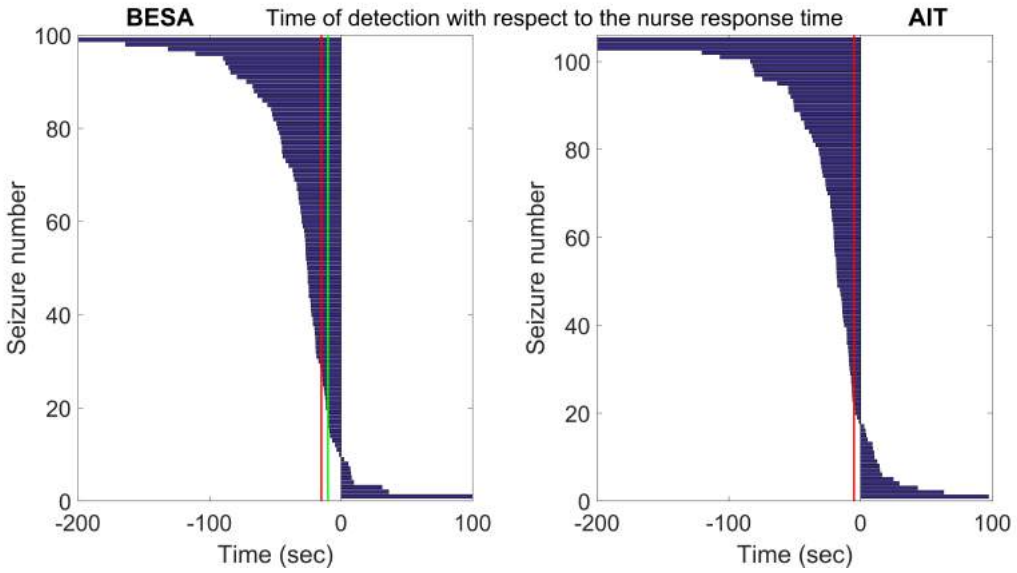


Fig. 4.5: The detection improvement with respect to the nurse response. On the x-axis at zero, the nurses enter the room. bar graphs to the left side show an improvement, and to the right show a detection after the moment the nurse entered the room. The vertical lines show time boundaries to take into account. A delay time of 5 seconds *(red)* is taken into account for the nurses to walk from the observation room to the room of the patient. Additionally, for BESA a time period of 10 seconds *(green)* is taken into account, as for online use, the algorithm needs ten seconds of seizure data before it results in an alarm.

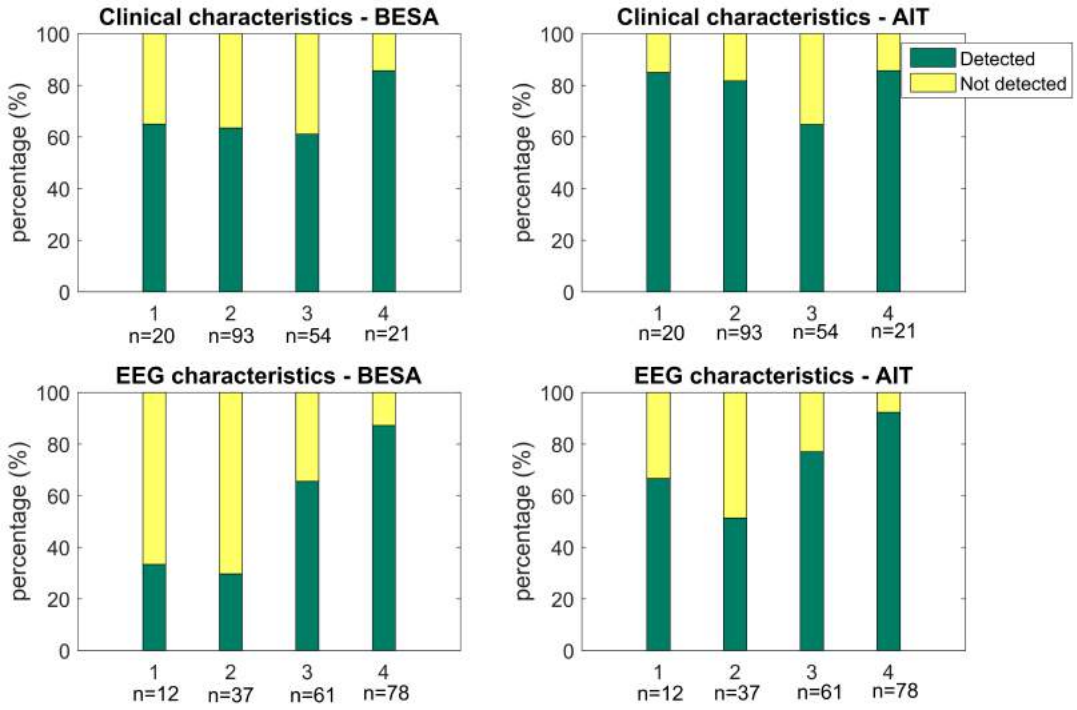


Fig. 4.6: The distribution of detected and not detected seizures for the four subgroups based on previously scored maximum values of the clinical (*top*) and EEG characteristics (*bottom*). The results of BESA are shown *left*, and of AIT *right*. Seizures where already medical staff was present in the room were not taken into account.

known delay of ten seconds for the algorithm of BESA, the results change to a slightly better performance of the AIT algorithm.

Comparing our AIT results with those reported by Fürbass et al. [16], we observe comparable sensitivity results. They showed a sensitivity of 72% on their entire data set, compared to a sensitivity of 76.1% that was obtained in this study. Fürbass et al. showed a gradual decrease in detection sensitivity when seizure certainty, as oberved by experts, decreased. This decrease in sensitivity is also observed in our data when the seizures are scored as more subtle (Figure 4.6). It seems however, that our sensitivity results for the subtle seizures are lower then the results of Fürbass et al. Nevertheless, a true comparison is difficult due to different seizure categories.

Recent work by Hopfengärtner et al. [27] reported detection sensitivity results considerably higher than the sensitivity values found in this current study. They reached a sensitivity of 87.3% on their data, whereas the results on our data show a sensitivity of 63.9%. This difference might be explained by different inclusion criteria. Where our study included all kinds of epileptic seizures, Hopfengärtner et al. only included presurgical patients and only seizures with evident clinical symptoms. The definition of evident clinical symptoms remains unknown. Furthermore, they excluded seizures without visually recognizable seizure patterns in the EEG.

Because detection performance was studied in an offline setting, the real improvement in an online situation could be discussed. The articles of Shin et al. [55] and Atkinson et al. [5] both show that even though they are alarmed by the automatic seizure detection methods, medical staff does not always respond to these seizure alarms. Therefore, it could

be questioned if the possible added seizure detections by both AIT and BESA, would result in nurse responses.

Further, regarding the response time, the translation to online use might change the results. In the offline results of this study, it was observed that BESA showed better results in response time than AIT. However, when we took the translation to the online setting for BESA into account, this difference altered. Further, we do not know on forehand, what consequences the online use includes precisely and how this influences the results.

During routine EEG analysis and documentation, only sections of interest in the EEG are selected to store. The various lengths of data prior to the seizure might have influenced the performance of the algorithms. During verbal communication, both BESA and AIT stated that the algorithms perform slightly more sensitive with a shorter amount of data prior to the seizure. Both algorithms need a baseline measure to compare EEG sections with previous EEG sections. AIT stated that the algorithm needed approximately 30 minutes of EEG data before the actual seizure started to perform best. In our data set, this amount of pre-seizure data was available for only 20 seizures (see supplementary materials, Figure 9.1). Therefore, it could be expected that the true sensitivity performance of BESA and AIT is slightly lower.

This study only inspected the sensitivity and latency, while the specificity is also a very important performance feature to take into account. Several studies mentioned that most seizure detection methods are not yet implemented due to the high false positive rate. Based on interviews and questionnaires on the EMU at SEIN, our nursing staff regards a false positive rate of approximately 0.5 per hour as acceptable. It could be questioned how the real acceptance is when algorithms are implemented. We believe that focusing on the improvement of the current performance is most important. This might include another kind of output to make the automatic detection method more applicable to an online EMU setting.

4.5 Conclusion

In this part of the project the performance of BESA and AIT are investigated. Regarding the sensitivity, AIT performs considerably better than BESA. Also when investigating the improvement to the current situation AIT seems to show a greater gain of detected seizures that were not recognized by the nurses.

When looking at the response time, BESA seem to show better results in the offline setting with respect to AIT. However, when translating this difference to an online setting this difference might shift towards an equal response time. With these results it cannot be concluded that BESA will perform better when investigating the response time. When investigating the response time we do see an improvement in time with respect to the nurse response. Also when translating this improvement in response time to an online setting it is expected they still benefit from an automatic detection method.

In conclusion, this study proves that improvements in response rate and response time could be possible by implementing BESA or AIT. Still, research in an online setting should be performed to study the real benefit from a automatic seizure detection algorithm.

5 Information about the selected features

5.1 Introduction

Beside commercially available software, also several other seizure detection algorithms were created and published in literature. Literature is filled with seizure detection possibilities. In order to make a promising algorithm features that can discriminate very good between non-seizure and seizure activity are needed. In our project we investigated a selection of promising features stated in literature.

For this study the following features were selected:

1. Line length
2. Power of the Daubechies 4 wavelet transform
   a) Power D3; 16 - 32 Hz
   b) Power D4; 8 - 16 Hz
   c) Power A4; 0 - 8 Hz
3. Mean cross correlation
4. Sample entropy
5. Fast weighted horizontal visibility
   a) Mean degree
   b) Mean strength

In this Chapter the selected features are described in more detail. In the next Chapter (*Chapter 6*) the study of the performance of these features on our EEG recordings is presented.

5.2 Line length

The first selected feature is line length. Line length is calculated by taking the absolute difference between the amplitudes of every successive point in time. This results in the calculation of the vertical distance between samples.

Translating this to the EEG, when a seizure occurs, changes in frequency and amplitude are expected. Line length is sensitive to these changes, and therefore probably able to detect the seizures.

Several studies mentioned line length as a promising feature for seizure detection [52, 12, 24, 32, 38]. In a review by Logesparan et al. [38] it was concluded that out of the 65 discussed features, line length and relative power in the $12.5 - 25Hz$ wavelet coefficient band were the best performing features. Beside performance in discriminating between epileptic and normal background EEG, they also took the complexity of the feature into account to study the applicability for online use. Since relative power is more complex to compute, line length might be preferable for online use. Logesparan et al. mentioned a

sensitivity of 85.4% and specificity of 52.1% for the line length feature. Mainly the sensitivity value seems promising. These results were based on 172 hours EEG data of 24 adults and 47 seizures.

In 2015, Logesparan et al. [39] discussed five normalization techniques for the line length feature and concluded that *median decaying memory* was the best approach. This normalization corrects for amplitude variations over time and variations between people. This method normalizes the value of line length by relating the considered line length value to the median value of line length calculated in previous EEG sections. In this study the feature line length is computed with the normalization technique *median decaying memory* according to the studies of Logesparan [39, 38].

Because subtle seizures do not stand out for their amplitude increase, it is hypothesized that line length will not be efficient for those seizures. Nevertheless, because of the promising expectations from literature, we implement it to see the performance on our seizure data.

Calculation EEG sections of one second with zero overlap were used. The feature was calculated for every electrode. This results in a new value per electrode for line length every second.

Per EEG section (k) we calculate line length (LL) with the following Equation;

$$LL(k) = \sum_{n=2}^{N} |y(n-1) - y(n)| \tag{5.1}$$

Where y is the raw EEG signal, n the sample index, and N the total number of samples of each EEG section.

After calculation of the line length value, normalization is carried out by the *median decaying memory* method. The normalized value of line length is calculated with the following equations;

$$Normalized\, LL(k) = \frac{LL(k)}{z(k)}$$

Where z is;

$$z(k) = (1-\lambda) median\{LL(k-1) \cdots LL(k-118)\} + \lambda z(k-1)$$

Where $\lambda = 0.99$ and the initial conditions of $z(1) = 0$ and $Normalized\, LL(1) = 0$ are used. For the first 118 epochs the median is calculated on all available epochs and with a λ of 0.92.

5.3 Power of the Daubechies 4 wavelet transform

The second feature is the power based on the Daubechies 4 (Db4) wavelet transform of the EEG signal.

Wavelet transform is a decomposition technique that is able to analyze signals at different frequency scales. Other than the Fourier transform that uses sine waves, it uses short mini waves. In this way the wavelet transform overcomes the time/frequency resolution problem of the Fourier transform. The wavelet transform is able to localize both in frequency and time. There are many possible shapes of these mini waves; Db4 is one of them (see Figure

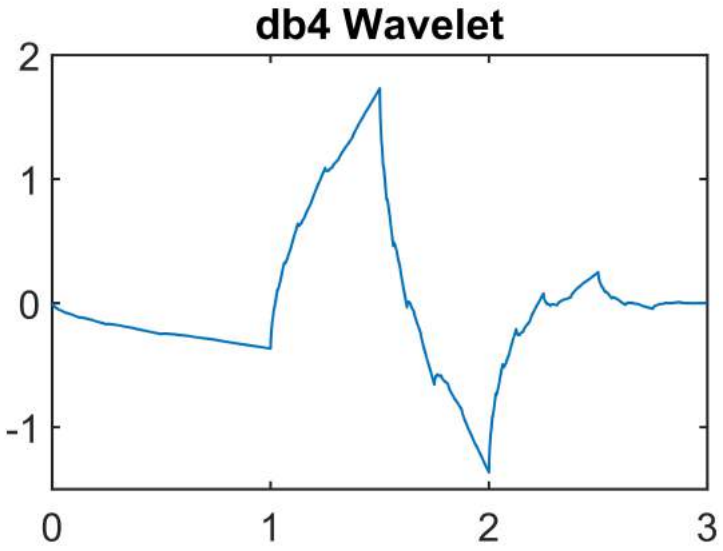


Fig. 5.1: The mother wavelet Daubechies 4 (Db4)

5.1). Once the wavelet is fixed, one can form dilations of the so called mother wavelet to focus on certain frequency bands. For high frequencies a compressed wavelet can be used and for low frequencies the wavelet is stretched out.

For the discrete wavelet transform (DWT) always the factor two is used to decompose the signal, both in time and frequency, whereas for the continuous wavelet transform (CWT) the parameters change smoothly. The CWT results in a higher resolution, but is also computational more complex.

In this study the DWT is used with the Db4 mother wavelet. The dilation of the DWT can be illustrated as a tree of filters (see Figure 5.3). In the first step the signal is decomposed into a component with lower frequencies(approximation coefficient), and a component including the high frequencies(detail coefficient). In the next levels, the approximation coefficients are further decomposed into next level of approximation and detail coefficients. In every level the time resolution and the frequency span is halved. An example of a decomposed signal is shown in Figure 5.2

In the review article of Faust et al. [13] the authors discussed wavelet-based EEG seizure detection algorithms. They state that wavelet based algorithms can capture subtle changes in the EEG signal very accurate. A wavelet is able to make minute changes clear, that are difficult to spot with the naked eye. The study of Faust showed that the Daubechies 4 (db4) wavelet is most commonly used and has the highest classification accuracy. Beside Faust et al. there are several more studies that looked in more detail to wavelets and especially to Db4 wavelets [34, 51, 60, 3, 4, 38]. Several articles based on the Db4 wavelet, claim to obtain accuracy values between 80% and 100%. Most results are based on publicly available data sets, or obtained with a small data set.

After wavelet transformation there are several features that can be computed with the transform coefficients. Several features are mentioned in literature, like for example energy and line length. We chose one features to calculate, namely the power over the decomposed signals that is used in several articles [38, 13, 4, 60]. Logesparan et al. [38] concluded that despite the relatively more complex method, the best performing feature of their study is the relative power in the 12.5-25 Hz band of the wavelet decomposition coefficient. With a sample frequency of 200 Hz, they decompose the signal with the db4 wavelet. The

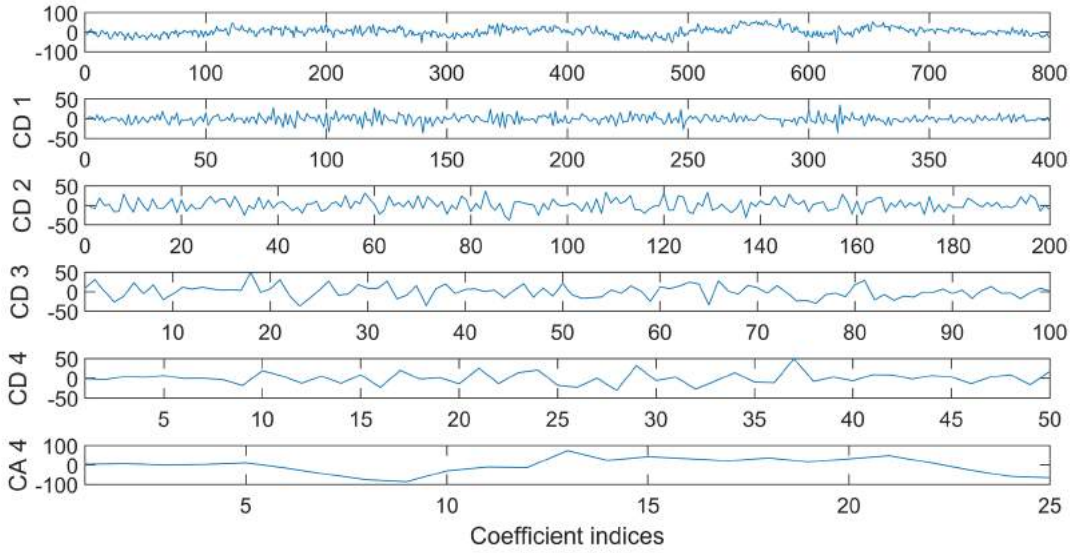


Fig. 5.2: An example of a decomposed signal by discrete wavelet transform. The top graph shows the original signal and the other graphs show decomposed versions of this signal. It can be observed that the signal frequency bands and time resolution change.

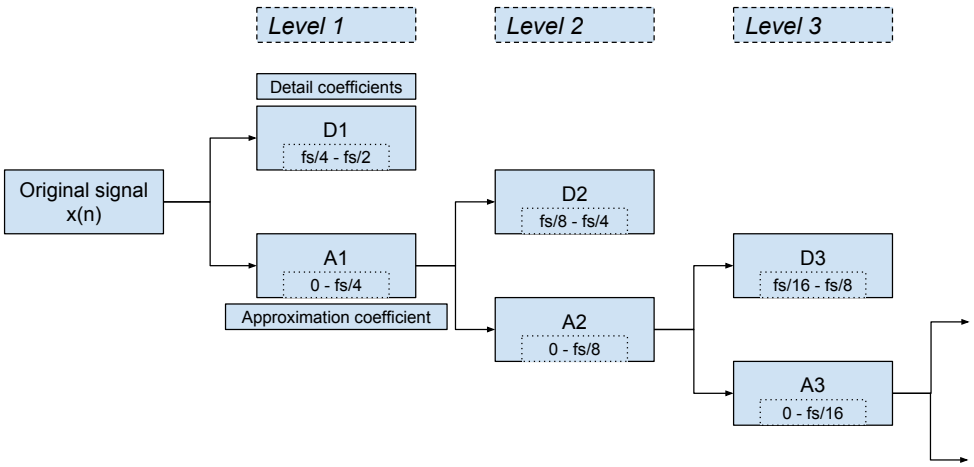


Fig. 5.3: The DWT decomposition of the signal in different frequency bands. Every step it produces an approximation(A) and a detail(D) information signal. With every step the frequency span and time resolution is halved.

detail coefficient values of level 3, spans the frequency band of 12.5-25 Hz. Logesparan et al. related the power values to a background power with using *median decaying memory* method.

Calculation EEG sections of one second with zero overlap were used. The feature was calculated for every electrode. This means that for every electrode every second a new value for power is calculated.

We will use three different scales to calculate the wavelet transform on.

- Detail 3: 16 - 32 Hz
- Detail 4: 8 - 16 Hz
- Approximation 4: 0 - 8 Hz

These bands are based on a sample frequency of 256 Hz. These frequency bands differ slightly from the 12.5-25 Hz band used by Logesparan et al.

We decomposed these EEG sections with the wavelet Db4 and calculated for the decomposition level 3, and 4, the power over the detail coefficients. This is calculated following the next equation as is written in the article of Logesparan et al. [38];

$$Power(k) = median\{DW^2\}$$

Where DW are respectively the D3, D4, and A4 coefficients. After calculation of the power, normalization is carried out by the method *median decaying memory*. This method is calculated with the following equations;

$$Normalized\ Power(k) = Power(k)/z(k)$$

Where z is;

$$z(k) = (1-\lambda)median\{Power(k-1)\cdots Power(k-120)\} + \lambda z(k-1)$$

Where $\lambda = 0.99923$ and the initial conditions of $z(1) = 0$ and $NormalizedPower(1) = 0$. For the first 120 epochs the Normalized Power is calculated on all available epochs and with a λ of 0.92

5.4 Mean cross correlation

Thirdly, the feature mean cross correlation (MCC) was selected. Cross correlation measures the similarity between two signals. MCC detects crosstalk between all electrodes. It measures the spread of the synchronicity of the electrode signals. During a seizure it is observed that the EEG shows synchronicity, therefore it is expected that MCC is able to detect seizures.

In 2008 Meier et al. [40] published a study that derived seven features for quantifying a seizure. In this study they analyzed the feature performance on different seizure types, like polyspikes, theta rhytm, delta rhythm, etcetera. Their results show that MCC achieved the best results of all studied features in discriminating between seizure en non-seizure epochs. In this study the MCC is calculated by only using the cross correlation between channels without shifting the signals in time. In 2011, Iscan et al. [28] proposes a seizure detection

algorithm that uses cross correlation. They obtained a 100% accuracy, whereas other feature studies obtained values of accuracy lower than 100% on the same data set. The study of Iscan et al. used a slightly different way of calculating the cross correlation with respect to the study of Meier et al.. Beside these two studies, there are more studies that conclude that cross correlation is a promising feature [62, 61, 29]. Nonetheless, not all articles about seizure detection show that MCC is applicable for seizure detection [19, 35, 30].

Calculation EEG sections of one second with an overlap of 50% were used. This means every half second a new value for mean cross correlation is calculated. Mean cross correlation is calculated with the following equation;

$$mean\, CC = \frac{2}{N_{ch}(N_{ch}-1)} \sum_{i \neq j} y_i y_j, \tag{5.2}$$

where N_{ch} is the number of channels, and i and j are the channel indices. y_i and y_j are the channel signals. In the calculation of the cross correlation between two signals, only the unshifted cross correlation is calculated.

5.5 Sample entropy

The next selected feature is Sample Entropy. Entropy is a nonlinear measure, that catches the degree of chaos in a system. An unpredictable signal results in high entropy values. The other way around, an ordered predictable signal will produce low entropy values. For instance, when flipping a coin, the outcome of head or tail is equal, and therefore very unpredictable, resulting in a high entropy. On the contrary, when you have a coin with two similar sides, the outcome, is very predictable and therefore the entropy of the outcome of that coin is very low.

Translating entropy to the EEG signal, in a normal healthy EEG, the signal is chaotic and random. During a seizure the signal becomes more organized and predictable. Therefore, it is hypothesized that the value of entropy drops during an epileptic seizure.

Several studies mention entropy as a possibly promising feature for seizure detection [58, 59, 31, 1, 14]. In 2012 Song et al. [58, 59] published a study about the use of sample entropy in a seizure detection algorithm. With the proposed algorithm they conclude that they can reach accuracy values of 99%. Additionally they state that the computation is fast and therefore applicable for online use. They obtained their results on a publicly available data set.

The study of Jouny et al. [31] investigated several features that address the classification of the onset of partial seizures. They selected several complexity measures to study this classification. Their results show that, among others, sample entropy was reliable to assess early seizure onset. This study used intracranial EEG recordings to obtain these results.

Acharya et al. [1] review several entropy measures. They conclude that Renyi's entropy, sample entropy, spectral entropy and permutation entropy are four features that are highly discriminative to distinguish between seizure and background EEG sections.

In this study we selected sample entropy to calculate.

Calculation We use 1 second EEG sections with zero overlap. The feature was calculated for every electrode. This results in a new value per electrode of sample entropy every second.

Step 1 First, the embedding dimension (m), and the comparison distance (r) should be specified. In this study we choose a embedding dimension of 2, and a comparison distance of 0.2 times the standard deviation of the considered EEG section, just as in the study of Song et al [58, 59] and Acharya et al. [1].

Step 2 Given N data points from a time series (x), the data is converted to vectors, defined as $X_m(i) = [x(1), x(i+1), ..., x(i+m-1)]$, for $1 \leq i \leq N-m+1$. These vectors comprise m consecutive x values, starting at the ith sample.

Step 3 The distance between vectors $X_m(i)$ and $X_m(j)$ is calculated. The distance is defined as the maximum absolute difference between their scalar components:

$$d[X_m(i), X_m(j)] = max_{k=0,...,m-1}(|x(i+k) - x(j+k)|)$$

Step 4 For every $X_m(i)$, the number of j ($1 \leq j \leq N-m, j \neq i$), such that the calculated distance is equal or smaller than r. This number per $X_m(i)$ is represented as B_i. Then, for $1 \leq i \leq N-m$,

$$B_i^m = \frac{1}{N-m-1} B_i$$

Only the first $N-m$ vectors of length m are considered, to ensure that for the next step also the vector $X_{m+1}(i)$ also exists.

Step 5 B^m is defined as

$$B^m = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r)$$

Step 6 Next, the embedding dimension is set to $m+1$ and calculations of step 2 till 5 are executed again, resulting in an A^m.

B^m and A^m represent the probability that two sequences will match for respectively$m$ and $m+1$ points.

Step 7 Finally, Sample entropy is calculated

$$Sample\ entropy(m, r) = ln[\frac{B^m(r)}{A^m(r)}] \tag{5.3}$$

Example Let $X = (1, 3, 6, 2, 5, 8, 1, 4)$. This time series includes 8 values ($N = 8$).

For this example $M = 2$, and $R = 3$. This results in
$X_2(1) = (1, 3)$
$X_2(2) = (3, 6)$
$X_2(3) = (6, 2)$

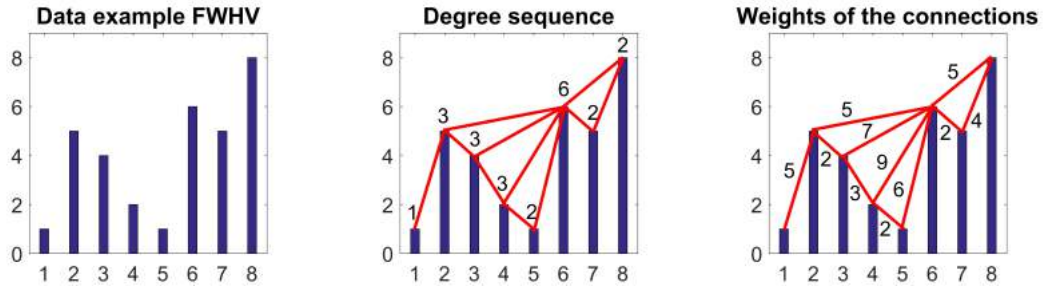


Fig. 5.4: The left bar graph shows the example data. The middle graph shows the network with corresponding degree values. The right graph shows the weight of the different connections.

$X_2(4) = (2, 5)$
...
$X_2(7) = (1, 4)$

Next, The amount of sequences, similar to the considered sequence, are summed. A sequence is defined as similar when each element of the compared sequences differ not more than $R = 3$. For instance, $X_2(3)$ is not similar to $X_2(1)$ because the first element in these two sequences differs by more than 3. The conditions of similarity to $X_2(1)$ are satisfied by $X_2(2)$, $X_2(4)$, and $X_2(7)$. Because only the first 6 ($N - m = 6$) elements are considered, $X_2(7)$ is excluded. This results in B_1 value of 2, which results in a B_i^m of $\frac{2}{8-2-1} = \frac{2}{5}$.

This can be calculated for the first 6 vectors in X_2, resulting in a vector of $B_i^2 = [2/5, 3/5, 1/5, 3/5, 2/5, 1/5]$. This results in a $B^m = \frac{1}{6} * 12/5 = 2/5$. After the calculation of B^2, we increment m to 3, and make the same calculations,

$X_3(1) = (1, 3, 6)$
$X_3(2) = (3, 6, 2)$
$X_3(3) = (6, 2, 5)$
$X_3(4) = (2, 5, 8)$
...
$X_3(6) = (8, 1, 4)$

Here, for instance, only $X_3(4)$ matches the criteria of similarity to $X_3(1)$. With these vectors, A_i^2 becomes $[1/5, 1/5, 1/5, 1/5, 1/5, 1/5]$. This results in $A^2 = 1/5$.

For this example the sample entropy results in $ln(\frac{2/5}{1/5}) = ln(2)$.

5.6 Fast weighted horizontal visibility

At last, a feature called Fast Weighted Horizontal Visibility (FWHV) was selected. The horizontal visibility graph, introduced by Lucasa et al. [36] is a way of converting the data in time series to a network. They consider the time series data as a landscape, that connects every point in time with all points that can be seen from the top of the considered one.

In 2014 Zhu et al. [69] published an article where they introduce the horizontal visibility algorithm in order to detect seizures. It was suggested as a feature applicable for online use, as it is computational fast and robust. Furthermore, the results of this study show a 100%

classification accuracy for identifying healthy from ictal EEG. They used a publicly available data set to acquire these performance results.

There are two features that are calculated in the article of Zhu et al. based on the horizontal visibility graph, namely mean degree, and mean strength. Mean degree only inspects the amount of connections, and mean strength also includes the difference in amplitude and distance of the connections.

Calculation EEG sections of 8 seconds with an overlap of 50% were used. The feature was calculated for every electrode. This results in a new value per electrode for mean degree and mean strength every 4 seconds.

A horizontal visibility graph converts the data of time series to a network. It connects each time point (x_i) with another time point (x_j) when; $x_k < x_i \wedge x_k < x_j \forall k \in \wedge i < j$. This results in a network with nodes that are connected with each other (see figure 5.4). The amount of nodes are equal to the amount of time points.

Mean degree Per node a degree (d_i) can be calculated. The degree is defined as the amount of connections a node creates with other nodes. Per EEG section the mean degree ($\bar{d}$) can be calculated by the following equation, where N is the amount of nodes in the EEG section.

$$\bar{d} = \frac{1}{N} \sum_{i=1}^{N} d_i \tag{5.4}$$

Mean strength For the calculation of the mean strength, first the weight of each connection should be calculated. The weight of each connection is defined as $|(x_i - x_j)(i - j)| + 1$. In this calculation the distance of the connection and the amplitude of the nodes is taken into account. Next the strength (s_i) per node is calculated by summing the weights of all connections of the considered node. At last, the mean strength $\bar{s}$ is calculated with the following equation, where N is the amount of nodes in the EEG section.

$$\bar{s} = \frac{1}{N} \sum_{i=1}^{N} s_i \tag{5.5}$$

Example Let $X = (1, 5, 4, 2, 1, 6, 5, 8)$, see figure 5.4. The first node is associated with the first value of X. As defined for the first value of X, the amount of connections is one. For this data, the degree sequence is (1,3,3,3,2,6,2,2). Consider the connection of node 1 to node 2, the weight of this connection is $|(1 - 5)(1 - 2)| + 1 = 5$. Calculating the strength sequence results in (5,12,12,14,8,34,6,9). For this example the mean degree of $22/8 = 2.75$, and a mean strength of $100/8 = 12.5$.

6 Sensitivity performance on detecting seizures of a selection of promising features

6.1 Introduction

Beside the commercially available algorithms, a lot other seizure detection algorithms were created and published in literature. In order to make a promising algorithm features that can discriminate between non-seizure and seizure activity are essential. Literature is filled with features that could help to detect seizures. In this study we investigated a selection of these promising features on the in this project obtained EEG recordings.

Promising features might be able to help nurses to respond to seizures more accurately. This study evaluates whether the selected features are indeed helpful to assist the nurses. This could for example be a contribution and improvement to the commercially available algorithms or resulting in another kind of output that could help the nurses, like a seizure probability value or a trend display of certain features.

Additionally, some articles claim to obtain very high accuracy values with their chosen features, higher values than validation studies of commercially available software have reached. It is of interest to inspect how the stated performance of the promising features in certain articles relate to the performance on our data set. Most literature results are obtained on publicly available EEG recordings or on a small amount of specific EEG data. With the aim of implementing these features in an online setting, it is essential to observe the performance on a more realistic data set. We believe that our data set is realistic, as it is a random selection of all kind of epileptic seizures, recorded in a year time on the EMU at SEIN.

Investigating promising features results in a better exploration of what could be expected at SEIN when implementing such features. In this chapter the sensitivity performance of the features on our previously obtained data (see Chapter 2) is inspected. The aim of this study is to investigate whether the chosen features show a change in case of a seizure. A change would indicate that this feature might help to distinguish between seizure and normal EEG. Furthermore, it is of interest to observe whether the feature responded to those seizures, where either the nurses did not respond, or where BESA and/or AIT were not able to detect those seizures.

6.2 Methods

To study whether the features could be of added value to help the nurses respond more accurately to seizures, the feature data, calculated on several EEG recordings, was analyzed. To inspect whether the features change during a seizure, we compared a pre-seizure section with a seizure section of feature data.

6.2.1 Data selection

In order to make a good comparison between a pre-seizure section and a seizure section, a selection of the 205 EEG recordings was used based on the duration of data available prior to the seizure. At SEIN, in the clinical setting only the important parts of the EEG recordings are stored. Consequently, for some EEG recordings only a little amount of data is available prior to the seizure. This could results in a very short pre-seizure section. Moreover, the features line length and power of the wavelet transform use a normalization technique that needs time to build up a baseline. Therefore, EEG recordings containing less than 200 seconds of data prior to the first sign of the seizure (*ESO or CSO*) were excluded. Moreover, EEG recordings without an ictal EEG pattern *(without ESO and ESE)* were excluded, because the seizure section was based on the ESO and ESE.

6.2.2 Data pre-processing

Of the selected EEG recordings the data of the electrodes of the international 10-20 system were included. This results in the inclusion of the Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2. The common average montage was used; the average of all electrodes is used as the reference input for each electrode.

6.2.3 Features

For the selection of promising features, we used the following criteria. We preferred features that were stated as computational fast enough to be implemented in an online system. Further, features that aimed to detect seizures with the shortest possible delay were favored. Lastly, features that were promising for more difficult seizure patterns were preferred.

Literature is filled with possible interesting features for online seizure detection. A fairly arbitrary selection was made while keeping the criteria described above in mind. It was attempted to get a range of features that address different kind of characteristics of the EEG seizure patterns. Because of time constraints and reproducibility of certain features not all promising features found in literature were used. It should be noted that the chosen features represent a subset of a lot of promising features. Consequently, there might be missing some very promising features in the subset used in this study.

We selected five categories of features;

1. Line length
2. Power of the Daubechies 4 wavelet transform
    a) Power D3; 16 - 32 Hz
    b) Power D4; 8 - 16 Hz
    c) Power A4; 0 - 8 Hz
3. Mean cross correlation
4. Sample entropy
5. Fast weighted horizontal visibility
    a) Mean degree
    b) Mean strength

Detailed information about the features is described in Chapter 5.

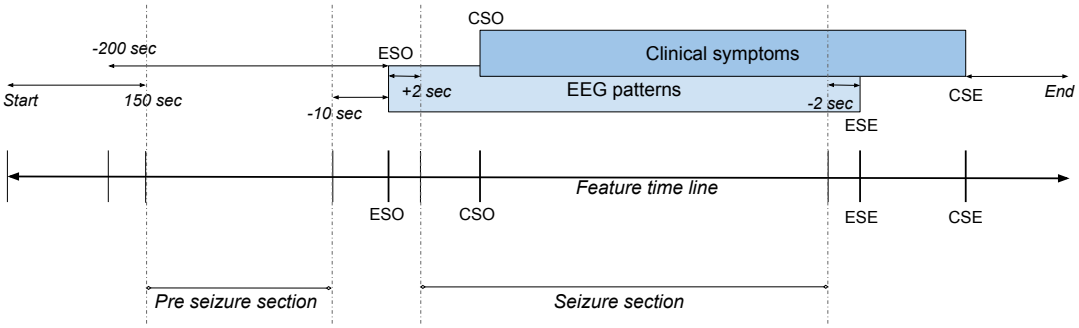


Fig. 6.1: The boundaries of the pre-seizure and seizure section. *CSO = Clinical seizure onset, CSE = Clinical seizure end, ESO = Electrographic seizure onset, ESE = Electrographic seizure end.*

6.2.4 Pre-seizure versus seizure section

The pre-seizure and seizure sections were defined as illustrated in Figure 6.1. The pre-seizure section was selected as the feature data from 150 seconds after the start of the EEG recording till 10 seconds before the first sign of the seizure (*ESO or CSO*). For the seizure section, the data between two seconds after the ESO and two seconds before the ESE was selected.

Difference between median values of pre-seizure and seizure section Per EEG recording, per electrode, the pre-seizure feature data was compared to the feature data of the seizure section. For this comparison, it was first tested whether the data was normally distributed. Then, the feature values of the two sections were compared with statistical tests. Since most data was not normally distributed, the Mann-Whitney U test was used. This test tests the hypothesis that the data comes from distributions with the same median value.

For the electrodes that showed a significant difference, it was calculated whether the median value of the seizure section was increased or decreased with respect to the median value of the pre-seizure section.

Separability between pre-seizure and seizure section Of the electrodes that showed a significant difference the size of the difference between the seizure median and the pre-seizure median value was investigated. In this study this value will be defined as a measure of *separability* of the two sections. We calculated the separability with help of the variation in the pre-seizure section. This variation was defined as the difference between the pre-seizure median value and 95th or 5th percentile. The difference between the median values was expressed in amount of pre-seizure variation, see equation 6.1. In this way the outcome results in a value of separability between the pre-seizure and seizure section. For electrodes where the median value of the seizure was lower than the value of the pre-seizure section, the 5th percentile score was used and for changes where the median value of the seizure is higher than the value of the pre-seizure section, the 95th percentile was used.

$$Separability = \frac{Median(Pre) - Median(Sei)}{abs((p95/5\ value - median(Pre)))} \tag{6.1}$$

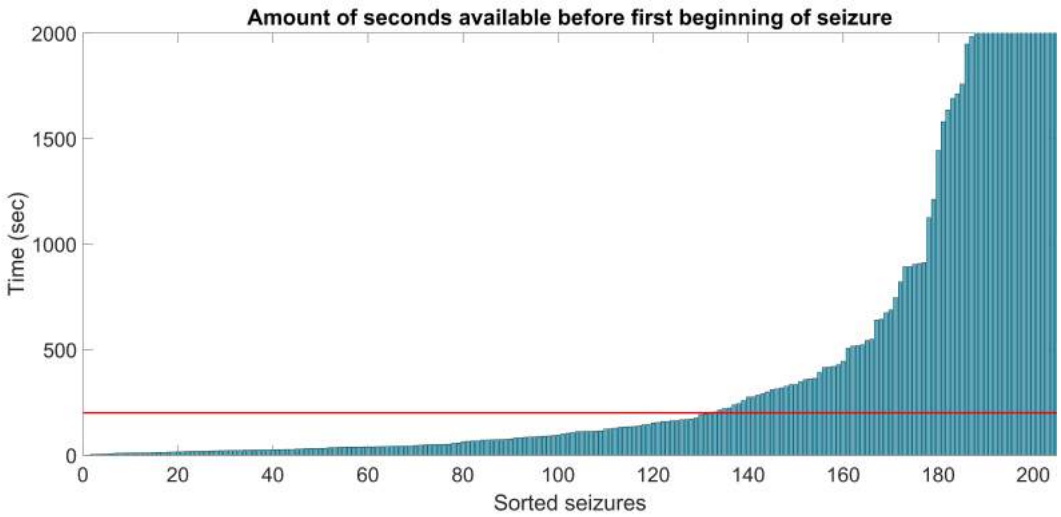


Fig. 6.2: The amount of available data prior to the first sign of the seizure *(CSO or ESO)* per EEG recording is displayed. The horizontal line represents the 200 seconds of data availability preceding the seizure. 74 seizures contained more than 200 seconds before the first start of the seizure.

6.2.5 Subgroup analysis

AIT, BESA, and Nurse response Lastly, the performance of the features was inspected with respect to the groups of seizures were either the nurses did not respond to, or the groups were BESA or AIT was not able to detect the seizures. We inspected how many undetected seizures had significant changes in the selected features.

EEG characteristics Furthermore, the previously scored EEG characteristics (see Chapter 2) were considered, to observe the feature changes per EEG characteristics group. The separability values were calculated per subgroup according to Equation 6.1.

6.3 Results

6.3.1 Data selection

Seizures that contained less than 200 seconds of EEG data prior to the first sign of the seizure were excluded. Figure 6.2 shows the amount of available data per EEG recording preceding the seizure. Of the 205 EEG recordings, 131 seizures were excluded for this study based on data availability prior to the seizure. Out of the remaining 74 seizures, one seizure was excluded, since it did not contain ictal EEG patterns. This resulted in 73 selected seizures for this study. It was inspected whether there was a bias in the selection of these seizures. We compared the included and excluded group in terms of distribution of seizure length and EEG characteristics. The selected seizures showed significantly longer seizures ($p=0.01$). For the EEG characteristics there was no significant difference between the two groups. Figure 9.4 and 9.3 in the supplementary materials illustrate the differences in length and EEG characteristics for the included and excluded recordings.

Tab. 6.1: Results of significant feature changes

	Line length	Wavelet D3	Wavelet D4	Wavelet A4	MCC	Sample Entropy	FWHV Degree	FWHV Strength
Amount of seizures (%)								
>1 significant electrodes	100	100	100	100	97.3	100	97.3	97.3
Increase	97.3	94.5	97.3	97.3	91.8	69.9	74.0	89.0
Decrease	26.0	34.2	21.9	19.2	5.5	83.6	49.3	86.3
>5 significant electrodes	98.6	100	98.6	91.8	-	98.6	86.3	91.8
Increase	93.1	93.1	89.0	82.2	-	46.6	54.8	64.4
Decrease	9.6	11.0	8.2	5.5	-	54.8	28.8	41.1
>10 significant electrodes	95.9	93.1	91.8	83.6	-	90.4	60.3	68.5
Increase	84.9	82.2	80.8	76.7	-	31.5	35.6	20.5
Decrease	4.1	5.5	5.5	5.5	-	45.2	17.8	9.6

MCC = mean cross correlation, FWHV = fast weighted horizontal visibility

6.3.2 Features

Figure 6.3 shows an example of all features of seizure 12 of the T7 electrode. Additionally, it shows an example of two corresponding boxplots displaying a significant difference between the pre-seizure and seizure feature data.

Per feature per electrode it was calculated whether the feature data of the pre-seizure section was statistically different in terms of median values to data of the seizure section. Figure 6.4 illustrates how many electrode channels per feature showed a significant difference between the pre-seizure and seizure sections. Since the feature mean cross correlation is not calculated per electrode, only one value is shown per seizure. Additionally, the figure shows the distribution of median increases and decreases among the significant channels. Table 6.1 shows the results of the features on seizure level. It shows for how many seizures more than one, more than 5, and more than 10 electrodes responded to the seizure.

For the features line length, the power in the wavelets, and the MCC we mainly observed an increase of the median value in case of a seizure. For the sample entropy, and the strength and degree of the FWHV, there is more spread between the increase or decrease of the median values. Further, it is noted that the sample entropy and FWHV show less significant responses with respect to the other features.

Separability For every electrode channel with a significant feature change the separability value is calculated according to Equation 6.1. Figure 6.5 shows the results of these separability values. This figure illustrates that for line length, the power over the wavelets and the MCC the majority of changes shows a clearly separable increase of the median value with respect to the pre-seizure section. For the features sample entropy, FWHV degree and strength, there is more spread in the decrease and increase of the feature data.

Lastly, all the feature data of the electrodes with a significant change were plotted in time. Figure 6.6 shows the significant data in time, the data with an increased median value is separated from the data with a decreased median value. It shows that for the features line length and the power over the wavelets the increase data dominates. For the MCC the signal shows outliers, which results in less clear observable changes. For the FWHV degree, strength, and sample entropy clearly two signals are shown, one signal with an increase of the median value, and one with a decrease of the median value.

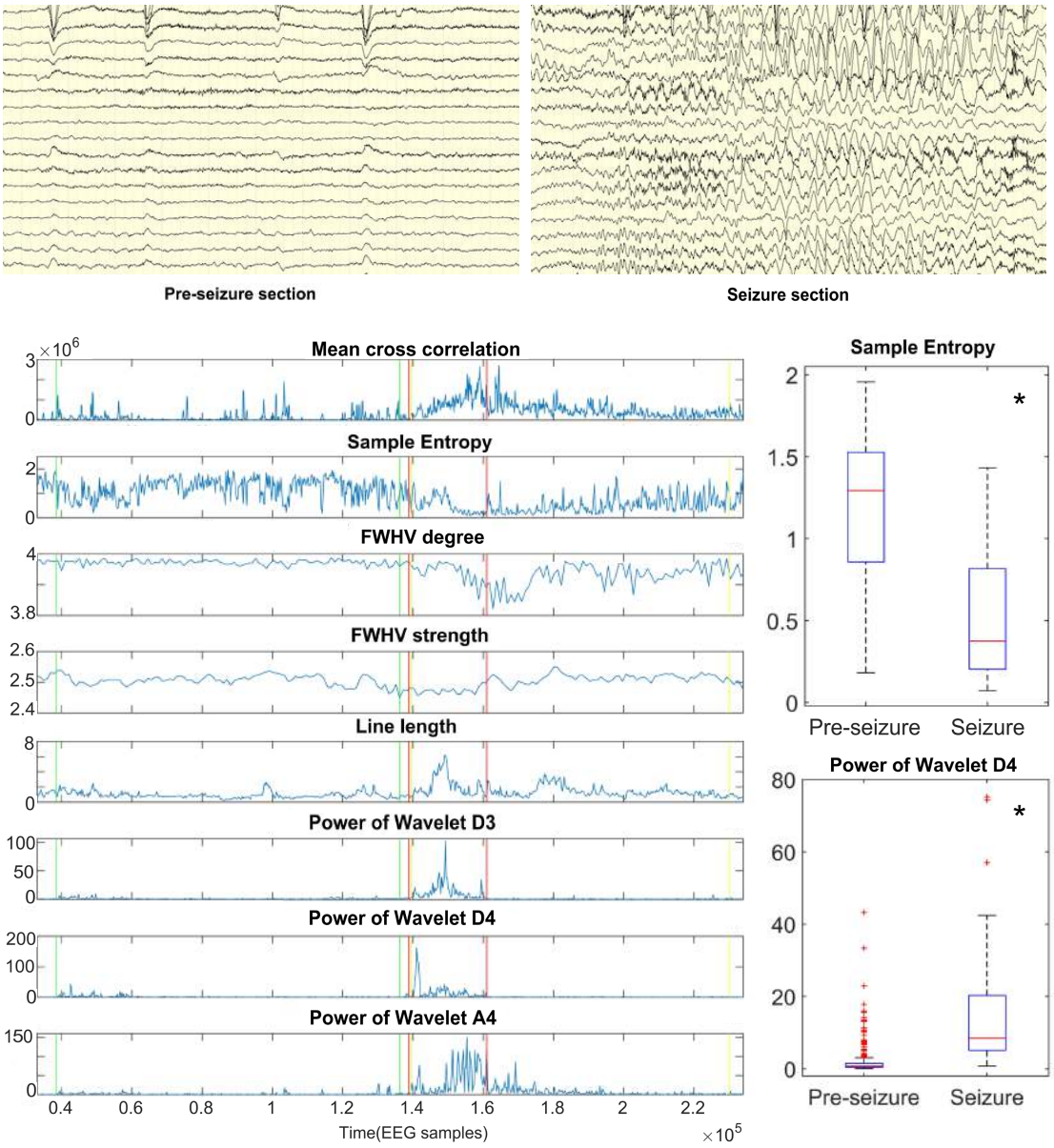


Fig. 6.3: An example of the features of the T7 electrode of seizure number 12 are displayed. The red vertical lines represent the boundaries of the electrographic seizure (ESO and ESE), and the yellow lines represent the boundaries of the clinical seizure (CSO and CSE). The green lines represent the pre-seizure section. The boxplots represent the feature data of the pre-seizure data and the seizure data.

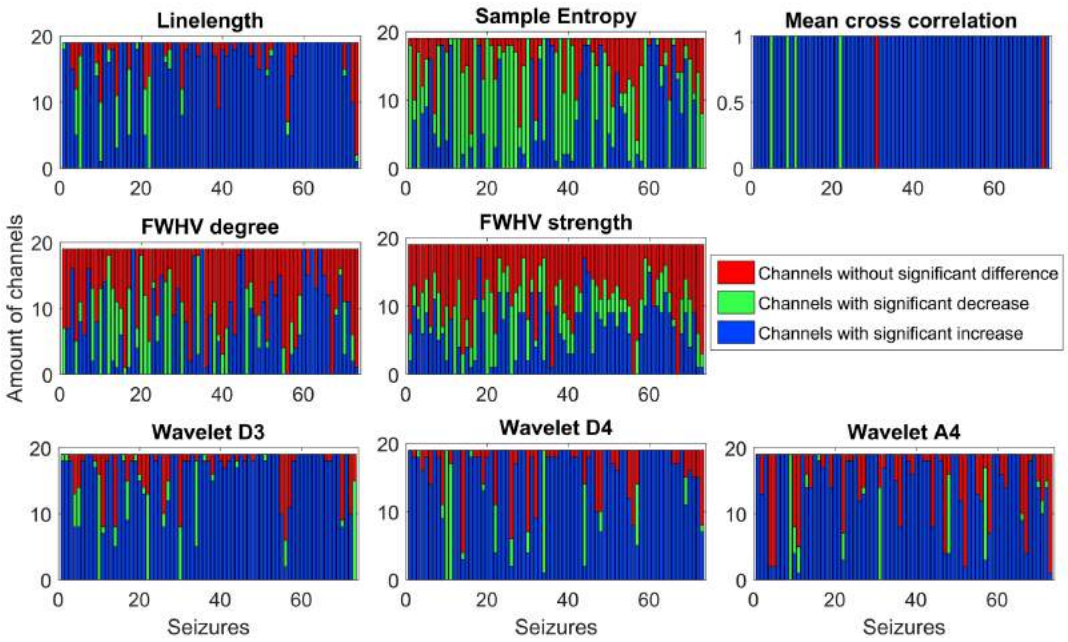


Fig. 6.4: Per feature the amount of channels that showed a significant difference between the pre-seizure feature data and the feature data of the seizure section is displayed. Note that for the mean cross correlation there is no value per electrode, but only one outcome per feature. Therefore, this feature shows either a difference, or no difference at all.

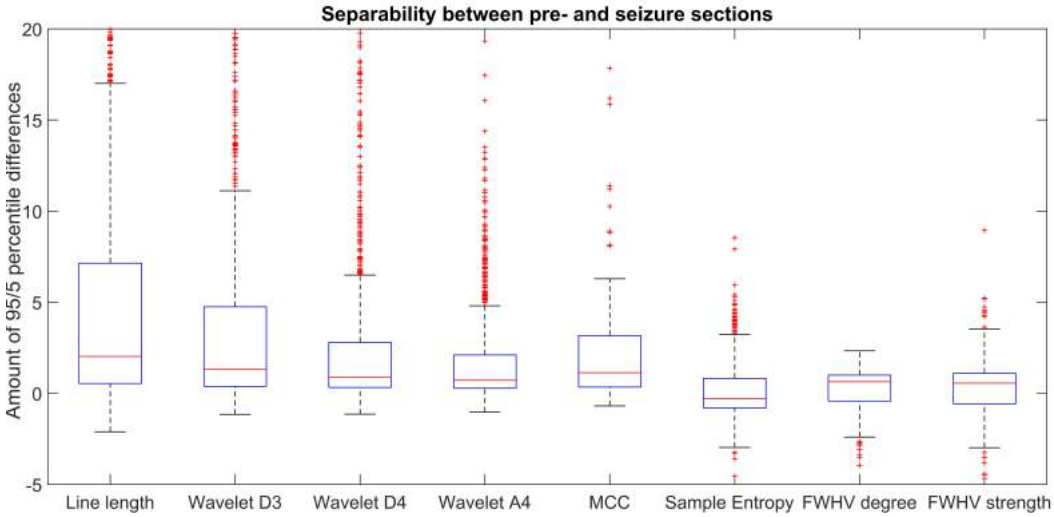


Fig. 6.5: The differences between the medians of the pre-seizure section and seizure section of the electrodes were there was a significant change are displayed. The difference is expressed with respect to the variation of the pre-seizure section. For the values of line length and the power over all wavelets, the outliers (up to 150) are not all shown in this graph.

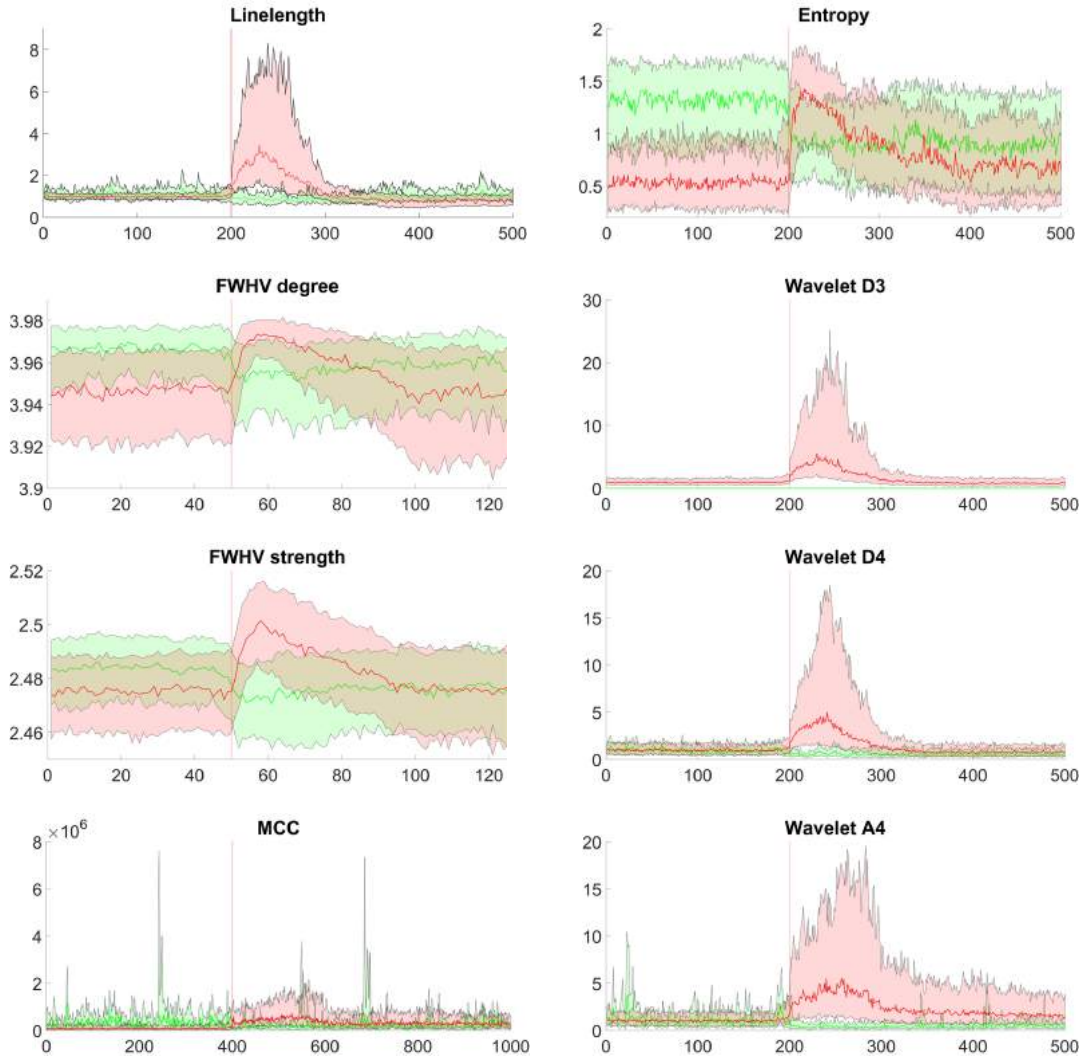


Fig. 6.6: The summed data of the the significant electrodes in time is shown. The red graphs show the significant data with an increase in median value and the green graphs the significant data with a decrease in median value. The vertical line represents the ESO. The graphs show the median value with the 25% and 75% intervals.

6.3.3 AIT, BESA, nurse response

Of the 73 selected seizures, BESA was able to detect 46 (63.0%) seizures, AIT was able to detect 55 (75.3%) seizures, for 50 (68.5) seizures the nurses responded, and for 6 seizures already medical staff was present. Table 9.1 in the supplementary materials shows the amount of electrodes per seizure that showed a significant response in the features of respectively the not detected groups of AIT, BESA, and the nurses. For all features significant changes are observed for the majority of the seizures. The features line length, power over the wavelet coefficients and the MCC seems to perform best based on significant observed differences.

For 5 seizures, nor BESA, nor AIT, nor the nurses noticed the seizures. In all of the five seizures, several features showed significant responses. Only for one seizure the FWHV based features did not show changes. Three of these five seizures did not obtain a EEG characteristic score higher than two, the other two seizures no higher score than 3 (How the scoring was executed see Chapter 2). Four of the five seizures were relatively short (range 8-30 seconds), the other recording showed a seizure of approximately 50 seconds of very subtle activity in only a very small selection of electrodes. Two of the five seizures showed some muscle artefacts. Figure 6.7 shows an example of a seizure that was not detected by any modality (BESA, AIT and/or nurses) but showed some significant results, as shown in the figure.

6.3.4 EEG characteristics

Lastly, differences in median values between the subgroups based on the EEG characteristics were investigated. Of the 73 seizures, 3 were scored as very subtle(*1*), 24 subtle (*2*), 26 as clear (*3*), and 14 as very clear (*4*). The 6 remaining seizures were not scored, since already medical staff was present in the room. Figure 6.8 shows the results of all the features and their different subgroups. For the features line length, sample entropy, and the power of the wavelet coefficients it is observed that for the very subtle (*1*) and very clear (*4*) seizures these features show better results in median difference than for the averaged EEG characteristics score of 2 and 3 ($p < 0.05$). Further, for line length and the power of the wavelet coefficients there is a gradual increase from the subtle group (*2*) to the very clear (*4*) seizures.

6.4 Discussion

In this study the sensitivity of a selection of promising features was studied on EMU EEG recordings. For the majority of seizures the features showed significant changes. The features line length and power of the wavelet coefficients produced significant changes in the most seizures with the most electrodes. For respectively 84.9% and 82.2% of seizures line length and the power of wavelet produced a significant increase in more than 10 electrodes. When observing the separability in the feature signal, also these two seizures showed the most difference between the pre-seizure and seizure feature data.

Furthermore, it was shown that for the seizures that BESA, AIT, and/or the nurses missed, the features line length, power over the wavelets, MCC, and also sample entropy showed convincing results in terms of amount of significant changes. Therefore, these features could be of added value. Further, in the subgroup analysis based on the different EEG characteristic groups, it was shown that not only to the very clear but also to the subtle seizures the features responded.

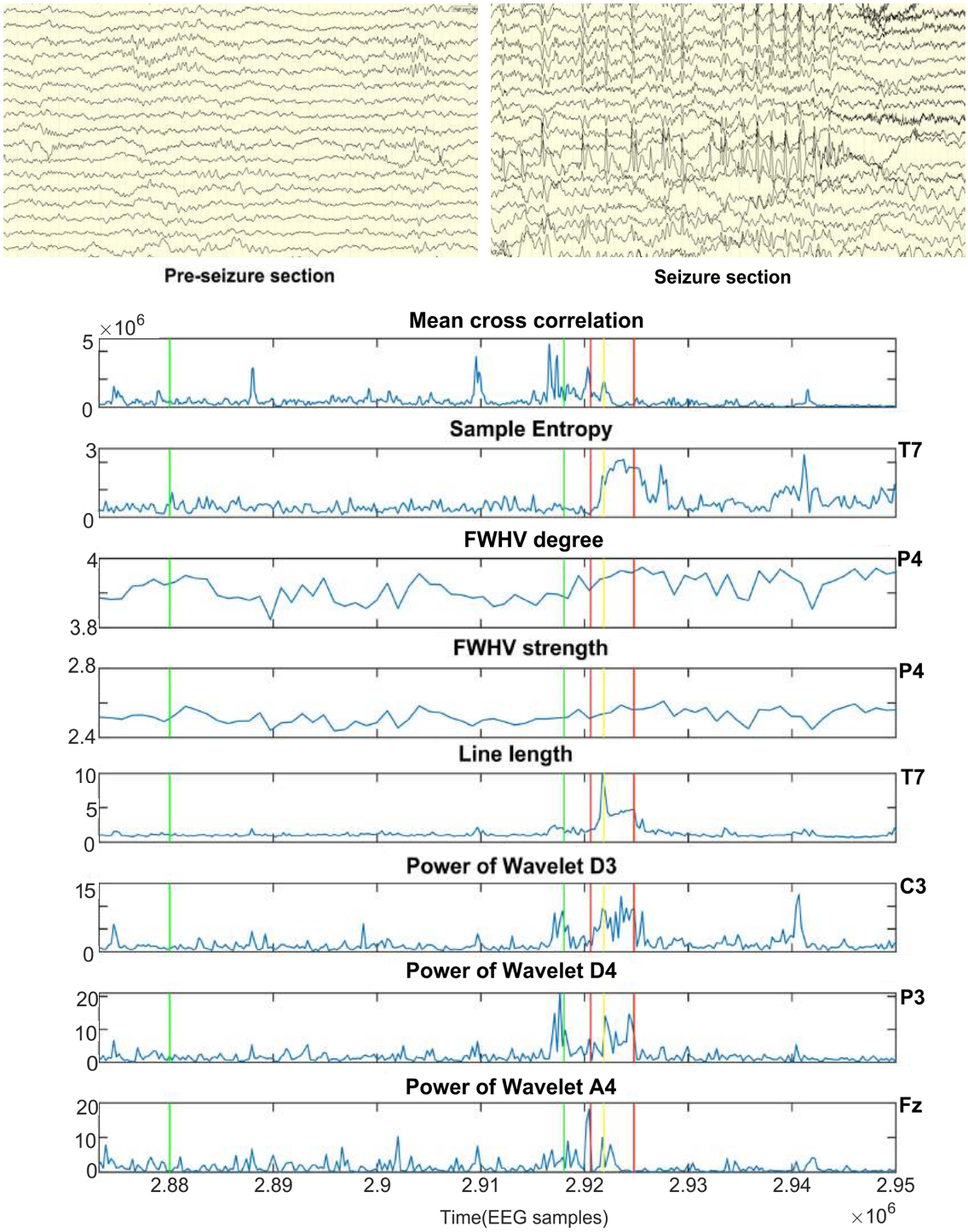


Fig. 6.7: The feature and EEG data of seizure 36 are shown. This seizure was not detected by the nurses, BESA, and AIT. The green lines represent the pre-seizure section, the red lines the electrographic seizure *(ESO and ESE)* and the yellow lines the clinical seizure *(CSO and CSE)*. On top a part of the EEG recording in the pre-seizure section and in seizure section are illustrated.

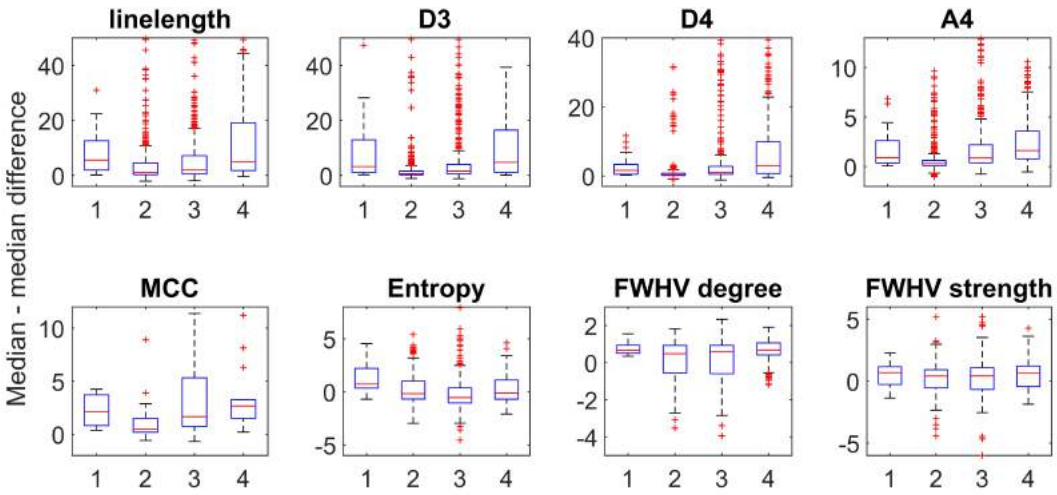


Fig. 6.8: For each feature the boxplot of the median differences calculated using equation 6.1 are shown. Only the differences of significant channels are shown. On the x-axis the different EEG characteristics groups are displayed from very subtle (1), to subtle(2), to clear(3), to very clear(4) EEG seizure pattern. The first group contains 3 seizures, the second 24, the third 26, and the fourth group 14 seizures.

We should be aware that for the feature line length also the false positive rate is very important, as this feature responds to amplitude and frequency changes. Artefacts normally are also depicted with major amplitudes. Logesparan et al. [38] obtained a specificity of 52.1% in their study, which might be not very user-friendly in online use. Nevertheless, in combination with other features, line length might be of good use to help the nurses on the EMU.

In the results it was shown that the changes in MCC were promising based on amount of significant changes, but due to the amount of variation in the signal, it might be difficult to really distinguish seizure from pre-seizure data. Furthermore, also this feature is very sensitive to amplitude changes. Still, we believe that a measure for electrode cross-talk could be very beneficial for seizure detection use, but whether mean cross correlation is the best option could be questioned. In literature also people question mean cross correlation and also other possible measures for crosstalk are suggested [68, 53, 41, 65].

The features of power based on the wavelet coefficients showed very promising results, both in amount of significant channels and in the size of the difference. Because the wavelet coefficients focus on a certain frequency band it is expected that the feature suffers less from artefacts, which is a positive aspect of this features category.

For the feature sample entropy sometimes the signal showed a promising increase instead of the expected drop of entropy. This might be explained by the amount of artefacts during the seizure. With these artefacts, the signal might become more chaotic. If artefact rejection is introduced, these results are expected to change [14].

Our results for the features based on the FWHV showed much less promising results than the 100% accuracy that was mentioned in the article of Zhu et al. [69]. In this case the used recordings might play a role or the classification method mentioned in the article Zhu et al. published. In our study we did obtain several significant changes, but less impressive compared to the other features.

For the subgroup analysis based on the EEG characeristics, the results show limitations, as only the first 60 seconds are taken into account for the EEG characteristics. For some subtle seizures the electrographic patterns might have evolved in very clear seizures.

In this project raw EEG was used without any artefact rejection. This might have influenced our results. Some features might have performed better with artefact rejection. However, other features might have performed poorer.

6.5 Conclusion

The features studied in this study are capable in showing changes when a seizure occurs in at least some electrode channels. Line length and the power of the wavelet coefficients showed the most promising results. Furthermore, we observed that for the missed seizures by BESA, AIT, or the nurses, the features line length, the power of the wavelet coefficients, MCC, and sample entropy might be of added value. The variation in the MCC feature might make this feature less applicable in the EMU setting.

Definitely, more research is needed to conclude whether the features really could contribute to BESA or AIT, or that the feature could be of direct use in the EMU at SEIN. The latency values of the feature changes is essential for the online setting. Furthermore, the amount of false positive alarms that might occur by implementing features, is also an important aspect to study.

Regarding the results the feature line length, the power over the wavelet coefficients, and sample entropy showed the best results and therefore it is advised to study these features more intensively.

7 Discussion

This project addressed the seizure nurse response on the EMU at SEIN and possible improvement possibilities with help of automatic seizure detection methods based on the EEG. This chapter presents some discussion points to take into account for an implementation tool to help the nurses on the EMU respond more accurately to seizures.

Artefacts The scalp EEG is often contaminated with artefacts. These artefacts can arise from various sources, like the patient themselves, caused by amongst others muscle contractions, eye blinking, or movements. For the field of automatic seizure detection this is a challenge, since it could cause false positive detections on the one hand and on the other hand, seizure activity often is obscured by these artefacts. In this project, when studying the features, these artefacts might have influenced the outcome. Features might have responded to artefacts, or features did not perform as expected because of the artefacts.

Inter-patient variability Another obstacle for automatic seizure detection methods is the inter-patient variability. A seizure pattern for the one patient, does not always resemble ictal activity of another patient. For one specific patient, an algorithms can be tweaked to perform very good, but for the next patient it could perform poorly. This is a difficult problem. There are many patient specific algorithms published that use for example pattern recognition. These methods however always need a certain amount of seizures to learn, before they perform good. This is an attractive method for monitoring purposes over a long period of time. Though, on the EMU this approach is not preferred due to the fact that we want to detect the first seizure as well, as it might be the only seizure that occurs during the EEG recording.

False positives In many articles the false positive rate is mentioned as major reason why all the possible seizure detection methods are not yet implemented. It is expected that nurses with a high false positive rate, will ignore the alarm. On the EMU we should be aware that the false positive rates mentioned in literature have to be multiplied by eight, since we can monitor eight patients simultaneously. Based on interviews and questionnaires on the EMU at SEIN, our nursing staff regards a false positive rate of approximately 0.5 per hour as acceptable. It could be questioned how the acceptance is when a online tool really is implemented.

Sensitivity At SEIN also a significant part of the EEG recordings contain seizures without epileptic origin. Nurses need to response to these seizures as well. The sensitivity that is mentioned in literature could therefore in the clinical setting be experienced lower. For seizure detection on recordings of patients with PNES, it is expected to result in no alarms, since the EEG does not show epileptic patterns during the PNES seizure. This decreased sensitivity could harm the user-friendliness of the automatic seizure detection method.

ECG Several studies have documented changes in the ECG during a seizure [11, 64, 37, 46]. Zijlmans et al. [70] published an article in which they researched heart rate changes and ECG abnormalities during epileptic seizures. They showed an increase in heart rate of more than 10 beats per minute in the majority of seizures. Furthermore, they showed that a noticeable part of the seizures, the ECG changes preceded both electrographic and

clinical onset. In some seizures they observed that where the seizure activity could not be registered in the EEG signal, the ECG could helped to notice the seizure. In the EMU the ECG is recorded with two supraclavicular electrodes. Using the ECG signal might be a promising addition to a seizure detection method.

Output In almost all seizure detection articles an algorithm was created that in the end results in an alarm in case of a seizure. We believe it should be questioned whether that is the best output method on the EMU at SEIN. The on/off sound alarm and false positives might be not accepted by the nurses in the EMU. We expect that another output might be more applicable and user-friendly. For example Persyst already published a seizure probability value. This value changes over time. Another possibility is a feature or combination of features that is displayed over time. One could see it as a simplified version of the EEG that can grab the nurses' attention when the signal changes. We believe that with such an output the false positives will be more accepted by the nurses.

Conclusion

8

In this project we studied the seizure nurse response on the EMU and possible improvements with help of commercially available software or features.

With a nurse response of 67% we conclude that improvements in responding more accurately to seizures is possible. Improving this increases the quality of the EMU diagnostics and safety. We observed that sounds accompanying seizures helped to alert the nurses. Further, it was noticed that to some seizures with clear EEG patterns no nurse response was observed. It is noticed in literature that automatic seizure detection methods perform better on clear EEG patterns. This suggests that by adding a tool that detects seizures in the EEG could improve the nurse response.

For the study where BESA and AIT were investigated, we conclude that AIT was able to detect the most seizures. For the improvement in response time in the offline analysis BESA performed better than AIT. Nevertheless, when taking the ten seconds delay of BESA into account, AIT performed better. For the real online improvement more research is needed.

From the feature analysis we concluded that the power of the wavelet coefficients and line length showed the most promising results. Moreover, in seizures that were missed by BESA, AIT, and the nurses, these features did show changes when the seizure occurred. This suggests that the features power of the wavelet coefficients and line length could be of added value to the nurse response. Nevertheless, more research needs to be carried out, to study other aspects like false positive rates and latency.

Lastly, we believe that another kind of output, other than an alarm, should be considered. It is expected that an on/off audio alarm is not user-friendly on the EMU. A trend display or seizure probability value could be more efficient and applicable on the EMU. Additionally, also the ECG information should be considered, since it could contain information about seizure occurrence, even when the EEG does not show changes. Furthermore, the EEG sometimes seems to precede clinical and electrographic changes.

Recommendations

9

AIT We advise to consider AIT as a possible partner in constructing a seizure detection tool specifically for SEIN. AIT showed promising results in our project. Thereby, AIT is a research institute and therefore it is expected that they, more than other commercially companies, might be open for such a project.

A technical physician could be a great partner in this project, since he/she can build the bridge between the programmers of AIT and the clinical setting at SEIN.

Output It is advised to study the possibility of showing a trend display over time of certain features. One could see this as a simplified version of the EEG, a version of the EEG that nurses could analyse very easily. For example when line length is used and the value increases, the attention of the nurses should be grabbed. This could be done with a trend display in combination of color changes on the screen.

Additionally, for safety reasons it is advised to combine such a trend display with a more specific seizure detection alarm, to make sure that major seizures are never missed.

ECG We advise to study the ECG signal in more detail in order to implement it in a system to help the nurses respond to seizures. The signal could be of great added value to the EEG.

Innovation We believe that SEIN as a specialized expertise centre should stand out for their high tech innovations. Investing in innovating projects and implementations in the clinical setting helps the expertise centre to increase the quality and deliver clinical care that cannot be achieved at the hospitals. The modern EMU is a perfect place to let those innovations take place.

We believe that SEIN could benefit in many ways from these improvements. Clinical care, quality improvements, other hospital's interest, patient's interest, published articles, and thereby blooming of the whole centre.

Supplementary materials

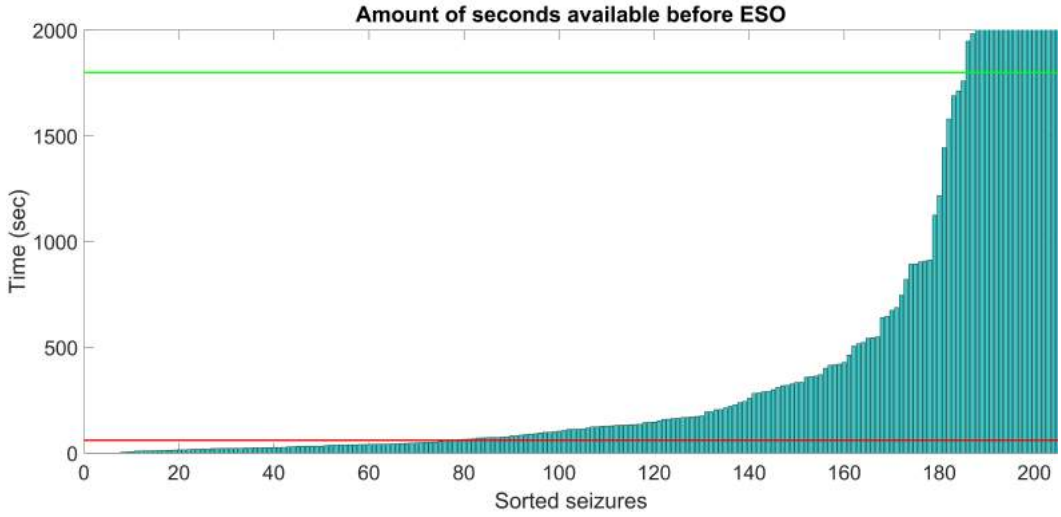


Fig. 9.1: This figure shows the amount of seconds available before ESO (*Electrographic seizure onset*) per seizure. The data is sorted based on the amount of data available prior to ESO. 20 seizures contain more than 30 minutes of data preceding the ESO and 76 seizures have less than one minute of data available before the start in the EEG. The horizontal lines represent 60 seconds and 30 minutes.

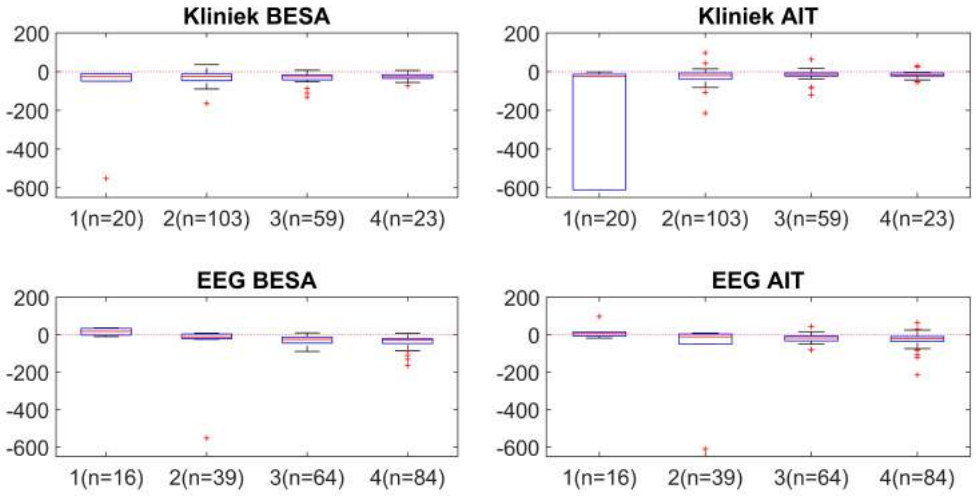


Fig. 9.2: This figure shows a boxplot of the response time of the different groups of BESA and AIT. For the very subtle (clinical characteristics = 1) of AIT there seems to be more improvement than to the clinically more clear seizures. This difference however, calculated with the Mann Whitney U test, resulted in a p-value of 0.32.

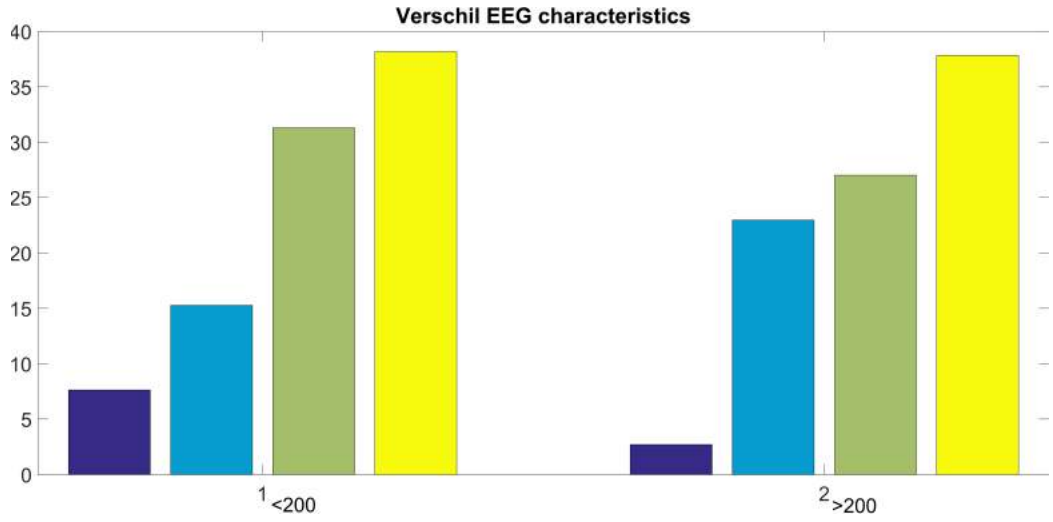


Fig. 9.3: This figure shows the difference in EEG characteristics between the included and excluded seizures. There was no significant difference between the two groups. Left the group with EEG recordings that included less than 200 seconds prior to seizure, right the seizures with more than 200 seconds preceding the first sign of the seizure.

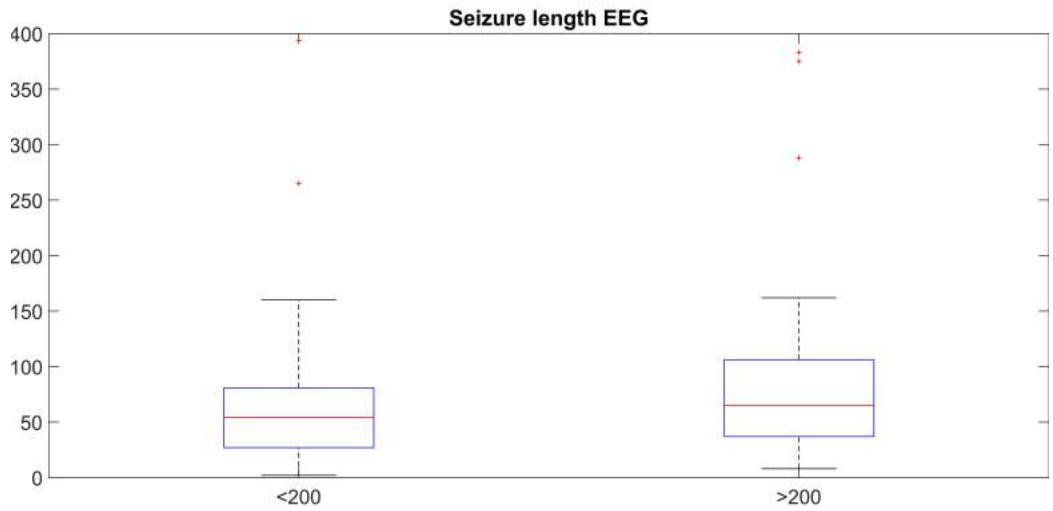


Fig. 9.4: This figure shows the difference in EEG seizure length (ESE - ESO) between the included and excluded seizures. The included group showed significant longer seizures compared to the excluded group. Left the group with EEG recordings that included less than 200 seconds prior to seizure, right the seizures with more than 200 seconds preceding the first sign of the seizure.

Tab. 9.1: Results of significant feature changes for the undetected group of AIT, BESA and the nurses.

AIT (n = 18)	Line length	Wavelet D3	Wavelet D4	Wavelet A4	MCC	Sample Entropy	FWHV Degree	FWHV Strength
Amount of seizures (%)								
>1 significant electrodes	100	100	100	100	100	100	88.9	88.9
Increase	94.4	88.9	94.4	100	88.9	88.9	72.2	77.8
Decrease	5.6	11.1	5.6	0	11.1	11.1	16.7	11.1
>5 significant electrodes	100	100	94.4	88.9	-	94.4	77.8	72.2
Increase	88.9	83.3	72.2	66.7	-	61.1	50	50
Decrease	11.1	16.7	22.2	22.2	-	27.8	27.8	22.2
>10 significant electrodes	94.4	77.8	83.3	72.2	-	88.9	50	27.8
Increase	77.8	66.7	55.6	55.6	-	50	33.3	5.6
Decrease	16.7	11.1	27.8	16.7	-	38.9	16.7	22.2

BESA (n=27)	Line length	Wavelet D3	Wavelet D4	Wavelet A4	MCC	Sample Entropy	FWHV Degree	FWHV Strength
Amount of seizures (%)								
>1 significant electrodes	100	100	100	100	96.3	100	92.6	92.6
Increase	96.3	92.6	96.3	92.6	85.2	81.5	74.1	81.5
Decrease	3.7	7.4	3.7	7.4	11.1	18.5	18.5	11.1
>5 significant electrodes	96.3	100	96.3	81.5	-	96.3	74.1	77.8
Increase	88.9	88.9	81.5	63.0	-	59.3	48.1	55.6
Decrease	7.4	11.1	11.1	18.5	-	37.0	25.9	22.2
>10 significant electrodes	92.6	85.2	77.8	70.4	-	85.2	51.8	44.4
Increase	77.8	66.7	59.3	51.8	-	48.1	29.6	7.4
Decrease	14.8	18.5	18.5	18.5	-	37.0	14.8	37.0

Nurse (n=17)	Line length	Wavelet D3	Wavelet D4	Wavelet A4	MCC	Sample Entropy	FWHV Degree	FWHV Strength
Amount of seizures (%)								
>1 significant electrodes	100	100	100	100	94.1	100	94.1	94.1
Increase	100	94.1	94.1	88.2	88.2	76.5	64.7	88.2
Decrease	0	5.9	5.9	11.8	5.9	23.5	29.4	5.9
>5 significant electrodes	100	100	100	94.1	-	94.1	64.7	82.3
Increase	94.1	88.2	94.1	64.7	-	41.2	35.3	52.9
Decrease	5.9	11.8	5.9	29.4	-	52.9	29.4	29.4
>10 significant electrodes	94.1	88.2	88.2	76.5	-	82.3	41.2	64.7
Increase	88.2	82.3	64.7	52.9	-	41.2	17.6	11.8
Decrease	5.9	5.9	23.5	23.5	-	41.2	23.5	52.9

MCC = mean cross correlation, FWHV = fast weighted horizontal visibility

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