

Master Thesis

*Using seizure detection algorithms in the
Epilepsy Monitoring Unit to improve staff
response to seizures*

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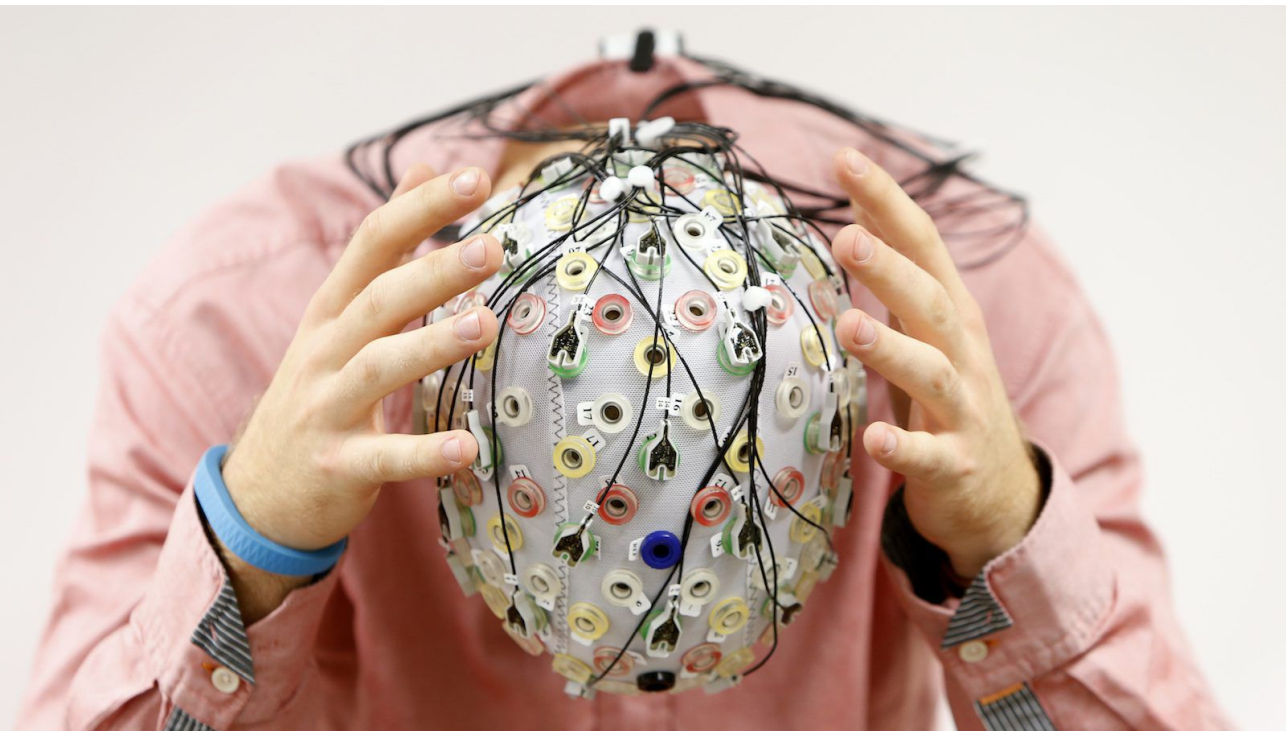
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Preface

Before you lies the thesis ‘**Using seizure detection algorithms in the Epilepsy Monitoring Unit to improve staff response to seizure**’. It was written to fulfil the graduation internship of the master study Technical Medicine at the University of Twente. I conducted this internship with great pleasure at Stichting Epilepsie Instellingen Nederland (SEIN) Heemstede from July 2016 to September 2017.

This project is a follow-up on previously performed research by Lisanne Jansen Holleboom. It is an applied research topic, with problems currently seen in clinic. I hope that SEIN can benefit from the results and recommendations given in this thesis. For me, this internship was very educational. I learned a lot about epilepsy, epilepsy care and got the possibility to grow as a person.

I would like to thank all my supervisors for their guidance during this project. I would like to thank Gjerrit Meinsma for the technical view on my project. Furthermore, I thank Gerhard Visser for his guidance and dedication during this year. Also, Fieke Cox for providing new views on my research topic. Michel van Putten for overseeing the project as chairman. I would like to thank Paul van Katwijk for his wise counsel and motivational words. And I would especially like to thank Evelien Geertsema for her daily supervision, critical view and support throughout my project.

To my other colleagues at SEIN: I would like to thank you for the wonderful time. It has been a very fun year with nice coffee breaks, game evenings and dinners. I really felt part of the research team.

Sapere aude

Nicole Rommens
Heemstede, August 31, 2017

Abstract

Background: At an Epilepsy Monitoring Unit, people with epilepsy can be admitted to answer different diagnostic questions. EEG, ECG and video are recorded and monitored by staff. When a seizure is recognized, patient safety is secured and standardized tests are performed. These standardized tests assess consciousness, cognitive and neurological functioning.

Objective: Around 33% of seizures are missed by staff at the Epilepsy Monitoring Unit of SEIN. A response time over 60 seconds is seen in 19% of responses. Research has shown that this can be improved with EEG seizure detection algorithms. However, the specificity was not researched. It remains unclear if the algorithm requires improvement before it can be used online. The goal for this project is to investigate which changes, in terms of sensitivity, specificity, latency and alarming, could make usage feasible.

Methods: EEG and ECG recordings of seizures were included in a seizure database and non-stop recordings in a 24-hour database. False positive rate for the EEG algorithms was researched. An ECG seizure detection algorithm was created to improve detection latency, which consists of the Pan Tompkins algorithm, processing of the heart rate and a classifier with self-adjusting thresholds. The performance and added value on top of the EEG seizure detection algorithm was researched. Lastly, a literature study was performed on how people respond to alarms and different alarm systems, to evaluate what kind of system would be suitable.

Results: The seizure database included 188 seizures and the 24-hour database 1235 hours of 60 patients. The EEG algorithms showed a false positive rate of 4.9 (Encevis EpiScan) and 2.1 (BESA Epilepsy) per 24 hours. The ECG algorithm showed a sensitivity of 47.8% with a median latency of 36.5 seconds and a median false positive rate of 0 per 24 hours. There was added value in terms of extra detected seizures when it would be used as an addition to the EEG algorithm. However, no faster latency was seen. Lastly, the response to alarms depends on different behavioural mechanisms, which have to be taken into consideration when designing an alarm system.

Discussion: Results show that it is feasible to use the EEG seizure detection algorithm in terms of a low false positive rate. The ECG seizure detection algorithm could be used to detect extra seizures. Further work should focus on improvement and optimization. For the alarm system, it is recommended to combine auditory and visual alarms. More research on novel alarm types is necessary.

Abbreviations

CSE = **C**linical **S**eizure **E**nd

CSO = **C**linical **S**eizure **O**nset

ECG = **E**lectro**C**ardiogram

EEG = **E**lectro**e**ncephalogram

EMD = **E**mpirical **M**ode **D**ecomposition

EMU = **E**pilepsy **M**onitoring **U**nit

ESE = **E**lectographic **S**eizure **E**nd

ESO = **E**lectographic **S**eizure **O**nset

ICU = **I**ntensive **C**are **U**nit

IMF = **I**ntrinsic **M**ode **F**unctions

PNES = **P**sycho**g**enic **N**on-**E**pileptic **S**eizures

SEIN = **S**tichting **E**pilepsie **I**nstellingen **N**ederland

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Chapter 1

Introduction

1.1 Epilepsy

Epilepsy is the most common chronic neurological disease, affecting 65 million people worldwide [2]. It is an unpredictable disease that can lead to loss of autonomy and can cause cognitive, emotional and psychological problems [3]. The mortality rate in epilepsy patients is two to five times higher than in the general population [4].

So what exactly is epilepsy? Epilepsy is a chronic disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures [5]. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [5]. This abnormal synchronisation is caused by an imbalance in excitation and inhibition [6]. Epilepsy can be caused by genetic disorders, structural or metabolic conditions (for example brain damage or malformations), but in most patients no cause is known [7].

Different symptoms can occur during seizures, depending on the site of onset and how seizures develop. Seizures can be divided into focal and generalised onset [8]. Focal seizures originate within networks limited to one hemisphere [7]. During those seizures consciousness can be lost, although some patients are awake and aware of the seizure. Focal seizures can then be divided into motor and non-motor seizures. Generalized seizures originate at some point within and rapidly engaging, bilaterally distributed networks [7], whereby consciousness is almost always lost. There are different types of generalised seizures, where the most common is a tonic-clonic seizure. A tonic-clonic seizure begins with a phase where all muscle stiffen (tonic phase), followed by a clonic phase where arms and legs begin to jerk. Epileptic seizures are sometimes confused with other types of seizures, like Psychogenic Non-Epileptic Seizures (PNES) or syncope (fainting).

A diagnosis of epilepsy can be made based on the semiology of seizures and an electroencephalogram (EEG). Around 70% of patients are seizure free with use of anti-epileptic drugs, but some are drug-resistant [6]. For those patients, surgical treatment might be an option. During this surgery, the seizure onset area will be removed. However, this is not suitable for every patient. It is important to timely identify epilepsy so a treatment can be started. Additionally, the specific seizure type and seizure onset area are essential to determine appropriate treatment.



Figure 1.1: Observation room of the EMU at SEIN Heemstede. All measured signals are displayed per patient; EEG, ECG, video and audio. Adapted from [14]

1.2 Clinical setting

People with epilepsy can be admitted to an Epilepsy Monitoring Unit (EMU), where registrations are used to answer different diagnostic questions. Registrations can be used to distinguish epilepsy from non-epileptic seizures, to determine seizure type and classification or to examine or evaluate therapeutic options [9, 10]. EEG, electrocardiogram (ECG) and video are recorded during a registration.

The EMU at SEIN Heemstede is an 8-bed unit, where all patients stay in separate rooms. Patients are admitted for up to 5 days. Per room, three to four remote control cameras are installed that can capture the whole room, except for the bathroom. The patient has an alarm button which can be used to alert staff. Patients are monitored continuously by staff in an observation room. At the EMU of SEIN this is done by specialized nurses. In the observation room, all recorded signals are shown for each room as can be seen in Figure 1.1. An intercom system can be used to communicate with patients. When a seizure is recognized by staff, patient safety is secured to reduce adverse events like falls and traumatic injuries [11]. Additionally, standardized tests are performed to assess consciousness, cognitive and neurological functioning during seizures. These standardized tests can help to determine seizure type [12, 13]. It is important to perform tests timely, since clinical symptoms can evolve during seizures.

1.3 Problem definition

Staff supervision demands skills and non-stop attention to be continuously vigilant for any sign of a seizure. Since non-stop attention is unreachable, seizures can be missed or recognized late. The study of Atkinson et. al. showed a response rate of 41% to seizures, with a mean response time over two minutes [15]. While response rate and time can vary between different EMUs, response rate is always limited by human capabilities. Seizures showing no or only subtle clinical semiology are more often missed, and seizures outside the scope of the cameras can be missed. A previous student, L. Jansen Holleboom, has researched the current performance in terms of staff response to seizures and response time at the EMU of SEIN Heemstede. Nurse response was seen in 67% of all seizures, with a median response time of 31 seconds

after the first sign of the seizure [14]. A response time over 60 seconds was seen in 19% of the responses [14]. While this is better than described in other literature [15], nurse response can still be improved.

Online seizure detection algorithms might help staff to detect seizures that are otherwise missed or recognized late. Research at SEIN showed that 66.1% of undetected seizures could be detected by an EEG seizure detection algorithm [14]. Additionally, an median improvement of -25.6 seconds in response time could be achieved [14]. While these results are very promising, the false positive rate was never researched. It remains unclear if it is feasible to use such algorithms online on the EMU at SEIN and what changes are still needed.

1.4 Aim of this project

The goal for this project is to research if it is feasible to use seizure detection systems on the EMU of SEIN and to make changes which make usages feasible. The following main question is researched:

What changes can be made (in terms of sensitivity, specificity, latency and alarming) to an available EEG based detection system to make it feasible for online use on the Epilepsy Monitoring Unit in SEIN to improve response rate and latency of nurses to epileptic seizures?

Chapter 2 explains the methods that are used throughout all chapters. It explains the complete data selection, scoring of the data and used definitions. Part of the data collection is performed by L. Jansen Holleboom and another part by myself.

In Chapter 3 the added value of EEG seizure detections techniques is reported. This provides information on the sensitivity, latency and false positive rate, if this has added value on the already present staff and which patients could specifically benefit from these algorithms. This research was partly performed by L. Jansen Holleboom.

Chapter 4 shows the methods and performance of an ECG seizure detection algorithm. The algorithm was created to improve detection latency. This chapter discusses which choices have been made in the algorithm. Additionally, information is provided on the sensitivity, latency and false positive rate and, if the algorithm has added value if it would be used on top of the EEG algorithm.

The last chapter, Chapter 5, discusses the possibilities for different alarm systems. Since the function of a detection algorithm is highly dependent on the alarms and response to alarms, this is an important research topic before implementation. The following questions were answered: How do people respond to alarms?, How does workload influence alarm response? What is known about alarm response in the medical sector? What type of alarms exist? And what is known about these alarm types?. And finally, what type of alarm system is recommended for the use of seizure detection algorithms in the EMU of SEIN?

Chapter 2

Mutual methods

Some of the methods and definitions are used throughout all chapters. Those methods are explained in this chapter. It will explain the data collection, scoring of data and the definitions that are used. Some of the methods were executed by a previous student, L. Jansen Holleboom [14]. The data collection and scoring of the seizure database were already completed. Scoring of the ECGs and the data collection and scoring of the 24-hour database was performed in the context of this thesis.

2.1 Registrations

EEGs and ECGs were recorded with a sample frequency of 256 Hz, in a frequency band of 0.01 to 1000 Hz. EEGs were placed using the international 10-20 electrode placement system [16]. ECGs were recorded with two lead electrodes placed under the left and right clavicle after polishing the skin.

For all registrations, video and audio recordings are available. After registration and reporting, EEG, ECG, video and audio files are standardly cut for data reduction to decrease storage space. Only important data of the registration is saved, like diagnostic tests and seizures.

2.2 Data inclusion

Two databases were created; a seizure database and 24-hour database. The seizure database consists of registrations with seizures that are standardly saved at SEIN. The sensitivity and latency of different algorithms can be determined using this database. False positive rate can only be determined on non-stop recordings without selection, to represent the complete setting on an EMU. Therefore, the 24-hour database included consecutive data. Inclusion criteria and the scoring process will be explained further.

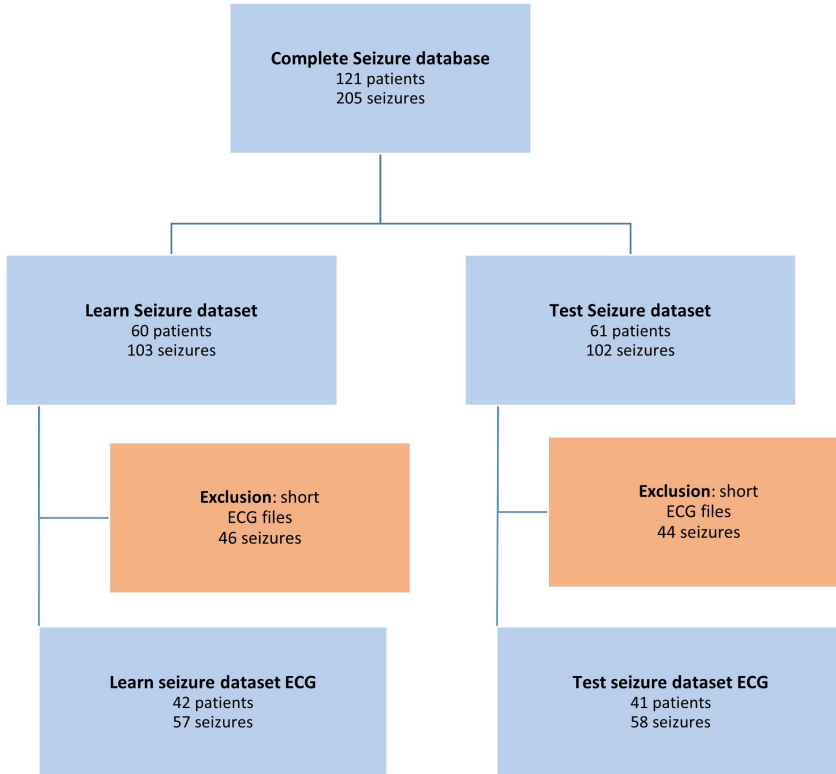


Figure 2.1: Inclusion and division of the seizure database. All epileptic seizures longer than five seconds between May 2014 and April 2015 were included, with a maximum of two seizures per patient. The seizure database was divided into a learn and test dataset. ECGs that were too short (<1.5 minutes before start seizures) were excluded for the analysis of the ECG algorithm.

2.2.1 Seizure database

Data inclusion

Seizures of patients admitted to the EMU at SEIN between May 2014 and April 2015 were included retrospectively in the Seizure database. Seizures were only included when they were defined as epileptic in the corresponding EEG report, so that detection by an algorithm is possible. All included seizures had to be longer than five seconds to make detection by staff and algorithms possible. A maximum of two seizures per patient were included to prevent over-representation of certain individuals or seizure types in the database. If more seizures were present in the recording, two were randomly selected out of the first five seizures. In these first seizures, it is important to perform diagnostic tests, so staff response is required. This might not be the case in later seizures. EEG and ECG file duration of seizures could vary depending on how files were cut.

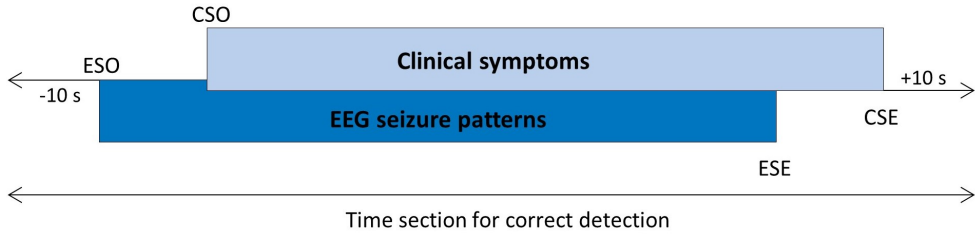


Figure 2.2: A visualisation of the timing of a seizure, this might vary between patients. CSO (clinical seizure onset), CSE (clinical seizure end), ESO (electrographic seizure onset) and ESE (electrographic end) were scored for every seizure in the seizure database and 24-hour database. A correct detection was defined as a detection within ten seconds before the first start (ESO or CSO) of the seizure until ten seconds after the last end of the seizure (ESE or CSE). Adapted from [14].

For the evaluation of the ECG algorithm, the database was further divided into a learn and test dataset. Patients and seizures were randomly divided in two datasets. Seizures with less than 1.5 minutes of data before the start of the seizure were excluded, since the ECG algorithm could only work properly when enough data before the seizure was present. An overview of the included seizures and how it is divided can be seen in Figure 2.1.

Scoring of seizures

The start and end of all epileptic seizures were identified by reviewers. Four different time points were scored; clinical seizure onset (CSO), clinical seizure end (CSE), electrographic seizure onset (ESO), and electrographic seizure end (ESE), as can be seen in Figure 2.2. The ESO was defined as the moment where the first changes in the EEG could be seen, which could range from small attenuations in the signal to generalized epileptiform discharges. The ESE was defined as the moment where the last pattern in the EEG ended. The CSO was defined as the start of the first clinical symptom. And the CSE was defined as the moment when patients were able to take care of themselves independently, since up to that point it is of value to respond to seizures. This point might be before, during or after the post-ictal phase.

The performance of the ECG algorithm can only be evaluated using seizures with an increase in heart rate. The heart rate was determined manually for the whole Seizure database. The heart rate was determined at three instances: before the seizure (30 seconds before ESO), during the start of the seizure (at ESO) and during the seizure (15 seconds after ESO). At every time point, five QRS-complexes were selected and with this time interval a heart rate was calculated. An increase in heart rate was defined as an increase of at least 30 beats per minutes at the start of a seizure or during the seizure, since research has shown an average increase of 30 beats per minutes during seizures [17].

Table 2.1: This table shows a description of how the electrographic and clinical characteristics were scored. Adapted from [14].

	EEG characteristics	Clinical characteristics
1	No visible changes	No visible changes
2	Subtle changes; these changes are hard to notice	Subtle changes; these symptoms might be missed
3	Clear focal changes; these changes might not directly catch ones attention	Clear clinical symptoms; these symptoms might not directly catch ones attention like tonic movement or wander
4	Clear diffuse changes; these changes immediately catch ones attention	Very clear clinical symptoms; these symptoms immediately catch ones attention like tonic clonic seizures

Additional data collection

The electrographic and clinical characteristics of seizures were scored to evaluate how clear changes were. Both characteristics were scored using values between 1 and 4, resembling no visible manifestations up to very clear manifestations from the perspective of the nurses that monitor the patients. A description for these different scores can be seen in Table 2.1. For every five seconds, the characteristics were scored until staff responded, up to the first 60 seconds of the seizure. From these scores, a mean value was calculated. Additionally, seizure classification was collected from the EEG report.

2.2.2 24 hour database

Data collection

Full EEG recordings were included in a 24-hour database. This database included 60 consecutive patients with EMU recordings at SEIN Heemstede from September 2016. For every patient, up to 24 consecutive hours of the recording were randomly included. The first 30 patients were included in the learn dataset and the next 30 into the test dataset. An overview of the included recordings and how it is divided can be seen in Figure 2.3.

Scoring of 24-hour database

For the 24-hour database the start and end of all seizures were determined, using the same definitions as for the seizure database. Additionally, the amount of abnormalities in the interictal EEG were scored based on the EEG report. The amount of abnormalities could be scored into four categories: Normal interictal EEG, Abnormal interictal EEG with non-specific non-epileptiform abnormalities, EEG with some epileptiform abnormalities and EEG with frequent epileptiform abnormalities.

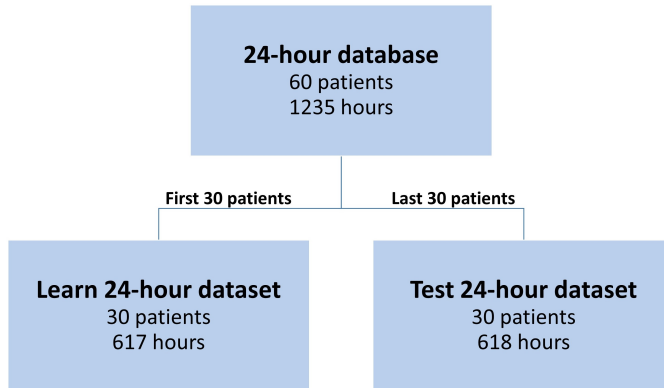


Figure 2.3: Inclusion and division of the 24-hour database. 60 consecutive patients with EMU recordings from September 2016 were included. For every patient 16 to 24 hours were included. The first 30 patients were included into a learn dataset and the last 30 patients into a test dataset.

2.3 Used definitions

The following definitions are used throughout all chapters:

Correct detection A correct detection for an algorithm was defined as a detection within ten seconds before the first start of a seizure (CSO or ESO) and up to ten seconds after the last seizure end (ESE or CSE) as can be seen in Figure 2.2. Correct detections were calculated using the Seizure database.

Detection latency All detection latencies were calculated from the ESO, since detection algorithms can only detect from these first changes. Additionally, latencies of different algorithms can be compared since once definition was used. All latencies were calculated using the Seizure database.

False positives A false positive was defined as a detection which was not during a seizure, as in beyond ten seconds before the first start of a seizure (CSO or ESO) and ten seconds after the last end (ESE or CSE). When a false positive occurred, a black-out period of 10 seconds was defined, in which no new false positives could occur. This black-out period was taken since if multiple warnings would occur, it would be seen as one. A median false positive rate was calculated by taken the median of the false positives per 24 hours of all patients.

Chapter 3

The added value of EEG seizure detection algorithms

3.1 Introduction

In an EMU it is of importance that seizures are recognized timely. When a seizure occurs, patient safety is secured to reduce adverse events [11] and standardized tests are performed to assess consciousness, cognitive and neurological functioning [12, 13]. Research has shown that the response to seizures needs improvement, with a response in only 41% of seizures, with a median response time over two minutes [15]. While response rate and time can vary between EMUs, response rate is always limited by human capabilities. Online seizure detection algorithms might help staff to detect seizures that are otherwise missed or recognized late. Seizures can be detected with a variety of signals, like movement, electrodermal activity, heart rate and EEG. This chapter will focus on seizure detection based on EEG, since it is closest to the source of epilepsy, specific to epilepsy and standardly measured on an EMU.

With an EEG, brain activity can be assessed by measuring potential differences over electrodes. Neuronal activity is measured, which mostly shows post-synaptic currents of pyramidal neurons which are spatially closest to the cortical surface. The electric potential generated by an individual neuron is too small to be measured. EEG activity reflect synchronous activity of thousands or millions of neurons.

When evaluating an EEG signal, normal phenomena and rhythms are examined. In people with epilepsy, interictal (in between seizures), ictal (during seizures) and postictal (after seizures) changes can be seen. Interictal changes are epileptiform discharges characterized by a spiky morphology like spike and sharp waves. These interictal changes are not present in all patients. Ictal discharges are repetitive and highly synchronous epileptiform discharges [18]. An example of ictal EEG changes can be seen in Figure 3.1. And lastly, postictal changes can occur as EEG depression or slowing, but this is not present in all patients [19]. Furthermore, certain seizure types can have specific EEG patterns. For example, absence seizures show 3-4 Hz generalized spike slow wave discharges [20].

EEG-based seizure detection tries to detect seizures based on the ictal changes in EEG. It has been studied since 1982 [21] and the following decades a lot of re-

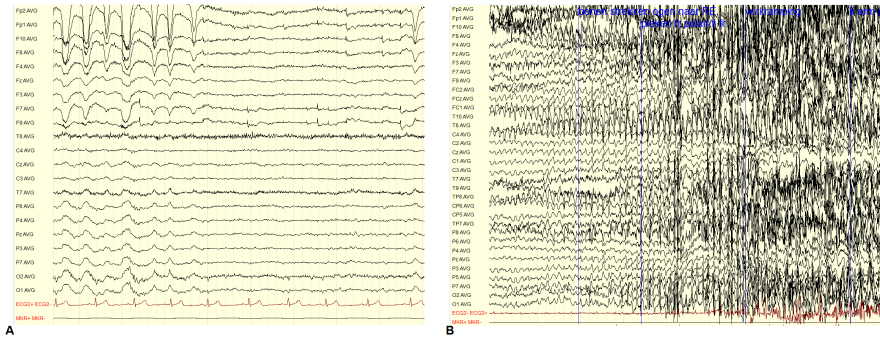


Figure 3.1: Example of a normal EEG versus an EEG during an epileptic seizure. Figure A shows a normal EEG. Large waves can be seen, which are artefacts caused by eye blinking. Figure B shows an example of an EEG during an epileptic seizure. It shows rhythmic discharges with increasing amplitude. Additionally, increasing muscle activity can be seen.

search has been done on various approaches to detect seizures [22–24]. Recently, EEG seizure detection software has also become commercially available, among them Encevis EpiScan and BESA Epilepsy. Encevis EpiScan uses two modules which detect rhythmic patterns and waves which are characteristics for epilepsy [25, 26]. To detect seizures, the extracted features are continuously compared with past information from the EEG. The BESA Epilepsy software calculates normalized energy and integrated power for different frequency bands [27, 28]. This algorithm is based on the hypothesis that seizure activity manifests itself by a change in frequency and amplitude that is distinct from non-seizure or background activity. When extracted features are above a threshold for over 10 seconds, a seizure is detected.

The performance of EEG detection algorithms has been studied thoroughly and show good sensitivity and specificity [22, 23]. For Encevis EpiScan a sensitivity of 81% with a false positive rate of 0.30 per hour has been reported [28]. BESA Epilepsy was reported to have a sensitivity of 87% with a false detection rate of 0.22 per hour [27]. Although seizure detection software is commercially available with good sensitivity and specificity, it is unclear what the added value is to seizure monitoring in an EMU. Since these algorithms are not widely implemented in clinical settings [29], this question remains unanswered. It is vital to research the added value of detection algorithms on top of the detection by already present staff. Seizure detection will not be a stand-alone system but an improvement to current staff. In this chapter, we will therefore investigate this added value, by answering the following questions:

- What is the current response rate and response time of staff to seizures?
- What is the sensitivity, response time and false positive rate of Encevis EpiScan and BESA Epilepsy in the same clinical data?
- What is the added value on the current response in terms of possible extra detected seizures and faster response time?
- Which people could specifically benefit from these algorithms?

The response of staff, Encevis EpiScan and BESA Epilepsy was already researched by a previous student, L. Jansen Holleboom [14]. The research on false positives and patient characteristics was researched during this project. For the readability, all methods and results will be shown.

This chapter was written as an article for the publication in a journal. Also, it was presented at the 32nd International Epilepsy Congress in Barcelona with a poster. The poster is shown in Appendix I and the draft article in Appendix II.

3.2 Methods

3.2.1 Included data

The sensitivity and latency were researched on the Complete Seizure database. Seizures where medical staff were already present at the start of a seizure, were excluded since staff response could not be evaluated. This resulted in 188 seizures of 115 patients. False positives were researched on the learn 24-hour dataset which included 30 patients of in total 617 hours. Inclusion criteria can be seen in Chapter 2.2.

3.2.2 Used algorithms

The detection algorithms Encevis EpiScan and BESA Epilepsy were tested. Encevis EpiScan first uses advanced filter steps to remove artefacts [28]. The detection of seizures is based on Periodic Waveform Analysis (which detects rhythmic EEG patterns) and Epileptiform Wave Sequence Analysis (which analysis different aspects of waves) [25, 26]. This last analysis can detect irregular structures, which are harder to detect with spectral analysis like Periodic Waveform Analysis. Features are calculated from these analysis and continuously compared with past information from the EEG.

The BESA Epilepsy software first removes artefacts by excluding high amplitude EEG sections. Next, the normalized energy and integrated power are calculated for different frequency bands [27, 28]. When extracted features are above a threshold for over 10 seconds, a seizure is detected. Both algorithms were tested retrospectively, due to online unavailability.

3.2.3 Sensitivity

Staff response was evaluated, by reviewing video retrospectively. A response was defined as staff entering the room of the patient or using the intercom, between the start of the seizure (10 seconds before ESO or CSO) and end of the seizure (10 seconds after ESE or CSE). A median sensitivity of staff, Encevis EpiScan and BESA epilepsy were calculated.

3.2.4 Latency

Latency of staff, Encevis EpiScan and BESA Epilepsy were calculated. For BESA Epilepsy, 10 seconds were added to account for the delay in the algorithms online functioning. A median latency of responses was calculated.

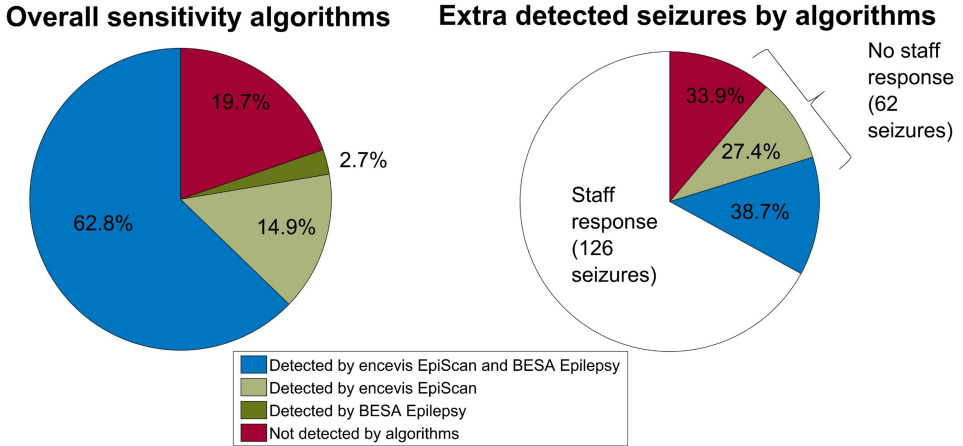


Figure 3.2: Overall sensitivity of seizure detection algorithms Encevis EpiScan and BESA Epilepsy on 188 seizures and sensitivity for seizures missed by staff. Based on the results of [14].

3.2.5 False positives

False positives of Encevis EpiScan and BESA Epilepsy were calculated on the 24-hour dataset. The median false positive rates were calculated.

3.2.6 Statistical analysis

The difference in patient and seizure characteristics (age, seizure classification, clinical characteristics and electrographic characteristics) between detected and undetected seizures (separately for staff, Encevis EpiScan and BESA Epilepsy) were tested for statistical significance with a Chi-square test.

The difference in false positive rate for age and amount of abnormalities in the EEG was tested for statistical difference with a Kruskal-Wallis test. Significance level was set at $p \leq 0.05$. All analysis were performed using MATLAB (R2017a., The MathWorks Inc.).

3.3 Results

3.3.1 Sensitivity

Sensitivity to seizures was 67.0% for staff, 77.6% for Encevis EpiScan and 65.4% for BESA Epilepsy. Of the 62 seizures that were missed by staff, 41 could be additionally recognized by Encevis EpiScan and 24 by BESA Epilepsy. There were 16 seizures that could only be recognized by staff. The comparison of sensitivity of Encevis EpiScan and BESA Epilepsy for all seizures and all undetected seizures by staff can be seen in Figure 3.2.

Table 3.1: Sensitivity of staff, Encevis EpiScan and BESA Epilepsy for seizures with different characteristics. All characteristics were tested for statistically significant differences with a Chi-square test.

		Staff		Encevis EpiScan		BESA Epilepsy	
All patients		67.0%	-	77.6%	-	65.4%	-
Age	Children under 18 years (n=54)	59.3%	0.034	79.6%	0.68	72.2%	0.21
	Adults (n=134)	70.1%		76.9%		62.7%	
Seizure classification	Generalised seizures (n=18)	88.9%	0.0038	100%		100%	
	Temporal seizures (n=80)	75.0%		86.3%	<0.001	71.3%	<0.001
	Extra-temporal seizures (n=86)	55.8%		64.0%		53.5%	
	Unclear classification (n=4)	-		-		-	
Clinical symptoms	No visible changes (n=27)	37.0%	<0.001	85.2%		66.7%	
	Subtle clinical symptoms (n=119)	67.3%		77.3%	0.51	61.3%	0.31
	Clear clinical symptoms (n=34)	82.4%		70.6%		73.5%	
	Very clear clinical symptoms (n=8)	100%		87.5%		87.5%	
Electro-graphic changes	No visible changes (n=6)	66.7%	0.030	66.7%		0%	
	Subtle changes (n=73)	54.8%		58.9%	<0.001	39.7%	<0.001
	Clear focal changes (n=73)	72.6%		89.0%		83.6%	
	Clear diffuse changes (n=36)	80.6%		94.4%		91.7%	

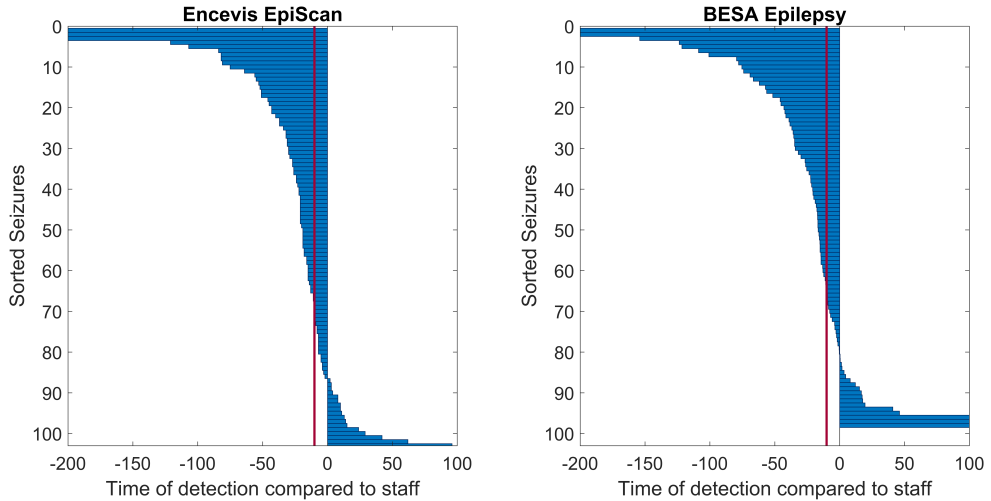


Figure 3.3: Time of detection of Encevis EpiScan and BESA Epilepsy compared to the staff latency (zero seconds). An extra red line is drawn to take walking time of staff into account (10 seconds). Some outliers could not be shown in the figure; for Encevis EpiScan this was -1579, -611 and -215 seconds and for BESA Epilepsy this was -552, -253, 309, 392 and 3173 seconds. Based on the results of [14].

The sensitivity for seizures with different characteristics can be seen in Table 3.1. Staff had significantly lower response rate for children, focal seizures and clinically less clear seizures. No statistical difference was found between children or adults in Encevis EpiScan and BESA Epilepsy. Extra-temporal seizures and seizures with (almost) no electrographic characteristics were still difficult to detect for these algorithms.

3.3.2 Latency

Staff had a median response time of 31 seconds, Encevis EpiScan of 10 seconds and BESA Epilepsy of 14 seconds. In 83.5% of the seizures detected by staff, Encevis EpiScan detected the seizure faster than the staff response. In 81.6% of the seizures detected by staff, BESA Epilepsy detected the seizure faster than the staff response. Figure 3.3 shows the time of detection of Encevis EpiScan and BESA Epilepsy compared to staff latency.

3.3.3 False positives

Encevis EpiScan had a median false positive rate of 4.9 per 24 hours per patient and BESA Epilepsy 2.1 per 24 hours per patient. A histogram of number of false positives can be seen in Figure 3.4. Encevis EpiScan had low false positive rates for almost every patient. Whereas BESA Epilepsy had zero false positives for most patients, but also some outliers with a lot of false positives. Additionally, Encevis EpiScan had most false positives during the first hours of the registrations, since the algorithm requires a learning period. When the alarm of Encevis EpiScan would be turned off

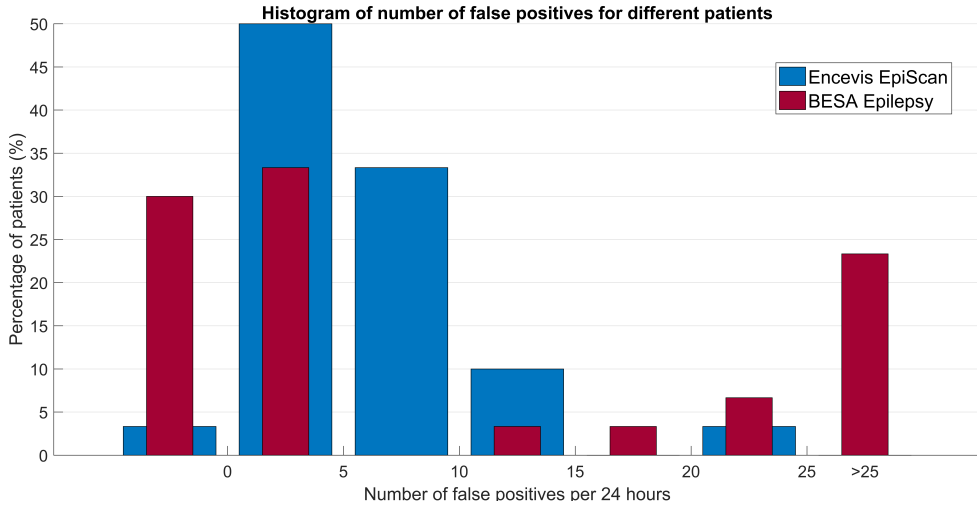


Figure 3.4: Histogram of number of false positives for different patients. It shows per bin the percentage of patients that have that many false positives per 24 hours.

during the first hour, false positive rate would decrease with 36.4% and even 46.1% if it would be turned off the first two hours.

Children had a higher false positive rate than adults for Encevis EpiScan ($p=0.043$), with a median false positive rate of 6.99 per 24 hours for children and 4.47 per 24 hours for adults. The difference in false positive rate between the amount of abnormalities in the EEG was not significant. BESA Epilepsy also had a higher false positive rate in children ($p=0.0057$), with a median false positive rate of 39.1 per 24 hours for children and 1.28 per 24 hours for adults. Additionally, EEGs with frequent epileptiform abnormalities had a significantly ($p=0.0308$) higher false positive rate, with a median false positive rate of 33.1 per 24 hours (compared to 1.16-9.86 for EEGs with less abnormalities).

3.4 Discussion

Staff response to seizures could be improved with online EEG seizure detection algorithms by improving response rate and response time. We were able to show that 66.1% of the undetected seizures by staff could be recognized by EEG seizure detection algorithms. Additionally, in most seizures the algorithm detection preceded detection by staff. The algorithms had acceptable median false positive rates. Especially children, patients with focal seizures and patients with seizures with clear electrographic changes could benefit from these algorithms. These seizures showed a lower response rate of staff, while the algorithms were able to detect seizures. Using seizure detection algorithms on these patients, might help to ensure patient safety and to assess consciousness, cognitive and neurological function. Seizures with none to very subtle electrographic characteristics were difficult to detect by the algorithms. Additionally, a higher false positive rate for both algorithms was found for children, and for EEGs with frequent epileptiform abnormalities for BESA Epilepsy.

The staff response and latency found in this study, is better than described in literature, which shows a response rate of 41% with an average response time of 142.3 seconds [15]. This can be explained by differences between EMU settings, e.g. staff experience or EMU layout. The sensitivity and specificity of the algorithms described in this study, is comparable to literature [27, 28]. Delay time was not described. Additionally, to our knowledge, the added value on already present staff has never been researched.

Staff response and sensitivity of detection algorithms is influenced by characteristics of seizures and patients. When there is a low response rate of staff but algorithms are able to detect seizures, patients could especially benefit from these algorithms. Staff response was highly dependent on the appearance of clinical characteristics, since staff mostly respond based on symptoms seen on a video stream. While the algorithms were dependent on presence of electrographic changes. This could also be seen in the sensitivity for different seizure classifications. For example, generalised seizures are electrographically and clinically very clear and therefore have a high response rate of staff and algorithms. On the contrary, extra-temporal seizures are short with little clinical and electrographic changes and therefore have lower response rate of staff and algorithms. So, patients with clinically less clear seizures with electrographic changes could benefit from these algorithms. Especially focal seizures had a low sensitivity of staff but a high sensitivity of the algorithms and might benefit from these algorithms. Additionally, a lower sensitivity of staff to seizures of children was seen. Therefore, children might also benefit from seizure detection algorithms. A higher false positive rate was also found for children, making it less applicable to use these algorithms. This might be caused since the EEG has more variations in children [18, 20]. Also, children had more often interictal abnormalities in the EEG, which also influenced the function of the algorithms. Encevis EpiScan still had an acceptable rate for children and is therefore preferable when used on children.

The algorithms could not be tested online, since at time of research they were not ready for online implementation. Therefore, the true effect of these algorithms could not be researched. For example, staff might not react to all alarms or take a long time to react to alarms. Therefore, the algorithms should be tested online before implementation. The used alarm system is then very important, since this will influence the decision of staff to respond to an alarm. Additionally, two different databases were used to test the algorithms on a large number of seizures and long periods of continuous data. Using full recordings can provide a better view on the function of the algorithms, since it shows the amount of false positives relatively to the true positives. However, this was not present at time of research. And lastly, staff response can vary between different EMU settings. Depending on how staff is educated and patients are monitored, response rate can be higher or lower. Therefore, the added value of EEG seizure detection algorithms can also be different in another setting. Besides the EMU setting, patient characteristics can vary between different EMUs, which could influence the performance of the algorithms. Since different patient characteristics were analysed, results still can be interpreted for different settings.

Since the results of this study were very promising, there is a wish to implement

one of the algorithms at SEIN. Based on the results of this study, SEIN will proceed with Encevis EpiScan. Encevis Episcan showed better sensitivity and a lower false positive rate than BESA Epilepsy. Additionally, Encevis EpiScan is closer to online implementation. From this point on, this study will focus on Encevis EpiScan. The results of Encevis EpiScan were discussed with clinicians. Sensitivity was already very satisfying, no further improvements needed to be made before implementation. However, false positive rate was seen as acceptable, but not great. The latency was also a point of improvement. While the latency is better than response time of staff, some seizures are still recognized late.

3.5 Conclusion

Online EEG seizure detection algorithms could improve the nurse response to seizures on an EMU, by detecting extra seizures and improving response time. This might help to ensure patient safety and to assess patient consciousness, cognitive and neurological function timely. Especially children, patients with focal seizures and patients with seizures with clear electrographic changes could benefit from these algorithms. Points of improvement are specificity and latency.

Chapter 4

An ECG seizure detection algorithm

Still, we would like to improve the performance of Encevis EpiScan as described in Chapter 3. The observed sensitivity was satisfying, but the false positive rate and time of detection are points of improvement. Therefore, for this project, we assessed the feasibility to improve detection latency by creating an additional algorithm based on heart rate changes. Heart rate changes have been researched extensively. These changes occur often during seizures. Most of the time they occur in the beginning or even before electrographic start of a seizure [17, 30–32]. The study by Furbass et al demonstrated that an ECG detection algorithm has a smaller detection delay than Encevis EpiScan. [33]. However, problems have also been reported with the use of ECG as a seizure detector, such as a low stability of electrodes, and difficulty with distinguishing normal heart rate changes from seizures [34, 35]. Therefore, we investigated if an ECG seizure detection algorithm could be developed that could be used on top of Encevis EpiScan. Additionally, the detection algorithm should show an added value in terms of extra detected seizures or faster detection time.

4.1 Introduction

Ictal alteration of the heart rate is caused by propagation of seizure activity in the central autonomic control centres. This can disturb the normal control of cardiac functions. The most common change during seizures is an increase in heart rate, which is called tachycardia. The most accepted theory explaining this mechanism is the propagation of epileptic discharges towards the right insular cortex [30]. Research has shown a predominance for ictal tachycardia in right sided temporal seizures, supporting this theory [30, 31]. However, not all studies observe this predominance, which suggests that other factors play a role in the pathogenesis of ictal tachycardia [30]. Ictal tachycardia occurs in a round 82% of patients [17]. There is intra-individual variability, meaning not all seizures of one patient result in an increase in heart rate. The prevalence of tachycardia is not particularly different between partial (64%) or generalized (71%) seizures [17]. The average increase in heart rate is 30 beats per minute or a relative increase of 50% [17]. These changes often occur before changes

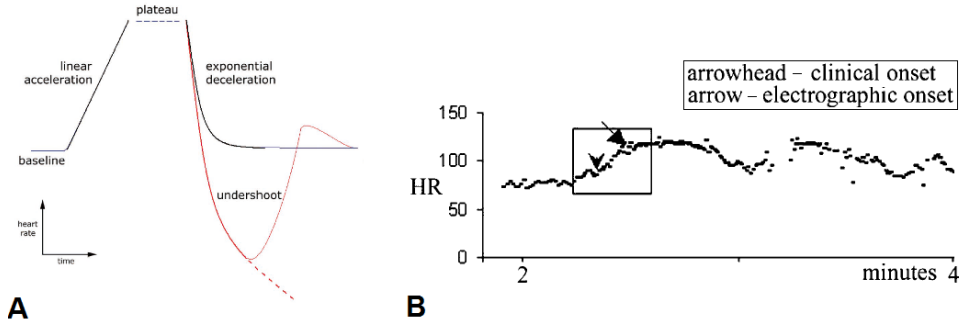


Figure 4.1: Panel A shows a model of ictal heart rate changes (adapted from [36]). The heart rate starts at a baseline. At seizure onset, there is a linear acceleration in heart rate, followed by a plateau, and an exponential deceleration, occasionally accompanied by an undershoot. Panel B shows an example of ictal heart rate changes in a patient where the heart rate was calculated manually (adapted from [32]). The arrowhead points at the clinical onset of the seizure and the arrow at the electrographic onset. This demonstrates that the heart rate increases rapidly after seizure onset.

can be observed in the EEG. Furthermore, almost all of these changes occur within the first 30 seconds of seizure onset. A model of ictal heart rate changes and an example of a patient can be seen in Figure 4.1.

One of the first steps of an ECG seizure detection algorithm is the detection of QRS-complexes, so a heart rate can be calculated. Different techniques to detect QRS-complexes are described in literature. One of the oldest and most described algorithms is the Pan-Tompkins algorithm. This algorithm was created in 1985 to detect QRS-complexes real-time in the ECG. It consists of extensive filters, after which adaptive thresholds are used to detect the QRS-complex. The algorithm has shown a correct detection of 99.3% QRS-complexes in a commonly used arrhythmia database (the 24h MIT-BIH arrhythmia database) [37]. The Pan-Tompkins algorithm has been thoroughly researched and demonstrates very low error rates [38–40]. Another frequently described technique is the use of continuous or discrete wavelet transforms [40, 41]. With these techniques, wavelets are shifted over the ECG. When the correlation between the wavelet and the ECG is high, a QRS-complex is detected. This technique is often described in literature, but research has shown that the Pan-Tompkins algorithm has a higher positive predictive value compared to wavelet transforms [40].

Moreover, a lot of techniques have been described to denoise the ECG, such as the Empirical Mode Decomposition (EMD) and the Hilbert-Huang transform. EMD breaks a signal down into multiple intrinsic mode functions (IMF). This technique can be compared with techniques such as Fourier transform or Wavelet transform. Another way to use this method is the Hilbert-Huang Transform. This transform does not only use EMD to decompose the signal into IMF, but also applies the Hilbert spectral analysis to obtain instantaneous frequency data.

Even more techniques are described in literature that can be used in an ECG algorithm, ranging from neural network approaches to advanced filtering, such as

matched filters [39, 41, 42]. For most ECGs, these algorithms provide the intended use. Nevertheless, all of them have problems in case of noisy signals, artefacts or deviating QRS-complexes [42, 43].

Several articles have been published that describe algorithms for ECG seizure detection. However, most of these described algorithms are not feasible for online use, investigate other features than tachycardia, need multiple seizures for the creation of patient specific algorithms, or require manual adjustments [44, 45]. The most described techniques for the detection of QRS complexes are pattern recognition or (an adjusted version of) the Pan Tompkins algorithm [31, 33, 44]. There is no agreement on one specific algorithm that surpasses all other algorithms in the detection of seizures. Therefore, the decision was made to develop an algorithm based on techniques often described in literature. In this chapter, the different steps of this algorithm will be described. Furthermore, reasons for choosing these different steps and settings will be explained. Thereafter, the performance and added value on top of Encevis EpiScan will be reported. This chapter will answer the following questions:

- What steps are needed to develop an ECG seizure detection algorithm? Additionally, the reason for choosing these steps will be explained.
- What is the sensitivity, latency and false positive rate of the developed ECG seizure detection algorithm?
- What is the added value on Encevis EpiScan in terms of possible extra detected seizures and faster response time?
- Is it feasible to use the ECG seizure detection algorithm on top of Encevis EpiScan in terms of extra false positives?
- Are there people that could or could not specifically benefit from the algorithm?

4.2 Methods

4.2.1 Algorithm

Different steps of the algorithm will be explained and the reason for choosing these steps will be explained.

Step 1: Pan Tompkins algorithm

We chose to use the Pan-Tompkins algorithm since it is very robust, has a low computational load, and because it has been extensively researched. The algorithm consists of multiple pre-processing steps; first a band-pass filter between 5-15 Hz is applied and next, the derivative, square and a moving average filter (of 0.15 seconds) is taken. Thereafter, QRS-complexes are detected based on adaptive thresholds. Lastly, missing peaks and peaks that are no QRS-complexes are detected and eliminated. A flow chart of the algorithm can be seen in Figure 4.2 and the complete technical background of the algorithm can be seen in Appendix III.

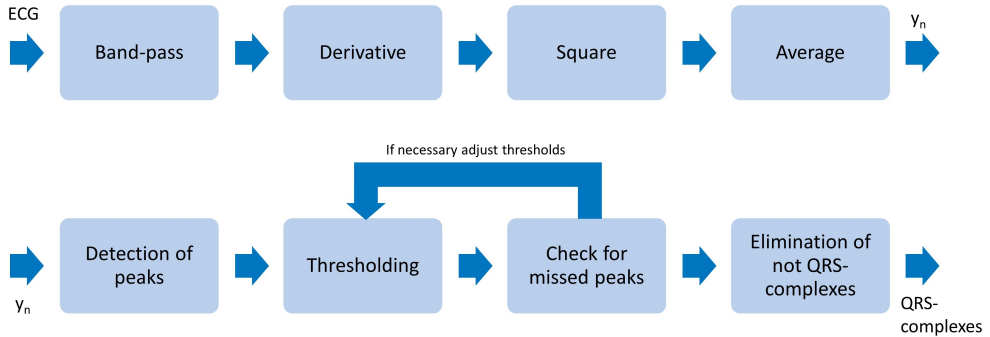


Figure 4.2: Flow-chart of the steps of the Pan-Tompkins algorithm to detect QRS-complexes. The pre-processing steps of the algorithm are shown; a bandpass filter between 5-15 Hz, a derivative and the square of the signal. Additionally, the different steps for the detection of QRS-complexes are displayed. First, all peaks in the signal are detected. Possible QRS-complexes are determined based on adaptive thresholds. There is checked for missed tops and thresholds are adapted based on that. Lastly, non QRS-complexes are eliminated.

Adaptations to the Pan Tompkins algorithm Some additions to the Pan Tompkins algorithm were necessary for a proper functioning of the algorithm. Four steps were added to reduce false positives and increase the sensitivity. These steps were focused on improving the thresholds and eliminating peaks that were likely no QRS-complexes. All details of the added steps are explained in Appendix III. The algorithm was executed with and without the adaptations to evaluate how it influences the performance.

Step 2: Processing the heart rate

The heart rate was calculated from every beat-to-beat interval. A lot of deviating non-physiological heart-rate values were calculated due to the fluctuating nature of the ECG. Therefore, three different steps were performed to increase the reliability.

First, all non-physiological values (heart rates above 220 beats/min) were removed. Second, outliers in the signal were removed. An outlier was defined as a data point that was more than two times the standard deviation measured from the mean. The standard deviation and mean were calculated for the data point and a window of 512 previous data points. Therefore, this step only uses data from the past and can be used online. Lastly, a moving average filter was applied, which calculated a new mean heart beat based on the last 10 heartbeats. This last step ensured that very fast changes are removed. Subsequently, a trend of the heart rate was saved.

Step 3: Identifying seizures

A seizure can be identified by an increase in heart rate. However, since this increase can also occur due to physiological changes or artefacts, the absolute increase in heart rate should not be used alone to detect seizures. An adjustable threshold was calculated based on the reliability of the heart rate. This reliability was calculated

with the standard deviation. When a sudden increase in heart rate occurred in a period with a small standard deviation it is more likely to be a seizure, whereas when an increase occurs over a period with a higher standard deviation which can be related to movement artefacts. Therefore, an adjustable threshold (T_{hr}) was calculated as given in Formula 4.1. When the heart rate (hr) exceeded this threshold, it was classified as a seizure. The mean and standard deviation of the heart rate were calculated over a period of 5 minutes. In this manner, fast changes could still be measured, but slow changes resulted in no detection, because the threshold would change together with the increase in heart rate. A blackout period of 10 seconds was applied after every detection. In this period, no new detection could occur. Different parameter settings for the threshold were tested to determine an optimum threshold.

$$T_{hr} = \text{mean}(hr) + 20 + 3\text{std}(hr) \quad (4.1)$$

Other explorations

Three other methods were tested as a possible addition to the algorithm. First, two methods were investigated that might filter out noise or artefacts; EMD and the Hilbert-Huang transform. These methods were tested on some of the data of the Learn dataset to investigate their effect.

The last exploration was to remove ECG when it was unreliable, which may reduce false positives. The reliability of the ECG was based on the energy, which will increase when noise or artefacts are present. An adaptive threshold was determined per patient and consisted of a mean energy plus the standard deviation. When the energy of the ECG exceeded this threshold, the heart rate in the corresponding window was deleted. An adaptive threshold was chosen, because the energy of the ECG is very patient depended. A maximum and minimum value was chosen for the threshold. The algorithm was run with and without this adaptation to evaluate how it influences the performance.

4.2.2 Effect of different steps

The algorithm, with different parameter settings, was tested on the 'Learn Seizure dataset ECG' and 'Learn 24-hour dataset'. The inclusion criteria can be seen in Section 2.2. The effect of different steps will be explained in the results. Additionally, a final parameter setting for the threshold for the identification of seizure was chosen based on these results.

4.2.3 Evaluation of the performance

The performance of the final algorithm was evaluated on a different dataset to prevent overfitting. The algorithm was evaluated on the 'Test Seizure dataset ECG' and 'Test 24-hour dataset'. The Test Seizure dataset consisted of 58 seizures of 41 patients. The Test 24-hour dataset included 30 patients with consecutive registrations of in total 618 hours. Inclusion criteria can be seen in Section 2.2.

Performance and added value

Sensitivity and latency were calculated on the Test Seizure dataset. The false positive rate was calculated on the Test 24-hour dataset. The added value on top of Encevis EpiScan was evaluated by running the algorithm on the same dataset. Thereafter, the added value of the ECG algorithm was determined as extra detections or faster detection time. The drawback of the developed algorithm was determined by evaluating the amount of extra false positives.

Statistical analysis

Different patient characteristics were evaluated that could be of possible influence on the performance of the ECG algorithm. The difference in subject age and seizure classification between detected and undetected seizures were tested for statistical significance with a Chi-square test. The difference in latency and amount of false positives for different age and seizure classifications were tested for statistical significance with a Kruskal-Wallis test.

4.3 Results

4.3.1 Effect of different steps

The different steps were evaluated on the learn dataset to evaluate if and where improvements were required. Additionally, the final settings were determined. Figures displaying examples of the functioning of the algorithm can be seen in Appendix IV.

Pan-Tompkins algorithm

The Pan-Tompkins algorithm showed promising results for most patients. However during artefacts, the heart rate could not always be calculated accurately. Additionally, in some very noisy ECGs the heart rate could also not be determined accurately.

Adaptations to the Pan-Tompkins algorithm

The algorithm was tested with and without the adaptations. With these adaptations, the false positive rate would decrease from a median false positive rate of 4.25 to 0 per 24 hour per patient. In addition, sensitivity increased slightly from 33.3% to 37.5% in seizures with an increase in heart rate of 30 beats/min. This demonstrates that the added steps improved the performance of the algorithm.

Processing of the heart rate

Different window sizes were evaluated for the processing step. When using a moving average filter on less data points, overly fast changes in heart rate were still in the signal. When using a window larger than 10 beats, these fast changes were deleted. However, this also resulted in a delay. The window size was, therefore, set to 10 heart beats. This step resulted in less outliers and a smoother heart rate signal.

Table 4.1: The sensitivity, detection time and false positive rates for multiple settings of the classifier. This was tested in the Learn Seizure dataset ECG on seizures with an increase in heart rate ($n=24$) and the Learn 24-hour dataset ($n=30$, 617 hours)

Setting threshold	Sensitivity	Median time of detection in seconds (p5-p95)	Median false positive rate per 24 hours (p5-p95)
$\text{mean}(hr) + 20 + 3 * \text{std}(hr)$	37.5%	40.2 (21.3 - 115)	0 (0 - 5.00)
$\text{mean}(hr) + 15 + 3 * \text{std}(hr)$	50.0%	34.8 (10.9 - 111)	2.30 (0 - 17.0)
$\text{mean}(hr) + 20 + 2 * \text{std}(hr)$	54.2%	33.4 (8.75 - 70.9)	5.03 (0 - 41.5)
$\text{mean}(hr) + 15 + 2 * \text{std}(hr)$	62.5%	33.4 (8.77 - 69.5)	17.7 (0 - 79.3)

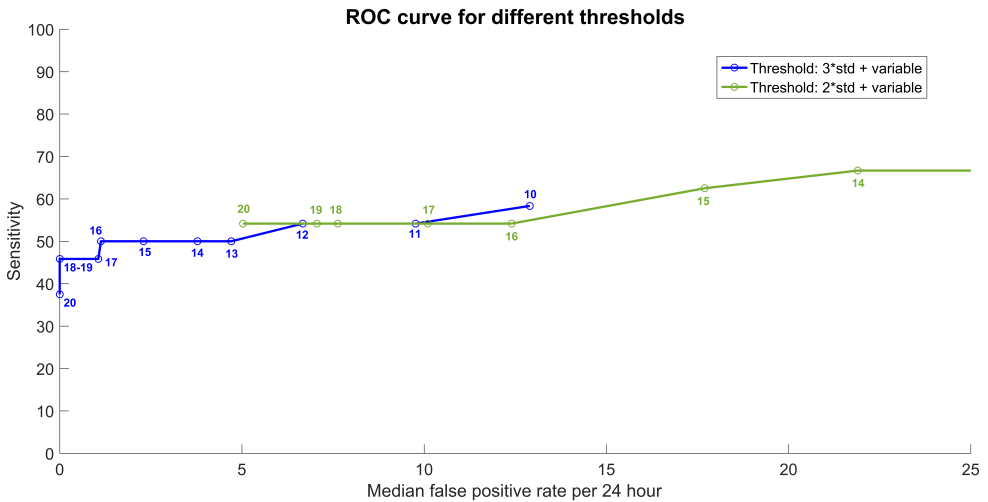


Figure 4.3: ROC-curve for different threshold settings. Two different thresholds were tested; two and three times the standard deviation. An additional variable was added ranging between 10 and 20. The sensitivity and false positive rate was calculated for these different thresholds. Results with a higher false positive rate than 25 per day were not displayed, as it is not feasible to use such a false positive rate online.

Identifying seizures

A sensitivity of 21.1% with a median detection time of 38.7 seconds was observed. There was a median false positive rate of 0 per 24 hour per patient. The sensitivity was low, but not all patients had an increase in heart rate during seizures. Therefore, the performance of the algorithm was researched on the seizures with an increase in heart rate of at least 30 beats/min ($n=24$). The sensitivity, detection time and false positive rates for multiple settings of the threshold can be seen in Table 4.1 and in Figure 4.3. Most undetected seizures had a lot of variation in the heart rate before the seizure start. This would result in a higher standard deviation, and hence, a higher threshold. Additionally, some of the seizures had a minimum increase in heart rate, thus not enough for detection.

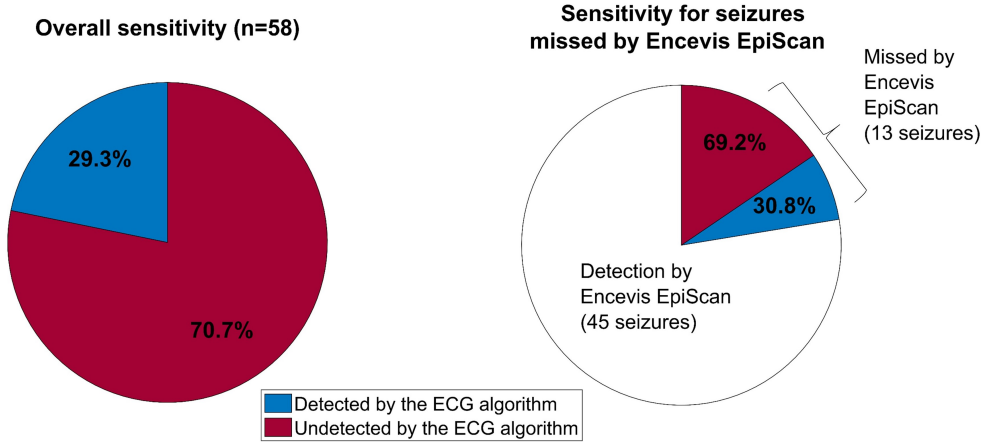


Figure 4.4: Overall sensitivity of the ECG seizure detection algorithm for all 58 seizures. Of the 13 missed seizures by Encevis EpiScan, 4 extra seizures were detected by the ECG seizure detection algorithm.

Since the algorithm will be used on top of Encevis EpiScan, only low false positive rates (<5 per day) were acceptable. A final threshold was selected with the highest possible sensitivity and that false positive rate. The following threshold was selected:

$$T_{hr} = \text{mean}(hr) + 16 + 3 * \text{std}(hr) \quad (4.2)$$

Other explorations

EMD did not show additional value besides of the developed algorithm. Signal and noise/artefacts were not separated into different IMF and they could therefore not be separated. Therefore, this method could not be used to reduce artefacts or noise. The Hilbert Huang transform was also investigated. When applying this technique, the ECG seemed less noisy. However, when using the filtered ECG in the Pan-Tompkins algorithm, this did not provide a better detection of QRS-complexes.

Removing unreliable ECG did result in a slightly lower false positive rate; the mean false positive rate decreased from 1.00 to 0.61 per 24 hours. However, the sensitivity also decreased (from 21.1% to 17.5%), and the detection latency increased substantially (from 42 seconds to 95 seconds). Data points that were removed during the beginning of the seizure caused this longer detection time. Since the ECG algorithm was created to improve latency, this method was not used in the final algorithm.

4.3.2 Evaluation of the performance

Sensitivity

Sensitivity was 29.3% in all 58 seizures and 47.8% in the 23 seizures with an increase in heart rate. Of the 13 undetected seizures by Encevis EpiScan, 30.8% could be additionally recognized by the ECG algorithm. The overall sensitivity and sensitivity for the missed seizures by Encevis EpiScan can be seen in Figure 4.4.

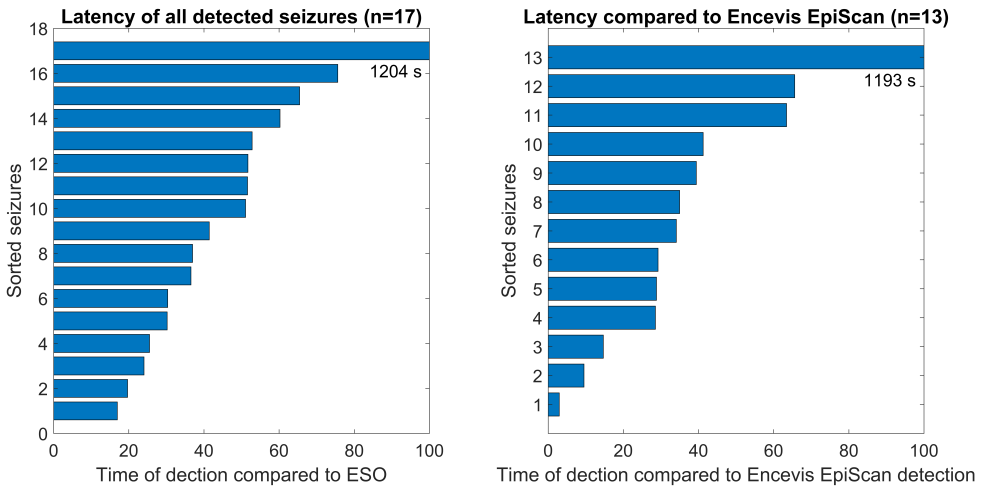


Figure 4.5: Detection time of the ECG seizure detection algorithm. The left panel shows the time from the beginning of the seizure (ESO) until the seizure was detected. The right panel shows the difference in detection time between the ECG algorithm and Encevis EpiScan. Encevis EpiScan was faster than the ECG algorithm for all seizures that were detected by both algorithms. Two outliers were not shown in the figure; 1204 seconds for the left panel and 1193 seconds for the right panel.

Latency

The latency of the algorithm compared to ESO and Encevis EpiScan can be seen in Figure 4.5. A median latency of 41.4 seconds was observed in all detected seizures and a median latency of 36.5 seconds in the group of seizures with an increase in heart rate. Encevis EpiScan was faster than the ECG algorithm for all 13 seizures that both algorithms detected.

False positive rate

The median false positive rate was 0 per patient per 24 hours. The distribution of the amount of false positives per patient can be seen in Figure 4.6. This figure shows that 60% of patients had no false positives and 90% had less than 4 false positives.

The distribution of false positives over time can be seen in Figure 4.7. False positives occur throughout the day. An increase in false positives was observed between 8:00 and 10:00. This is most likely caused by movements artefacts due to waking up, getting dressed and having breakfast.

When combining the ECG and the Encevis EpiScan algorithms, a total median false positive rate of 7.62 per 24 hour can be attained.

Patient characteristics

Different patient and seizure characteristics were tested for their influence on the performance of the ECG algorithm. The difference in sensitivity and latency can be seen in Table 4.2.

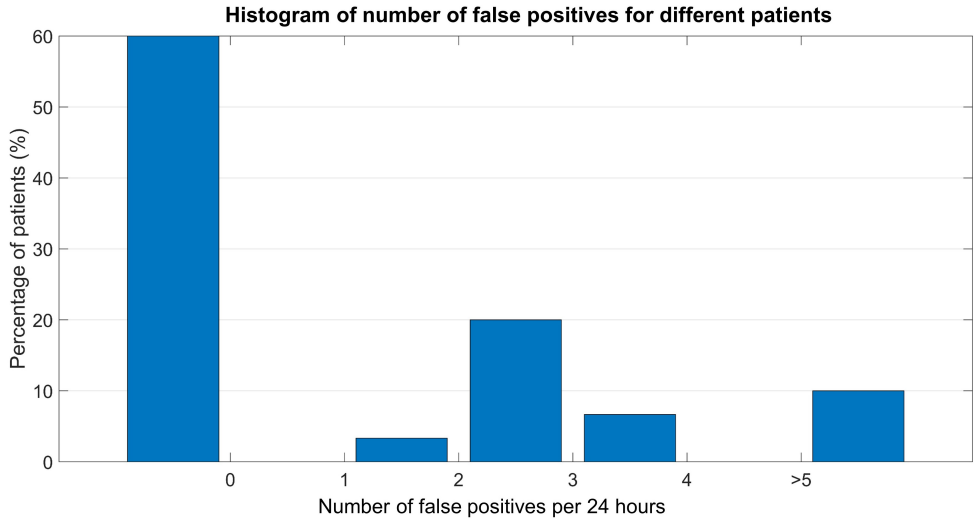


Figure 4.6: Histogram of number of false positives for different patients. It shows per bin the percentage of patients that have that many false positives per 24 hours. This figure shows that 60% of patients have 0 false positives. Additionally, 90% of patients had less than 4 false positives per 24 hours.

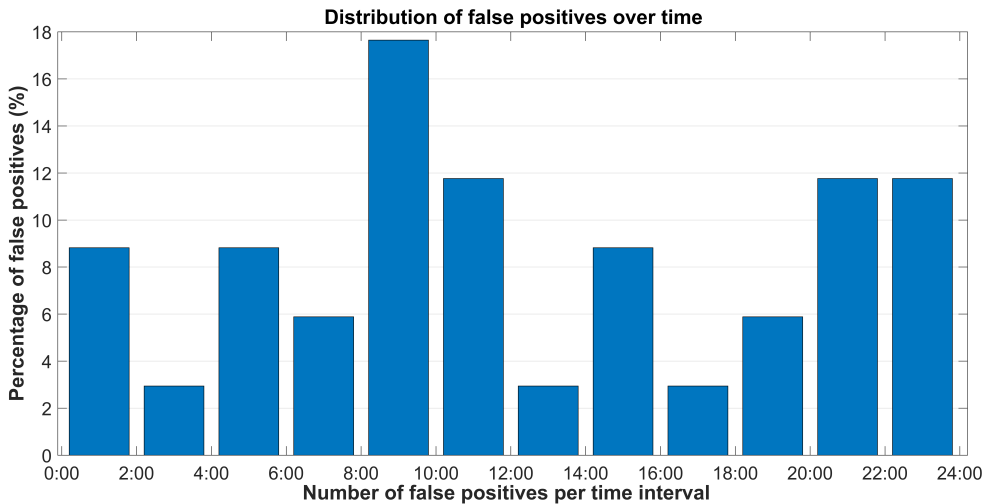


Figure 4.7: Distribution of all false positives ($n=34$) over time.

Table 4.2: Sensitivity and latency for the ECG seizure detection algorithm for seizures with different characteristics. The difference in sensitivity was tested with a Chi-square test and the difference in latency with a Kruskal-Wallis test.

		Sensitivity		Median latency in seconds (p5-p95)	
All seizures (n=58)		29.3%	-	41.4 s (17.9 s - 809 s)	-
Subject age	Children under 18 years (n=18)	31.6%	0.791	51.6 s (25.5 s - 65.4 s)	0.421
	Adults (n=39)	28.2%		37.0 s (17.1 s - 1147 s)	
Seizure Classification	Generalised (n=6)	16.7%	0.512	1204 s (-)	0.0301
	Temporal (n=21)	23.8%		24.1 s (16.9 s - 41.4 s)	
	Extratemporal (n=31)	35.5%		51.6 s (25.8 s - 75.1 s)	
Seizures with an increase in heart rate (n=23)		47.8%	-	36.5 s (17.3 s - 74.4 s)	-
Seizure Classification	Generalised (n=2)	0%	0.361	-	0.257
	Temporal (n=8)	50%		30.5 s (16.9 s - 41.4 s)	
	Extratemporal (n=13)	53.8%		36.5 s (25.5 s - 75.6 s)	

Only the seizure classification had a significant influence on the latency. Children had a slightly higher median false positive rate; 0.73 per patient per 24 hour compared to 0.00 for adults. This was however not statistically significant ($p=0.884$).

4.4 Discussion

An ECG seizure detection algorithm was created that consisted of the Pan-Tompkins algorithm, processing the heart rate, and a classifier. An acceptable sensitivity and latency and a very good false positive rate was seen. There was added value on Encevis EpiScan in terms of extra detected seizures. However, no added value was seen in terms of detection time. It is feasible to use the ECG algorithm on top of Encevis EpiScan, because of the very low false positive rate.

4.4.1 Sensitivity

In the literature, a better sensitivity is reported than observed in this study. However, algorithms described in literature are not always applicable for online use [46] or do not provide information on the latency and false positive rate [44]. Additionally, making a comparison to other algorithms is difficult, since performance is also depended on the used dataset. This study used an unselected patient group, while in other studies this is not always the case.

The moderate sensitivity in this study was a result of excessive movement prior to seizures or a minimal increases in heart rate during the seizure. Additionally, a

high threshold for identifying seizures was taken to decrease the false positive rate as much as possible. Adjusting this threshold can lead to a better sensitivity.

4.4.2 Latency

The detection latency is not often described in literature. The latency is however important on the EMU, because standardized tests are ideally performed during the beginning of a seizure. This research showed a good latency with the ECG algorithm, but no faster detections than Encevis EpiScan. However, this was researched on thirteen seizures that were detected by both algorithms. An improvement in latency was described in literature [33]. Such an improvement, may be achieved when investigating the algorithm on a bigger patient group. The detection time of the ECG algorithm cannot be improved tremendously, using other methods or settings. It took a while before an increase in heart rate was seen in the used dataset. Significantly faster detection is therefore not possible, since a detection is only possible when a heart rate change is present.

4.4.3 False positive rate

The false positive rate was very low, a median false positive rate of 0 was achieved. Since the ECG algorithm would be used on top of Encevis EpiScan, only an extreme low false positive rate was acceptable. This research has proven that a low false positive rate using ECG is possible. Nevertheless, further research should focus on a reduction of false positives. That way, a lower threshold for the identification of seizures can be taken and the entire performance of the algorithm will improved.

4.4.4 Patient characteristics

Different patient and seizure characteristics were evaluated to research their influence on the performance of the ECG algorithm. The added value of the algorithm might be highest in extra detected extra-temporal seizures or faster detection in temporal seizures. Encevis EpiScan has the lowest sensitivity in extra-temporal seizures, whereas the ECG algorithm had the highest sensitivity. Additionally, the ECG algorithm has the fastest response time in temporal seizures. These results are very promising, since the ECG algorithm performs best in the seizures in which Encevis EpiScan performs the worst. This shows that even though the ECG algorithm may not have a good sensitivity on its own, it does have added value on top of Encevis EpiScan. However, most of these results were not statistical significant, probably due to the small patient cohorts.

4.4.5 Future work

As explained previously, future research should focus on the reduction of false positives. The first step would be to collect noise-free ECGs. Some of the data that was used was very noisy which influenced the performance of the algorithm. Collecting data more carefully could already significantly improve the performance. Moreover,

it should be investigated if other methods for the measuring of the heart rate will improve the performance of the algorithm. For example, different placements of electrodes, different types of electrodes or even a completely different technique such as photoplethysmography might improve signal to noise ratio.

After collecting signals with a better signal-to-noise ratio, the algorithm itself could be further improved. First, not all parameter settings were optimized and this should be done before the implementation. As explained in the results, the Pan-Tompkins could not accurately determine the QRS-complexes in the presence of artefacts or in noisy ECGs. We would suggest to improve the performance of the Pan-Tompkins algorithm by using sophisticated algorithms. For example, by only searching for a new QRS-complex in a time frame when a new QRS-complex is suspected or by using advanced filter methods.

We do not believe there is added value of using other types of detectors (for example EMG or accelerometers) on top of Encevis EpiScan. Those detectors perform best on tonic-clonic seizures or hypermotor seizures. Staff almost always recognizes these types of seizures and the algorithm of Encevis EpiScan can already accurately detect these types of seizures. On the contrary, the ECG algorithm excels in the seizures that need improvement.

4.5 Conclusion

An ECG seizure detection algorithm was created with a sensitivity of 47.8% a median detection time of 36.5 seconds and a median false positive rate of 0.0 per day. Added value on Encevis EpiScan was seen in terms of extra detected seizures. No added value was seen in terms of faster detection time, but this needs to be researched on a larger patient group. The added value might be highest in extra-temporal and temporal seizures. Further research should focus on collecting noise-free ECGs. Thereafter, the detection of QRS-complexes can be improved.

Chapter 5

Alarm systems

The past chapters have shown that seizure detection algorithms can improve staff response to seizures. Nonetheless, a response to these algorithms can only occur when an alarm is given, and this function is currently not provided by Encevis EpiScan. Therefore, an alarm system has to be designed. The design of an alarm system is frequently overlooked, resulting in inefficient alarm systems. Impractical alarms can lead to alarm fatigue; alarms are considered as an annoyance and will be disabled, silenced or ignored by the observer. Rather than creating a safer environment, nurses are desensitized by alarms. These problems can be overcome, but the design of an alarm system is very important. An appropriate alarm system can result in a better response to warnings and therefore create a safer environment.

What a good alarm system is, is however not clear. Alarms come in different types, and what is best depends on the situation. To give an example, a housebreaking alarm is designed to induce flight and is therefore not suitable in a work situation, but very effective to scare burglars. So there is not one clear design that works in every environment. We will therefore review different alarm systems and why people do or do not respond to it. With this information, recommendations can be made to what design would be suitable for an alarm system at the EMU of SEIN.

The main question in this chapter is what type of alarm system is recommended for the use of seizure detection algorithms at the EMU of SEIN. To answer this question, we will research the following questions with a literature study:

- Why do people respond to alarms?
- How does workload influence alarm response?
- What is known about alarm response in the medical sector?
- What type of alarms exist? And what is known about these alarm types?

5.1 Response to alarm

An alarm is a stimulus which gives information about a future event with a possible negative outcome. People perceive it as a possible threat on which they need to act. How people respond to these threats depends on different properties of the threat. In case of alarms, the following are especially important: the extent to which active coping is possible, the imminence of the danger and the probability of the impending danger to actually materialize [47].

This first property is **to which extent active coping is possible**; can something be done to eliminate the threat? So if there are directions how to cope with an alarm, it might be easier to react on an alarm. Additionally, alarm systems are only beneficial if something can be done to eliminate the threat. In the EMU setting, it has to be very clear what needs to be done when an alarm occurs. This way, staff knows how to react and can respond accurate to an alarm.

The second property embeds **the imminence of the danger**. For example, if an alarm occurs when someone might be dying, people are very likely to respond. The threat is very detrimental if it would materialize. In the setting of an EMU, the threat (a possible seizure) is mostly fixed. However, the perception of this threat can be different. It is therefore important, that during the implementation of such a system, that is explicitly told that reaction to alarms can possibly prevent harm to the patient.

The last property is **the probability of the threat to actually occur**. In the EMU setting, this is the probability an alarm is true. When many false positives are present, the likelihood an alarm is true will decrease and the motivation to act on the threat will decline, this is also called the cry wolf effect [48, 49]. Research has even shown that response rate is comparable to the reliability of the system [49–51]. This can be explained by the choice strategy most people use; probability matching. When one outcome appears with a higher probability than the other, people tend to match their choice based on the probability. For example, if people need to guess which color of light will be shown (and 75% of the trials the light is green and 25% is red), people will tend to choose 75% of the trials for green and 25% for red [52]. Another choice strategy than can be used in the response to alarms is maximizing; where people tend to react to all or no alarms in the given set. In other words, in the same example of red and green light, people will tend to always choose for green since this will have the highest chance of good results [52]. So the response to alarms depends on choice strategy, but it also depends on personality traits [53]. Choices are not only made on chances, but as well based on norms, habits, and expectancies of the decision maker [54].

False positives have a negative effect on this third mechanism. The impact of this effect is partly irreversible. When a person has an experience with a lot of false positives, he or she will perceive a new alarm system as less reliable, even when the experience is independent and not relevant [48]. This is also the case in the medical workforce, where alarms can represent life-threatening conditions [55]. Luckily, when a true alarm occurs, the credibility of the alarm will increase and reverse this effect.

Futhermore, there are methods to overcome the cry wolf effect. As already ex-

plained, there is a high tendency of humans to respond to a high-urgency alarm [47]. So the imminence of the danger is more important than the probability it will occur. Additionally, people can perceive the probability that the danger will occur differently than the actual reliability of the alarm system. Research has shown that when participants were told that false alarms would be less frequent than they actually were, the response rate was higher [47].

Concluding, the response to alarms is dependent on three different behavioural mechanisms. In EMU setting it should be clear what actions should be taken when an alarm is set off. Additionally, the perception of the system is more important than the actual reliability of the system. And lastly, the amount of false positives should be decreased as much as possible to diminish the cry wolf effect.

5.2 Influence of workload on response rate

In EMU settings, the primary work of staff is monitoring of patients, next to giving medication, helping patients with daily activities, filling in reports and discussing patients with physicians and EEG technicians. When busy with other work, alarms might not always be noticed directly. To overcome this problem, an alarm has to be picked up by the nurses parallel of other work [56]. For example, when staff at the EMU is filling in reports, a visual alarm might be missed since attention is focused on the reports, while an audible alarm is less easily missed. Therefore an alarm system has to be designed in such a way that it attracts people's attention even when busy with other work. Another issue to overcome the attention problem, is that the observer needs to assess directly if the alarm needs a shift in attention or not [56]. Research has shown that people can only remember a small amount of unrelated information like different sounds [57]. Like on ICU's, often too many sounds are used whereby only a small amount can be recognized [58]. Therefore it is very important than only a few different sounds are used. At the EMU of SEIN Heemstede, currently only one other alarm is used; that of the alarm button. When this button is pressed, the patient feels a seizure or a visitor of the patient recognizes a seizure. To keep it manageable, we would recommend only two sounds; one for definitely a seizure (alarm button) and one for possibly a seizure (seizure detection).

When the attention goes to the alarm, the observer has the choice if he is going to respond to it. If the staff is busy with other tasks, there occurs a dual-task paradigm; whether attention must be shifted from the primary task to the response to an alarm. If the primary workload is important, alarm task performance worsens when primary task workload increases [50]. Operators need to prioritize their time and effort between different tasks and base this on task-critical and likelihood information [56, 59]. So how critical is it to respond to an alarm and what is the likelihood that the alarm is true? For example, if staff is busy and they think a patient is not having a seizure, they might not respond to an alarm. The dual-task paradigm can be overcome at the EMU when it is protocol to always leave primary workload and to shift to the response of an alarm. In other words, it is more critical to respond to an alarm than to go further with the primary task. Protocols need to be made on how staff needs to respond. For example, at every alarm diagnostic questions must be asked to the

patient to evaluate if the patient has a seizure. When this is the case, all standardized tests can be performed, when this is not, staff can go back to their primary workload.

5.3 Alarms in the medical section

5.3.1 Alarms in the EMU

Only one article on alarms in the EMU was found during the literature search. Available safety signals at EMUs were telemetry (cardiac/pulse oximetry), nurse call buttons, event push buttons, patient noise and video [60]. Not all events lead to response, in fact 10% of the signals were missed [60]. It was not reported if the type of alarm influenced the alarm rate.

5.3.2 Alarms at other departments

More research is present in other fields of medicine; most articles written on the ICU setting where alarm fatigue is a well-known problem. A lot of existing alarm systems try to achieve the best sensitivity, even with an extremely high false positive rate. Research has shown that only 1% to 20% of alarms at an ICU is relevant, whereas 44% are technical false alarms [61, 62]. These alarms are known as 'nuisance' alarms [63]. The alarm is considered as an annoyance and will be disabled, silenced or ignored by the observer. Rather than creating a safer environment, observers are desensitized by all alarms. So, an excessive amount of alarms should be avoided to reduce alarm fatigue. This can be incorporated in the EMU by only setting alarms where patient safety is at risk or when diagnostic tests are necessary. When multiple seizures have already occurred, a seizure detection algorithm might not be necessary. Also when the chance of detection a seizure is extremely low, it might be better to turn off seizure detection (for example in very short seizures). Since in that case positive predictive value is very low and alarms will be seen as more nuisance.

The response mechanism to alarms in the medical sector, is the same as already described. Nurse response is dependent on the criticality of the patient, signal duration, rarity of alarming device and workload [50, 61, 64–67] Nurses determine the danger of the threat, use probability matching which takes reliability of the alarm into account and dual-task paradigm occurs based on the primary workload. Primary workload can also lead to alarms that are unnoticed, for example if nurses have to do off-floor activities [68]. A good monitoring system, high enough alarm volumes and a beeper system can solve these problem.

Another problem with most alarms in a medical sector is that they are designed to forcefully disrupt attention in stead of providing information [68]. A reaction to alarms is only possible when enough information at the time of an alarm is given to decide what an appropriate response would be. For example, is there a life threatening situation or is it less dangerous? As already explained, in the EMU setting this information can be given by having different alarm sounds for the alarm button (patient asks for help) and for the seizure detection algorithm (there is possibly a seizure).

From the alarm sounds has to be clear which of these alarm is more alarming and needs a faster response.

5.4 Different types of alarms

Different alarm types were found in literature; auditory alarms, visual alarms, tactile alarms and smart alarm systems. These will be discussed in further detail.

5.4.1 Auditory alarm

People react faster to auditory warnings than to visual warnings [69, 70]. Hearing is our natural warning sense, when hearing a sound is natural instinct to identify its source [71]. Some believe that auditory alarms should only be used to gain attention and that visual alarms should be used to direct and give information [72]. Auditory alarms are less useful for providing additional information about the detection.

When using an auditory alarm, it has to have multiple characteristics. First of all, there has to be a small number of alarm sounds, to ensure easy recognition [73]. There are standard audio alarms, of which the IEC 60601 is an example [74]. There are some indications that these standardized alarm sounds may be effective [72], while other research has shown that physicians found it difficult to distinguish the different alarm sounds [75]. When a new alarm sound is made it has to be easy to localize, resistant to masking by other sounds, allow communication and easy to learn and retain [73]. The duration of the sound is also important for two reasons, shorter sounds are more difficult to recognize [71] and response rate is higher in longer alarm duration [65, 67]. This response rate can be explained by a higher perceived urgency due to the longer signal duration. However, a very long signal duration might be perceived as annoying and the signal might lose its power.

When using multiple alarm sounds, it is important that they have a different rhythm. Since sounds can easily be confused when they have the same rhythm [73].

5.4.2 Visual alarms

Visual alarms have multiple benefits; best response rate can be seen when auditory and visual alarms are combined [69, 70], auditory warnings can be missed in high-visual-load conditions [76] and visual warnings can provide more information to sounds [72]. However, visual alarms have the disadvantage of not always being noticed immediately. Observers tend to only look at the area that provides most information [77] and in an EMU setting this might not be a fixed place. The primary task of nurses is monitoring the patients, so the main focus will be on the screens. However, staff also has other work, where the focus does not lay on the screen. If visual warnings are given at the screen, the warning might be missed.

When a visual alarm system is designed, multiple characteristics have to be taken into consideration; the placement, visibility, and prioritization. These characteristics will be discussed in further detail.

One of the most important characteristic is the **placement** of the warning, since it will influence the likelihood the warning will be seen by the user [78]. There are guidelines for what area can be directly seen from a fixed view [79], but due to multiple monitors and no fixed viewing point this cannot be implemented at the EMU of SEIN. However, there is a bigger peripheral vision where things can be noticed without direct attention. With pre-attentive processes, the brain filters where interesting parts are and where the perceptual field of view should lie [56]. So if something happens that attracts attention in the peripheral view, attention will be automatically shifted to it. At the EMU, the best place for visual warnings might be somewhere in or around the screen of the corresponding patient. This way, the alarm is often in peripheral vision, it shows which patient is affected and attention shifts automatically to the right patient and information (EEG and video of the patient).

A visual warning can only be seen when it is clearly visible for the user. For a good **visibility**, multiple factors need to be considered; size, luminance and background contrast [78]. Peripheral vision is especially good at picking up change [56], so flickering warnings might be better for attracting attention. The size of the target is dependent on the viewing distance and contrast [78].

Visual warnings are usually more **prioritized** when it is perceived as a high hazard. This can be easily influenced by the colour of the warning. Red and orange increase the hazard when compared to green, blue and white [80]. Higher priority warnings will also lead to being more easy to detect in peripheral vision. However, high priority signals will also be perceived as more nuisance [56].

Colours can also be used to code for different situations, but a higher amount of features also will result in more confusion [78]. In the EMU setting, colours could be used to provide information on the threat of the information. For example, red when it is clearly a seizure and orange when it is possibly a seizure.

5.4.3 Tactile alarms

Tactile alarms are worn on the body of the observer and warn by sense or touch, for example by vibrating, pressure or temperature changes. It is most suited for situations when visual or auditory warnings are impractical or when switching the attention to a visual display might be unsafe [81–83]. An example of a vibro-tactile warning system can be seen in Figure 5.1. Tactile warnings are a new elegant way of warning that can easily direct attention. However, in the EMU visual and auditory warnings may be less nuisance for the observer. A vibrating alarm could be used as a type of pager, when staff is off-floor. However, there is always at least one nurse at the monitoring unit.

5.4.4 Smart alarms

When researching smart alarms, a lot of techniques are described in literature to reduce false positives, for example; signal filtering, combining features and smarter classifiers [62, 63, 84, 85]. However, these described techniques focus more on a smart and better algorithm than in the creation of a good alarm system. Of course this is

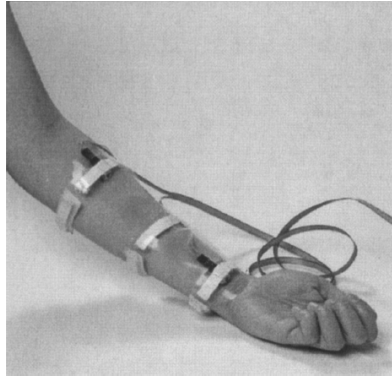


Figure 5.1: Example of a vibro-tactile warning system. This system was used during surgery to warn on deviating heart rates. Vibrations at the wrist implied a decrease in heart rate and vibrations at the elbow implied an increase in heart rate. Adapted from [81].

very important, but not in the scope of this chapter. Additionally, the ECG seizure detection algorithm already uses a smart-classifier with adjustable thresholds. The algorithm of Encevis EpiScan also compares features with past results to reduce false positives. We will therefore focus on ideas for smart alarms systems.

A **time delay** could be implemented before an alarm goes off [86]. A parameter needs to reach a certain threshold during an amount of time, before a alarm goes off. Research has shown, that implementation of a 14-second delay could reduce false alarms by 50% in a medical alarm system and a delay of 19 seconds a reduction of 67% [87]. However, since we are focussing on fast detection (in example a few seconds), we would not suggest to implement this.

A suitable alarm system for the EMU, might be to generate **different levels of warning**. For example, a watch level and an emergency level [88, 89]. This way, when there is a possible seizure (with lower thresholds in the algorithms), staff is notified that they should watch the patient. And when there is certainly a seizure (with higher thresholds in the algorithms), staff need to respond immediately. Research has shown that using this type of alarm system, observers could clearly identify the urgency and this was reflected in response time, while perceived annoyance was lower [89]. This could be implemented at the EMU by showing a visual alarm for the watch level and an auditory alarm can be added at the emergency level. Additionally, the colour of the visual alarm could be used to explain the level of alarm. While this type of system would be very practical at the EMU, Encevis EpiScan and the ECG algorithm do not provide the information to build this system. Only one output is given; a detection or no detection.

Trend display can be used to provide more information on top of alarms. A trend display cannot be called an alarm system, since it does not alarm the users. However it might have benefits as an addition to an alarm system. It can provide in-

formation on the reason why a seizure is detected. To give two examples, the location of a detection can be shown or the probability someone is having a seizure can be shown. Research has shown that when displaying information, graphic information is better than numeric information and displaying history is also beneficial [90]. While the design of displays is extensively researched, it is unclear what effect trend displays have instead or on top of an alarm system.

Another possibility, might be to have an **alarm at the patient side**. During that alarm, patients have to press a button or answer some cognitive questions to evaluate if they have a seizure [91, 92]. This might lead to a high response rate and fast response time, since the patient can answer themselves. It might also reduce how nuisance an alarm is experienced by staff. If such a system would be used, pilot studies have to be performed to evaluate if it would be a good solution at the EMU. Additionally, such an alarm system would only be applicable during day-time.

5.5 To take into consideration

Different types of alarm system have been explained, but more characteristics play a role [92]. Some of these will be explained further.

First of all, when will the alarm be **disabled**? Is it after a while or only when nurses disable it? A good system at the EMU might be to disable the alarm, when the intercom is used to communicate with the patient. This way, the alarm will automatically be silenced when there is a response.

Should it be possible to **silence** future alarms for a specific patient? This might come in handy when a patient has a high false positive rate. It should however be clear when an alarm can be silenced, and when not. Otherwise, alarms might be silenced too often. It also would be good if only one of the algorithms can be silenced, if only one causes false positives. However, this information should then be present. Additionally, it would be beneficial if there is a visual indicator that the alarm is silenced [92]. Lastly, it might be good to have a time-limit to the silencing, for example when a new nurse shift starts.

In the ideal situation, **customized** thresholds are set for individual patients. This can be used for decreasing false positives. One study has shown that customizing alarm settings can reduce warnings with 43%, while increasing response rate to warnings and decreasing the perceived noise by staff [93]. However, another study showed a reduction of warnings with 24%, while no difference in nurses' attitude towards alarms was seen [94]. In the EMU setting, the thresholds of the ECG seizure detection algorithm could be increased when it gives too many false alarms. However, knowledge of the algorithms is necessary to customize thresholds for specific patients. Additionally, one or even more seizures have to be measured before good choices can be made at levels of thresholds. Since patients typically have only a few seizures during their stay, it probably would not be feasible to manually adjust thresholds.

5.6 Recommendations

With all information in mind, we would suggest to combine an auditory alarm with an visual alarm. We would recommended two levels of warnings; one for the already present alarm button and one for the seizure detection technique. Two different sounds should be used for the different alarm levels. The sound should be played close the screen of the corresponding patient, that way visual attention automatically shifts to the patient. The visual alarm should be present somewhere around the screen of the patient. A clear orange colour could be used for the first level of warning and a red colour for the second level of warning. If only the visual alarm is used, we would recommend to use flickering light, so that it attracts attention more easily. If the visual alarm is used in combination with the auditory alarm, this flickering might not be necessary while it does increase perceived nuisance.

In terms of smart alarm, different levels of warning might work well for the seizure detection algorithm. Then a third level of warning should be created. However, the algorithms currently do not provide the information to build this system. Additionally, an alarm at the patient side might work good at the EMU. A pilot study at the EMU should be performed, to evaluate if this would work in this setting.

And lastly alarm protocols and clear instructions have to be made. It has to be clear what needs to be done during an alarm and what is expected from the nurses. We would suggest that during every alarm, some cognitive questions are asked to the patient. This way can be evaluated if the patient has a seizure, and there is always a response even in clinically less clear seizures or sub-clinical seizures.

Chapter 6

Conclusions

The goal of this study was to make improvements to an available EEG based detection system to make it feasible for online use on the EMU. Results show good sensitivity of EEG seizure detection algorithms, but the latency and false positive rate are points of improvement. An ECG seizure detection algorithm was created that has added value in terms of extra detected seizures. No alarm system was available, hence recommendations for an alarm systems were given.

The algorithms Encevis EpiScan and BESA Epilepsy were researched. We were able to show that 66.1% of the undetected seizures by staff, could be recognized by one of the algorithms in a dataset of 188 seizures. Additionally, in the majority of the seizures the algorithm detection preceded the detection by staff. The algorithms had acceptable false positive rates in most cases. Based on the results of this study, Encevis EpiScan will likely be implemented at SEIN. However, the false positive rate and latency are still points of improvement.

An ECG seizure detection algorithm was created. This algorithm consisted of the Pan Tompkins algorithm, processing the heart rate and a classifier. The algorithm showed a sensitivity of 47.8% with a median latency of 36.5 seconds in a dataset of 23 seizures. It is feasible to use the algorithm on top of Encevis EpiScan, since it has a very low false positive rate (median of 0 per 24 hours). Added value on Encevis EpiScan was observed in terms of extra detected seizures. No faster detection time was observed, but this needs to be researched on a larger patient group. The added value might be highest in extra-temporal and temporal seizures. Further research should focus on collecting noise-free ECGs and improving QRS-complexes detection.

Lastly, different alarm systems were studied. The response to alarms depends on different behavioural mechanisms, for example to which extent active coping to an alarm is possible and the probability an alarm is true. Other work of staff can negatively influence response rate. All these behavioural mechanisms should be taken into consideration when designing an alarm system. Different alarm systems are available, combining visual and auditory alarms may result in the best response. Using a smart alarm could also be beneficial, but these new techniques have not yet been extensively researched.

Chapter 7

Recommendations

Implementation of Encevis EpiScan Based on the results of this study I find it feasible to use Encevis EpiScan. It has proven added value on top of the nurse staff. Secondly, as a expertise centre, I believe SEIN should stand out for hightech innovations. Investing in new implementations in the clinical settings helps the centre to increase the quality and deliver care that cannot be achieved at other hospitals.

Improving an ECG seizure detection algorithm The created ECG seizure detection algorithm can be used on top of Encevis EpiScan to improve sensitivity and possibly reduce detection time. I believe an ECG seizure detection algorithm can provide the best added value compared to other types of detectors. I would therefore suggest to proceed with the created algorithm. However, I advise to first collect noise-free ECGs or explore other methods for data collection. Whereafter, parameter settings need to optimized and the performance of the Pan-Tompkins algorithm can be improved. These improvements are necessary for an optimum performance.

Alarm system A good alarm system has to be designed before implementation. I suggest to combine auditory and visual alarms. Different alarms can be used to distinguish the alarm button from the seizure detection algorithm. Additionally, alarm protocols and clear instructions have to be made, to ensure an appropriate response to alarms. I would suggest that during every alarm, staff should ask cognitive questions to the patient to evaluate if he/she is having a seizure.

Smart alarms Using a smart alarm might be beneficial, but more research on this topic is necessary. Creating different levels of warning with a different sensitivity might be a good system for the EMU. Another possibility is to create an alarm at the patient side. This is a highly innovative solution, so pilot studies need to show if this would be a good solution at the EMU.

Online evaluation When the system is implemented, I suggest to evaluate the effect online. Current research has focused on retrospective analysis and therefore the online performance is still unclear.

Bibliography

- [1] Conor Friedersdorf. *Immortal but Damned to Hell on Earth*, 2015.
- [2] David J. Thurman, Ettore Beghi, Charles E. Begley, Anne T. Berg, Jeffrey R. Buchhalter, Ding Ding, Dale C. Hesdorffer, W. Allen Hauser, Lewis Kazis, Rosemarie Kobau, Barbara Kroner, David Labiner, Kore Liow, Giancarlo Logroscino, Marco T. Medina, Charles R. Newton, Karen Parko, Angelia Paschal, Pierre-Marie Preux, Josemir W. Sander, Anbesaw Selassie, William Theodore, Torbjörn Tomson, and Samuel Wiebe. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia*, 52(SUPPL. 7):2–26, sep 2011.
- [3] Rui Quintas, Alberto Raggi, Ambra M. Giovannetti, Marco Pagani, Carla Sabariego, Alarcos Cieza, and Matilde Leonardi. Psychosocial difficulties in people with epilepsy: A systematic review of literature from 2005 until 2010. *Epilepsy & Behavior*, 25(1):60–67, sep 2012.
- [4] Aidan Neligan, Gail S. Bell, Simon D. Shorvon, and Josemir W. Sander. Temporal trends in the mortality of people with epilepsy: A review. *Epilepsia*, 51(11):2241–2246, nov 2010.
- [5] Robert S Fisher, Walter Van Emde Boas, Warren Blume, Christian Elger, Pierre Genton, Phillip Lee, and Jerome Engel. Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, 46(4):470–472, apr 2005.
- [6] Solomon L Moshé, Emilio Perucca, Philippe Ryvlin, and Torbjörn Tomson. Epilepsy: new advances. *The Lancet*, 385(9971):884–898, mar 2015.
- [7] Anne T. Berg, Samuel F. Berkovic, Martin J. Brodie, Jeffrey Buchhalter, J. Helen Cross, Walter van Emde Boas, Jerome Engel, Jacqueline French, Tracy A. Glauser, Gary W. Mathern, Solomon L. Moshé, Douglas Nordli, Perrine Plouin, and Ingrid E. Scheffer. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*, 51(4):676–685, apr 2010.
- [8] Robert S. Fisher, J. Helen Cross, Jacqueline A. French, Norimichi Higurashi, Edouard Hirsch, Floor E. Jansen, Lieven Lagae, Solomon L. Moshé, Jukka Peltonen, Eliane Roulet Perez, Ingrid E. Scheffer, and Sameer M. Zuberi. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, pages 1–9, mar 2017.

- [9] Gregory D. Cascino. Video-EEG Monitoring in Adults. *Epilepsia*, 43(SUPPL. 3):80–93, jun 2002.
- [10] Daniel F. Ghougassian, Wendyl D’Souza, Mark J. Cook, and Terence J. O’Brien. Evaluating the Utility of Inpatient Video-EEG Monitoring. *Epilepsia*, 45(8):928–932, aug 2004.
- [11] Firas Fahoum, Nurit Omer, Svetlana Kipervasser, Tal Bar-Adon, and Miri Neufeld. Safety in the epilepsy monitoring unit: A retrospective study of 524 consecutive admissions. *Epilepsy & Behavior*, 61:162–167, aug 2016.
- [12] Mirja Johanson, Katja Valli, and Antti Revonsuo. How to assess ictal consciousness? *Behavioural Neurology*, 24(1):11–20, 2011.
- [13] Andrew Bauerschmidt, Nika Koshkelashvili, Celestine C. Ezeani, Ji Yeoun Yoo, Yan Zhang, Louis N. Manganas, Kailash Kapadia, Deanna Palenzuela, Christian P. Schmidt, Regina Lief, Bridget T. Kiely, Tenzin Choezom, Michael McClurkin, Andrew Shorten, Kamil Detyniecki, Lawrence J. Hirsch, Joseph T. Giacino, and Hal Blumenfeld. Prospective assessment of ictal behavior using the revised Responsiveness in Epilepsy Scale (RES-II). *Epilepsy & Behavior*, 26(1):25–28, jan 2013.
- [14] Lisanne Jansen Holleboom. Technical Medicine Master thesis - Improving the nurse response to seizures in the Epilepsy Monitoring Unit with help of EEG-based automatic seizure detection, 2016.
- [15] Marie Atkinson, Karthika Hari, Kimberly Schaefer, and Aashit Shah. Improving safety outcomes in the epilepsy monitoring unit. *Seizure*, 21(2):124–127, mar 2012.
- [16] G Klem, H Luders, H Jasper, and C Elger. Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology*, 10(2):370–375, may 1958.
- [17] Katherine S. Eggleston, Bryan D. Olin, and Robert S. Fisher. Ictal tachycardia: The headheart connection. *Seizure*, 23(7):496–505, aug 2014.
- [18] William Tatum, Aatif Husain, Selim Benbadis, and Peter Kaplan. *Handbook of EEG Interpretation*. 2008.
- [19] Norman K. So and Warren T. Blume. The postictal EEG. *Epilepsy & Behavior*, 19(2):121–126, oct 2010.
- [20] Chrysostomos P. Panayiotopoulos. *A clinical guide to epileptic syndromes and their treatment: Based on the new ILAE diagnostic scheme*. mar 2002.
- [21] J. Gotman. Automatic recognition of epileptic seizures in the EEG. *Electroencephalography and Clinical Neurophysiology*, 54(5):530–540, nov 1982.
- [22] U. Rajendra Acharya, S. Vinitha Sree, G. Swapna, Roshan Joy Martis, and Jasjit S. Suri. Automated EEG analysis of epilepsy: A review. *Knowledge-Based Systems*, 45:147–165, jun 2013.

- [23] Turkey N Alotaiby, Saleh A Alshebeili, Tariq Alshawi, Ishtiaq Ahmad, and Fathi E Abd El-Samie. EEG seizure detection and prediction algorithms: a survey. *EURASIP Journal on Advances in Signal Processing*, 2014(1):183, dec 2014.
- [24] Sriram Ramgopal, Sigride Thome-Souza, Michele Jackson, Navah Ester Kadish, Iván Sánchez Fernández, Jacquelyn Klehm, William Bosl, Claus Reinsberger, Steven Schachter, and Tobias Loddenkemper. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy & Behavior*, 37:291–307, aug 2014.
- [25] Manfred M. Hartmann, F. Furbass, Hannes Perko, Ana Skupch, Katharina Lackmayer, Christoph Baumgartner, and Tilmann Kluge. EpiScan: Online seizure detection for epilepsy monitoring units. In *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 6096–6099. IEEE, aug 2011.
- [26] F. Furbass, M Hartmann, H Perko, A Skupch, P. Dollfuss, G Gritsch, C Baumgartner, and T Kluge. Combining time series and frequency domain analysis for a automatic seizure detection. In *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 1020–1023. IEEE, aug 2012.
- [27] Rüdiger Hopfengärtner, Burkhard S. Kasper, Wolfgang Graf, Stephanie Gollwitzer, Gernot Kreiselmeyer, Hermann Stefan, and Hajo Hamer. Automatic seizure detection in long-term scalp EEG using an adaptive thresholding technique: A validation study for clinical routine. *Clinical Neurophysiology*, 125(7):1346–1352, jul 2014.
- [28] F. Furbass, P. Ossenblok, M. Hartmann, H. Perko, A. M. Skupch, G. Lindinger, L. Elezi, E. Pataraiia, A. J. Colon, C. Baumgartner, and T. Kluge. Prospective multi-center study of an automatic online seizure detection system for epilepsy monitoring units. *Clinical Neurophysiology*, 126(6):1124–1131, 2015.
- [29] Guido Rubboli, Sandor Beniczky, Steven Claus, Maria Paola Canevini, Philippe Kahane, Hermann Stefan, Walter van Emde Boas, Demetrios Velis, Elise Reus, Antonio Gil-Nagel, Bernhard J. Steinhoff, Eugen Trinkka, and Philippe Ryvlin. A European survey on current practices in epilepsy monitoring units and implications for patients’ safety. *Epilepsy & Behavior*, 44:179–184, mar 2015.
- [30] K. Jansen and L. Lagae. Cardiac changes in epilepsy. *Seizure*, 19(8):455–460, oct 2010.
- [31] Fritz Leutmezer, Christiana Schernthaner, Stefanie Lurger, Klaus Pötzelberger, and Christoph Baumgartner. Electrocardiographic Changes at the Onset of Epileptic Seizures. *Epilepsia*, 44(3):348–354, mar 2003.
- [32] Maeike Zijlmans, Danny Flanagan, and Jean Gotman. Heart Rate Changes and ECG Abnormalities During Epileptic Seizures: Prevalence and Definition of an Objective Clinical Sign. *Epilepsia*, 43(8):847–854, aug 2002.

- [33] F Fürbass, S Kampusch, E Kaniusas, J Koren, S Pirker, R Hopfengärtner, H Stefan, T Kluge, and C Baumgartner. Automatic multimodal detection for long-term seizure documentation in epilepsy. *Clinical Neurophysiology*, 128(8):1466–1472, aug 2017.
- [34] Anouk Van de Vel, Kris Cuppens, Bert Bonroy, Milica Milosevic, Katrien Jansen, Sabine Van Huffel, Bart Vanrumste, Lieven Lagae, and Berten Ceulemans. Non-EEG seizure-detection systems and potential SUDEP prevention: State of the art. *Seizure*, 22(5):345–355, jun 2013.
- [35] A. Ulate-Campos, F. Coughlin, M. Gaínza-Lein, I. Sánchez Fernández, P.L. Pearl, and T. Loddenkemper. Automated seizure detection systems and their effectiveness for each type of seizure. *Seizure*, 40:88–101, aug 2016.
- [36] M. Van Bussel, J. B. A. M. Arends, F. Massé, A. Serteyn, I. Y. Tan, J. Penders, and P. A. M. Griep. A state-of-the-art wearable sensor for heart rate based seizure detection in epilepsy. In *Proceedings of the 9th European Congress of Epileptology*, 2010.
- [37] Jiapu Pan and Willis J. Tompkins. A Real-Time QRS Detection Algorithm. *IEEE Transactions on Biomedical Engineering*, BME-32(3):230–236, mar 1985.
- [38] Szi-Wen Chen, Hsiao-Chen Chen, and Hsiao-Lung Chan. A real-time QRS detection method based on moving-averaging incorporating with wavelet denoising. *Computer Methods and Programs in Biomedicine*, 82(3):187–195, jun 2006.
- [39] F. Portet, A. I. Hernández, and Guy Carrault. Evaluation of real-time QRS detection algorithms in variable contexts. *Medical & Biological Engineering & Computing*, 43(3):379–385, jun 2005.
- [40] Iñaki Romero, Bernard Grundlehner, and Julien Penders. Robust beat detector for ambulatory cardiac monitoring. *Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Engineering the Future of Biomedicine, EMBC 2009*, pages 950–953, 2009.
- [41] B.-U. Kohler, Carsten Hennig, and Reinhold Orglmeister. The principles of software QRS detection. *IEEE Engineering in Medicine and Biology Magazine*, 21(1):42–57, 2002.
- [42] G M Friesen, T C Jannett, M Jadallah, S L Yates, S R Quint, and H T Nagle. A comparison of the noise sensitivity of nine QRS detection algorithms. *IEEE Transactions on Biomedical Engineering*, 37(1):85–98, 1990.
- [43] Bert Uwe Köhler, Carsten Hennig, and Reinhold Orglmeister. The principles of software QRS detection. *IEEE Engineering in Medicine and Biology Magazine*, 21(1):42–57, 2002.
- [44] Carolina Varon, Katrien Jansen, Lieven Lagae, and Sabine Van Huffel. Detection of Epileptic Seizures by Means of Morphological Changes in the ECG. *Computing in Cardiology Conference (CinC)*, pages 863–866, 2013.

- [45] Thomas De Cooman, Carolina Varon, Borbála Hunyadi, Wim Van Paesschen, Lieven Lagae, and Sabine Van Huffel. Online Automated Seizure Detection in Temporal Lobe Epilepsy Patients Using Single-lead ECG. *International Journal of Neural Systems*, 0(0):1750022, feb 2017.
- [46] Carolina Varon, Katrien Jansen, Lieven Lagae, and Sabine Van Huffel. Can ECG monitoring identify seizures? *Journal of Electrocardiology*, 48(6):1069–1074, nov 2015.
- [47] James P. Bliss, Richard D. Gilson, and John E. Deaton. Human probability matching behaviour in response to alarms of varying reliability.pdf. *Ergonomics*, 38(11):2300–2312, 1995.
- [48] Shlamo Breznitz. *Cry Wolf: The Psychology of False Alarms*. 1984.
- [49] J. Bliss, M. Dunn, and B. S. Fuller. Reversal of the Cry-Wolf Effect: An Investigation of Two Methods to Increase Alarm Response Rates. *Perceptual and Motor Skills*, 80(3_suppl):1231–1242, jun 1995.
- [50] James P Bliss and Mariea C Dunn. Behavioural implications of alarm mistrust as a function of task workload. *Ergonomics*, 43(9):1283–1300, sep 2000.
- [51] David R. Shanks, Richard J. Tunney, and John D. McCarthy. A re-examination of probability matching and rational choice. *Journal of Behavioral Decision Making*, 15(3):233–250, jul 2002.
- [52] Derek J. Koehler and Greta James. Probability matching in choice under uncertainty: Intuition versus deliberation. *Cognition*, 113(1):123–127, oct 2009.
- [53] J B Biggs and J P Das. Extreme response set, internality-externality and performance. *The British journal of social and clinical psychology*, 12(2):199–210, jun 1973.
- [54] A Tversky and D Kahneman. Rational Choice and the Framing of Decisions. *Journal of Business*, 59(4):S251–S278, 1986.
- [55] Christopher P Bonafide, Richard Lin, Miriam Zander, Christian Sarkis Graham, Christine W Paine, Whitney Rock, Kathryn E Roberts, Margaret Fortino, and Vinay M Nadkarni. Association between exposure to non-actionable physiologic monitor alarms and response time in a children’t hospital. *J Hosp Med.*, 10(6):345–351, 2016.
- [56] David D Woods. The Alarm Problem and Directed Attention in Dynamic Fault Management. *Ergonomics*, 38(11):2371–2393, 1995.
- [57] George A Miller. The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological review*, 63(2), 1956.
- [58] Kathryn Momtahan, Raymond Hetu, and Brian Tansley. Audibility and identification of auditory alarms in the operating room and intensive care unit. *Ergonomics*, 36(10):1159–1176, 1993.

- [59] Ernesto A Bustamante. A Signal Detection Analysis of the Effects of Workload, Task-Critical and Likelihood Information on Human Alarm Response. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 49(17):1513–1517, sep 2005.
- [60] Hae W. Shin, Page B. Pennell, Jong W. Lee, Heidi Doucette, Shraddha Srinivasan, and Barbara A. Dworetzky. Efficacy of safety signals in the epilepsy monitoring unit (EMU): Should we worry? *Epilepsy & Behavior*, 23(4):458–461, apr 2012.
- [61] Michael F Rayo and Susan D Moffatt-Bruce. Alarm system management: evidence-based guidance encouraging direct measurement of informativeness to improve alarm response. *BMJ Quality & Safety*, 24(4):282–286, apr 2015.
- [62] Sylvia Siebig, Silvia Kuhls, Michael Imhoff, Julia Langgartner, Michael Reng, Jürgen Schölmerich, Ursula Gather, and Christian E Wrede. Collection of annotated data in a clinical validation study for alarm algorithms in intensive care: a methodologic framework. *Journal of Critical Care*, 25(1):128–135, mar 2010.
- [63] Maria Cvach. Monitor Alarm Fatigue : An Integrative Review. *Biomedical Instrumentation & Technology*, 46(4):268–277, jul 2012.
- [64] E. A Bustamante, J. P. Bliss, and B. L. Anderson. Effects of varying the threshold of alarm system and workload on human performance. *Ergonomics*, 50(7):1127–1147, 2007.
- [65] James P. Bliss, Corey K Fallon, and Nicolae Nica. The role of alarm signal duration as a cue for alarm validity. *Applied Ergonomics*, 38(2):191–199, mar 2007.
- [66] Todd A Mondor and G Allen Finley. The perceived urgency of auditory warning alarms used in the hospital operating room is inappropriate. *Canadian journal of anaesthesia*, 50(3):221–228, 2003.
- [67] Yuval Bitan, Joachim Meyer, David Shinar, and Ehud Zmora. Nurses’ reactions to alarms in a neonatal intensive care unit. *Cognition, Technology & Work*, 6(4):239–246, nov 2004.
- [68] Yan Xiao, F Jacob Seagull, Fe Nieves-khouw, Nancy Barczak, and Sherry Perkins. Organizational-Historical Analysis of the Failure to Respond to Alarm Problems. *IEEE Transactions on Systems, Man, and Cybernetics-Part A: Systems and Humans*, 34(6):772–778, 2004.
- [69] Michael S. Wogalter and Stephan L. Young. Behavioural compliance to voice and print warnings. *Ergonomics*, 34(1):79–89, 1991.
- [70] R.W. Morris and S.R. Montano. Response times to visual and auditory alarms during anaesthesia. *Anaesthesia and intensive care*, 24(6):682–684, 1996.
- [71] James A Ballas, R Timothy Mullins, Stu Gittelman, Blair Dodds, Kristin Dick, Mary Groshek, John Harding, and Nathan Weber. Common Factors in the Identification of an Assortment of Brief Everyday Sounds. *Journal of experimental psychology: human perception and performance*, 19(2):250–267, 1993.

- [72] Frank E Block, John D Rouse, Matti Hakala, and Chris L Thompson. A proposed new set of alarm sounds which satisfy standards and rationale to encode source information. *Journal of clinical monitoring and computing*, 16(7):541–546, 2000.
- [73] Jed Edworthy. Alarms and human behaviour: implications for medical alarms. *British Journal of Anaesthesia*, 97(1):12–17, may 2006.
- [74] International Standard IEC 60601. Medical Electrical Equipment Parts 18: general requirements for safety collateral standard. General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems. Technical report, International Electrotechnical Commission, 2005.
- [75] P M Sanderson, A Wee, and P Lacherez. Learnability and discriminability of melodic medical equipment alarms. *Anaesthesia*, 61(2):142–147, feb 2006.
- [76] James S P Macdonald and Nilli Lavie. Visual perceptual load induces inattentional deafness. *Attention, Perception, & Psychophysics*, 73(6):1780–1789, aug 2011.
- [77] David D. Woods. Visual momentum: a concept to improve the cognitive coupling of person and computer. *International Journal of Man-Machine Studies*, 21(3):229–244, sep 1984.
- [78] Shobha Phansalkar, Judy Edworthy, Elizabeth Hellier, Diane L Seger, Angela Schedlbauer, Anthony J Avery, and David W Bates. A review of human factors principles for the design and implementation of medication safety alerts in clinical information systems. *Journal of the American Medical Informatics Association*, 17(5):493–501, sep 2010.
- [79] Andries Frans Sanders. Some aspects of the selective process in the functional visual field. *Ergonomics*, 13(1):101–117, 1970.
- [80] C.C. Braun and N.C. Silver. Interaction of signal word and colour on warning labels: differences in perceived hazard and behavioural compliance. *Ergonomics*, 38(11):2207–2220, 1995.
- [81] Jessie Y C Ng, Jo C F Man, Sidney Fels, Guy Dumont, and J. Mark Ansermino. An Evaluation of a Vibro-Tactile Display Prototype for Physiological Monitoring. *Anesthesia & Analgesia*, 101(6):1719–1724, dec 2005.
- [82] K.E. MacLean. Designing with haptic feedback. In *Proceedings 2000 ICRA. Millennium Conference. IEEE International Conference on Robotics and Automation. Symposia Proceedings (Cat. No.00CH37065)*, volume 1, pages 783–788. IEEE, 2000.
- [83] Henricus A.H.C. van Veen and Jan B.F. van Erp. Tactile information presentation in the Cockpit. *Haptic Human-Computer Interaction*, pages 174–181, 2001.
- [84] Michael Imhoff, Silvia Kuhls, Ursula Gather, and Roland Fried. Smart alarms from medical devices in the OR and ICU. *Best Practice & Research Clinical Anaesthesiology*, 23(1):39–50, mar 2009.

- [85] Michael Imhoff and Silvia Kuhls. Alarm Algorithms in Critical Care Monitoring. *Anesthesia & Analgesia*, 102(5):1525–1537, may 2006.
- [86] Felix Schmid, Matthias S Goepfert, and Daniel a Reuter. Patient monitoring alarms in the ICU and in the operating room. *Critical care (London, England)*, 17(2):216, mar 2013.
- [87] Matthias Görge, Boaz A. Markewitz, and Dwayne R. Westenskow. Improving Alarm Performance in the Medical Intensive Care Unit Using Delays and Clinical Context. *Anesthesia & Analgesia*, 108(5):1546–1552, may 2009.
- [88] Scott C. Sheridan and Laurence S. Kalkstein. Progress in Heat Watch-Warning System Technology. *Bulletin of the American Meteorological Society*, 85(12):1931–1941, dec 2004.
- [89] Ioannis Politis, Brewster Stephen, and Pollick Frank. Evaluating multimodal driver displays of varying urgency. *Proceedings of the 5th International Conference on Automotive User Interfaces and Interactive Vehicular Applications*, pages 92–99, 2013.
- [90] R. R. Kennedy, A. F. Merry, G. R. Warman, and C. S. Webster. The influence of various graphical and numeric trend display formats on the detection of simulated changes. *Anaesthesia*, 64(11):1186–1191, nov 2009.
- [91] George Touloumes, Elliot Morse, William C. Chen, Leah Gober, Jennifer Dente, Rachel Lilenbaum, Emily Katzenstein, Ashley Pacelli, Emily Johnson, Yang Si, Adithya Sivaraju, Eric Grover, Rebecca Khozein, Courtney Cunningham, Lawrence J. Hirsch, and Hal Blumenfeld. Human bedside evaluation versus automatic responsiveness testing in epilepsy (ARTiE). *Epilepsia*, 57(1):e28–e32, jan 2016.
- [92] JoAnne Phillips. Clinical Alarms: Complexity and Common Sense. *Critical Care Nursing Clinics of North America*, 18(2):145–156, jun 2006.
- [93] Kelly Creighton Graham and Maria Cvach. Monitor Alarm Fatigue: Standardizing Use of Physiological Monitors and Decreasing Nuisance Alarms. *American Journal of Critical Care*, 19(1):28–34, jan 2010.
- [94] Azizeh Khaled Sowan, Tiffany Michelle Gomez, Albert Fajardo Tarriela, Charles Calhoun Reed, and Bruce Michael Paper. Changes in Default Alarm Settings and Standard In-Service are Insufficient to Improve Alarm Fatigue in an Intensive Care Unit: A Pilot Project. *JMIR Human Factors*, 3(1):e1, jan 2016.

Appendix I - Poster presentation

The poster on the following page with the topic **‘Improving staff response to seizures on the Epilepsy Monitoring Unit with online EEG seizure detection algorithms’** was presented at the 32nd International Epilepsy Congress in Barcelona by N. Rommens. An IBE Travel Bursary was awarded.

Improved staff response to seizures on the EMU with online EEG seizure detection algorithms

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Purpose

Patient safety and quality of diagnostics on the Epilepsy Monitoring Unit (EMU) depends on the response to seizures. Online seizure detection might improve this response. While studies report good sensitivity to detect seizures ^{1,2}, the added value on staff detection is unclear.

In this study, we investigated the added value on already present staff, in terms of extra detected seizures or faster detection time, of two EEG seizure detection algorithms (Encevis EpiScan and BESA Epilepsy).

Methods

- Seizure recordings of patients admitted to the EMU at SEIN between May 2014 and April 2015 were included (maximum of two seizures per patient).
- All recordings were analysed retrospectively by Encevis EpiScan and BESA Epilepsy.
- Sensitivity and latency of the algorithms were compared to staff responses to seizures.
- False positive rates were calculated on 30 uninterrupted recordings (which included up to 24 hours per patient).
- Different patient characteristics were collected or scored and tested if they influenced detector performance (with a Chi-square and a Kruskal-Wallis test).

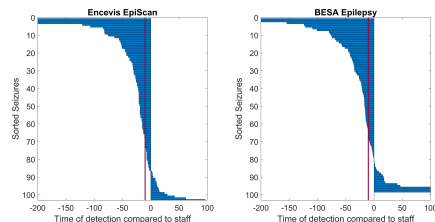


Figure 2: Time of detection of Encevis EpiScan and BESA Epilepsy compared to the staff latency (zero seconds). An extra red line is drawn to take walking time of staff into account (10 seconds).

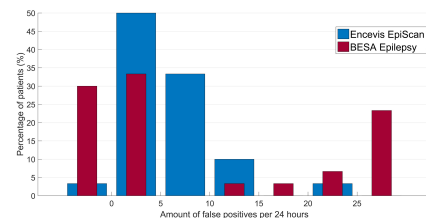


Figure 3: Distribution of false positives for all patients

References

- FURBASS, F., et al. Prospective multi-center study of an automatic online seizure detection system for epilepsy monitoring units. *Clinical Neurophysiology*, 2015, 126.6: 1124-1131.
- HOPFENGÄRTNER, Rüdiger, et al. Automatic seizure detection in long-term scalp EEG using an adaptive thresholding technique: a validation study for clinical routine. *Clinical Neurophysiology*, 2014, 125.7: 1346-1352.

Overall sensitivity algorithms

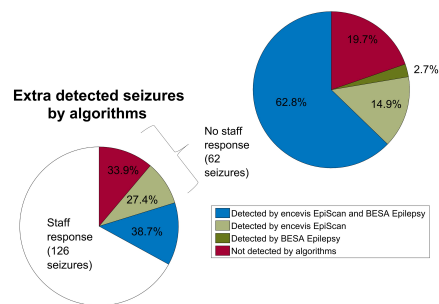


Figure 1: overall sensitivity and sensitivity on seizures missed by staff

Results

Seizure recordings consisted of 188 seizures from 115 patients. Response rate can be seen in Figure 1. Of the 62 seizures missed by staff, 66.1% were recognized by Encevis EpiScan and 38.7% by BESA Epilepsy. Staff performed significantly worse in children and clinically less clear seizures. The algorithm performed best in seizures with clear EEG changes.

The median latency of staff was 31 seconds, 10 seconds for Encevis EpiScan and 14 seconds for BESA Epilepsy. Encevis EpiScan detected earlier than staff in 83.5% and BESA Epilepsy in 81.6%, as can be seen in Figure 2.

The full recordings included 617 hours of EEG. Encevis EpiScan had a median false positive rate of 3.1 per 24 hours and BESA Epilepsy of 2.1 per 24 hours. The distribution of amount of false positives can be seen in Figure 3. False positive rate was significantly higher in children; 7.0 per 24 hours for Encevis EpiScan and 39.1 per 24 hours for BESA Epilepsy. BESA Epilepsy also performed worse in EEGs with frequent epileptiform abnormalities (33.1 per 24 hours).

Conclusion

The use of EEG seizure algorithms in the EMU setting results in both a faster detection of seizures and a larger number of detected seizures. The false positive rate is feasible for use in a clinical situation. Implementation of these algorithms can improve patient safety during EMU recordings and diagnostic quality.

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Appendix II - Draft article

The study described in Chapter 3 was also written as an article for the publication in a journal. The draft article can be seen on the following pages.

Improved staff response to seizures on the EMU with online EEG seizure detection algorithms

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Summary

Objective: Patient safety and quality of diagnostics on the Epilepsy Monitoring Unit (EMU) depends on the staff response to seizures. Online seizure detection might improve this response. While good sensitivity and specificity is reported in literature, the added value in terms on staff response to seizures is unclear. In this study, we investigated the added value of two EEG seizure detection algorithms (encevis EpiScan and BESA Epilepsy) in terms of extra detected seizures or faster detection time.

Methods: EEG-video recordings with seizures of patients admitted to an EMU during one year were included with a maximum of two seizures per patient. All recordings were analysed retrospectively by encevis EpiScan and BESA Epilepsy. Seizures were annotated by experienced observers, with a 10 second margin before and after seizures. Detection sensitivity and latency of the algorithms were compared to staff responses to seizures. False positive rates were calculated on 30 uninterrupted recordings (roughly 24 hours per patient) of consecutive patients admitted to the EMU.

Results: Included EEG-video recordings consisted of 188 seizures in 115 patients. The response rate of staff was 67%, for EpiScan 67% and for BESA Epilepsy 65.4%. Of the 62 missed seizures by staff, 66.1% were recognized by EpiScan and 38.7% by BESA Epilepsy. The median latency of staff response was 31 seconds, for EpiScan 10 seconds and for BESA Epilepsy 14 seconds. In 83.5% of the seizures EpiScan detected earlier than staff and BESA Epilepsy in 81.6%, respectively 65.0% and 65.3% when corrected for walking time from the observation room to the patient. The full recordings included 617 hours of EEG. EpiScan had a median false positive rate of 4.9 per 24 hours and BESA Epilepsy of 2.1 per 24 hours.

Significance: EEG seizure detection algorithms can improve the response to seizures by improving the total number of detected seizures and the speed of detection. The false positive rate is feasible for use in a clinical situation. Implementation of these algorithms might result in more and faster diagnostic testing and observation during seizures.

KEYWORDS: Seizure detection, EEG, Epilepsy, Performance, Real-time, EMU

Introduction

Video-EEG monitoring on an Epilepsy Monitoring Unit (EMU) is widely used as a diagnostic tool in people suspected of a seizure disorder. It can be used to determine seizure type and classification, to distinguish epilepsy from non-epileptic seizures, or to examine or evaluate therapeutic options^{1,2}. People admitted to our EMU are monitored continuously by staff in a separate observation room, using real-time video, audio and EEG measurements. When seizures are detected, nursing staff enter the patient room to reduce the risk of adverse events like falls and traumatic injuries³. Additionally, standardized tests are performed to assess consciousness and cognitive & neurological functioning during seizures, which can help to

determine seizure semiology and type^{4,5}. Staff supervision demands skills and non-stop attention to be continuously vigilant for any sign of a seizure. Seizures may be missed when observation skills are lacking or the attention of the observer is deviated. The study of Atkinson et. al. showed a response rate of 41% to seizures with a mean response time over two minutes⁶. While response rate and time can vary between different EMU's, response rate is always limited by human capabilities. Seizures showing no or only subtle clinical semiology are more often missed, and also seizures outside the scope of the cameras can be missed.

Online seizure detection algorithms might help staff to detect seizures that are otherwise missed or recognized

late. Seizure detection can be done with a variety of signals, like movement, electrodermal activity, heart rate and EEG. This research will focus on seizure detection based on EEG, since it is closest to the source of epilepsy, specific to epilepsy and standardly measured on the EMU. EEG seizure detection has been studied since 1982⁷ and the following decades a lot of research has been done on various approaches to detect seizures⁸⁻¹⁰.

Recently, EEG seizure detection software has also become commercially available, among them encevis EpiScan and BESA Epilepsy. Encevis EpiScan uses two modules which detect rhythmic patterns and waves which are characteristic for epilepsy^{11,12}. To detect seizures, the extracted features are continuously compared with past information from the EEG. The BESA Epilepsy software calculates normalized energy and integrated power for different frequency bands^{13,14}. This algorithm is based on the hypothesis that seizure activity manifests itself by a change in frequency and amplitude that is distinct from non-seizure or background activity. When extracted features are above a threshold for over 10 seconds, a seizure is detected. The performance of EEG detection algorithms has been studied thoroughly and show good sensitivity and false response rate^{8,9}. For encevis EpiScan a sensitivity of 81% with a false detection rate of 0.30 per hour has been reported¹⁵. BESA Epilepsy was reported to have a sensitivity of 87% with a false detection rate of 0.22 per hour¹⁴. Although seizure detection software is commercially available with good sensitivity and specificity, it is unclear what the added value is to seizure monitoring in an EMU. Since these algorithms are not widely implemented in clinical settings¹⁶, this question remains unanswered. It is vital to research the added value of detection algorithms on top of the detection by already present staff, as seizure detection won't be a stand-alone system but an improvement to current staff. In this study, we will therefore investigate this added value, by answering the following questions: 1) What is the current response rate and response time of staff to seizures?, 2) What is the sensitivity, response time and false positive rate of encevis EpiScan and BESA Epilepsy in the same clinical data?, 3) What is the added value on the current response in terms of possible extra detected seizures and faster response time?, and 4) Which people could specifically benefit from these algorithms?

Methods

EMU setting

The EMU at Stichting Epilepsie Instellingen Nederland (SEIN) Heemstede is an 8-bed unit, where all patients stay in separate rooms. Patients are admitted for up to 5 days. Per room, three to four remote control cameras

Key Point Box

- The added value of EEG seizure detection algorithms on top of staff was studied on 188 seizure in EEG recordings and 617 hours of unselected EEG.
- 66.1% of seizures missed by staff were detected by encevis EpiScan and 38.7% by BESA Epilepsy.
- Algorithm detection preceded staff response in 82% to 84% for respectively encevis EpiScan and BESA Epilepsy.
- False positive rate of these algorithms was between 2.1 (BESA Epilepsy) and 4.9 (encevis EpiScan) per 24 hours.
- EEG seizure detection algorithms can improve the response to seizures by improving the total number of detected seizures and the speed of detection

are installed that can capture the whole room. The patient has an alarm button which can be used to alert staff. Patients are monitored continuously by staff (specialized nurses) in an observation room. In this observation room, a real-time EEG, ECG, video and audio stream is shown for each room. An intercom system can be used to communicate with patients. When a seizure is recognized by staff, they attend to the patient to ensure safety and execute standardized diagnostic tests. During daytime three nurses are present and during night two nurses. No automated seizure detection techniques are used.

EEG recordings

A Micromed EEG system (Micromed, Mogliano Veneto, Italy) was used to record EEGs with a sample frequency of 256 Hz, in a in a frequency band of 0.01 to 1000 Hz. The international 10-20 electrode placement system was used. Some patients had additional electrodes to provide higher spatial sampling. After recording and reporting, it is standard practice to cut EEG and video files for data reduction to decrease saving space. Only important data of the registration is saved, like diagnostic tests and seizures.

Data selection

Seizures of patients admitted to the EMU at SEIN Heemstede between May 2014 and April 2015 were included retrospectively in a seizure database. This study was carried out in accordance with the Code of Ethics of the Worlds Medical Association (Declaration of Helsinki) for experiments involving humans. Seizures were only included when they were defined as epileptic in the corresponding EEG report, so that detection by an algorithm is possible. All included seizures had to be longer than five seconds. A maximum of two seizures per patient were included to prevent overrepresentation of certain individuals or seizure types in the database. If more seizures were present in the recording, two were

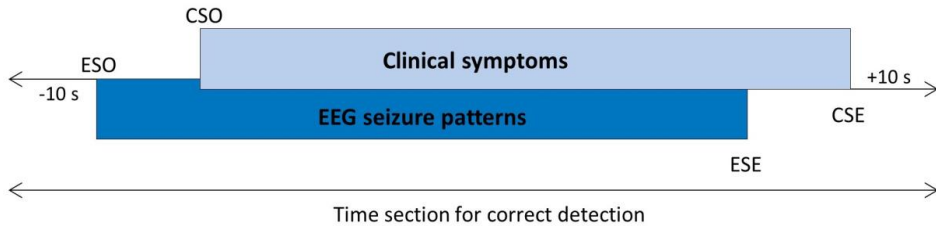


Figure 1: A visualisation of timing of a seizure, this might vary between patients. CSO (clinical seizure onset), CSE (clinical seizure end), ESO (electrographic seizure onset) and ESE (electrographic end) were scored for every seizure in the seizure database and 24-hour database. A correct detection was defined as a detection within ten seconds before the first start of the seizure until ten seconds after the last end of the seizure.

randomly selected out of the first five seizures. In these first seizures, it is important to perform diagnostic tests, so staff response is required. This might not be the case in later seizures. The seizure database encompasses a representative sample of all seizure types occurring in the EMU. Seizures where medical staff was already present at the time the seizure began, were excluded since staff response could not be evaluated. EEG file duration of seizures could vary depending on how files were cut.

False positives were determined on non-stop recordings without selection, to represent the complete setting on an EMU. Therefore, full EEG recordings were included in a 24-hour database. This database included 30 consecutive patients with EMU recordings at SEIN Heemstede in September 2016. For every patient, 16 to 24 consecutive hours of the recording were randomly included.

Scoring of the EEGs

The start and end of all seizures (in the seizure and 24-hour database) were identified by trained reviewers (EG, LJH, NR and an EEG technician). Four different time points were scored; clinical seizure onset (CSO), clinical seizure end (CSE), electrographic seizure onset (ESO), and electrographic seizure end (ESE), as can be seen in Figure 1. The ESO was defined as the moment where the first EEG seizure pattern could be seen and the ESE the last pattern. The CSO was defined as the start of the first clinical symptom. And the CSE was defined as the moment when patients were able to take care of themselves independently, since up to that point it is of value to respond to seizures.

For the seizure database, the electrographic and clinical characteristics of seizures were also scored to evaluate how clear changes were. Both characteristics were scored using values between 1 and 4, resembling no visible manifestations up to very clear manifestations from the perspective of the nurses that monitor the patients. For every 5 seconds, the characteristics were

scored until staff responded, up to the first 60 seconds of the seizure. From these scores, a mean value was calculated. Additionally, seizure classification was collected from the EEG report.

For the 24-hour database the interictal EEG was scored based on the EEG report in four categories: 'Normal interictal EEG', 'Abnormal interictal EEG with non-specific non-epileptiform abnormalities', 'EEG with some epileptiform abnormalities' and 'EEG with frequent epileptiform abnormalities'.

Sensitivity

Staff response was evaluated for the seizure database, by reviewing video retrospectively. A response was defined as staff entering the room of the patient or using the intercom, within 10 seconds after the end of the seizure (when EEG and clinical manifestations have both stopped).

The detection algorithms encevis EpiScan and BESA Epilepsy were tested. The detection algorithms operate the same as in an online situation, but due to online unavailability this could not be tested. A correct detection was defined as a detection within ten seconds before the start of a seizure (CSO or ESO) and up to ten seconds after the seizure end (ESE or CSE) as can be seen in Figure 1. A median sensitivity of staff, encevis EpiScan and BESA epilepsy was calculated.

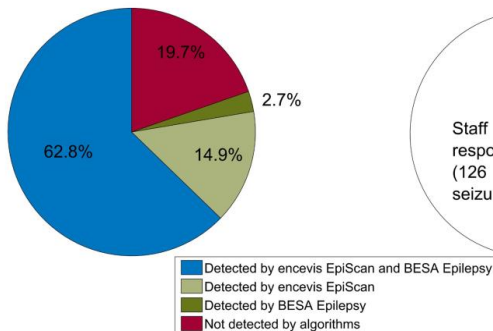
Latency

Latency of staff, encevis EpiScan and BESA Epilepsy were calculated from electrographic seizure onset (ESO). For BESA Epilepsy, 10 seconds were added to account for the delay in the algorithm's online functioning. A median latency and percentile ranges p5-p95 of response were calculated.

False positives

The false positive rate of encevis EpiScan and BESA Epilepsy was calculated on the 24-hour database. A false positive is defined as a detection which is not

Overall sensitivity algorithms



Extra detected seizures by algorithms

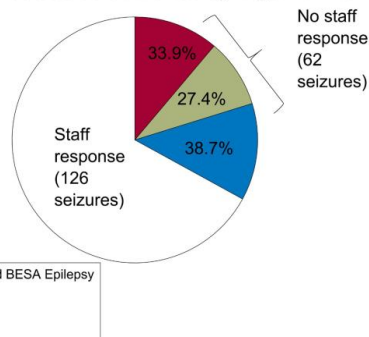


Figure 2: Overall sensitivity of seizure detection algorithms encevis EpiScan & BESA Epilepsy on 188 seizures and sensitivity for seizures missed

Table 1: Performance of staff, encevis EpiScan and BESA Epilepsy

Table 1. Performance of staff, encevis EpiScan and BESA Epilepsy			
	Staff	Encevis EpiScan	BESA Epilepsy
Sensitivity	67.0%	77.6%	65.4%
Median latency in seconds (p5-p95)	31 (-5 – 98)	10 (-4 – 50)	14 (6 – 68)
Median false positives per 24 hours (p5-p95)	-	4.9 (1.2- 13.8)	2.1 (0 – 223)

during a seizure, i.e. beyond ten seconds before the start of a seizure (CSO or ESO) and ten seconds after the last end (ESE or CSE). When a false positive occurred, a black-out period of 10 seconds was defined, in which no new false positives could occur. The median false positive rate and percentile ranges p5-p95 were calculated.

Statistical analysis

The difference in seizure characteristics (age, seizure classification, clinical characteristics and electrographic characteristics) between detected and undetected seizures (separately for staff, encevis EpiScan and BESA Epilepsy) were tested for statistical significance with a Chi-square test. There was tested for statistical difference in false positive rate for age and amount of abnormalities in the EEG, with a Kruskal-Wallis test. Significance level was set at $p \leq 0.05$. All analysis was performed using MATLAB (R2017a., The MathWorks Inc.).

Results

Patients

In total 188 seizures of 115 patients were included in the seizure database and 617 hours of 30 patients in the 24-hour database. The mean age in the seizure database was 28.7 years (SD \pm 17 years) and 24.2

years (SD \pm 15.5 years) in the 24-hour database. Included seizures were generalized onset seizures (9.6%), focal onset seizures with temporal lobe semiology (42.6%), focal onset seizures with extratemporal lobe semiology (45.7%) and seizures that could not be classified (2.1%).

Sensitivity

Performance of staff, encevis EpiScan and BESA Epilepsy can be seen in Table 1. Sensitivity to seizures was 67.0% for staff, 77.6% for encevis EpiScan and 65.4% for BESA Epilepsy. Of the 62 seizures that were missed by staff, 41 could be additionally recognized by encevis EpiScan and 24 by BESA Epilepsy. There were 16 seizures that were only recognized by staff. The comparison of sensitivity of encevis EpiScan and BESA Epilepsy for all seizures and all undetected seizures by staff can be seen in Figure 2.

The sensitivity for seizures with different characteristics can be seen in Table 2. Staff had significantly lower response rate for children, focal onset seizures and clinically less clear seizures. No statistical difference was found between children or adults in encevis EpiScan and BESA Epilepsy. Focal onset seizures with extra-temporal lobe semiology and seizures with (almost) no electrographic characteristics were still difficult to detect for these algorithms.

Latency

Staff had a median response time of 31 seconds, encevis EpiScan of 10 seconds and BESA Epilepsy of 14 seconds as can be seen in Table 1. In 83.5% of the seizures detected by staff, encevis EpiScan detected the seizure faster than the staff response. In 81.6% of the seizures detected by staff, BESA Epilepsy detected the seizure faster than the staff response. Figure 3 shows the time of detection of encevis EpiScan and BESA Epilepsy compared to staff latency.

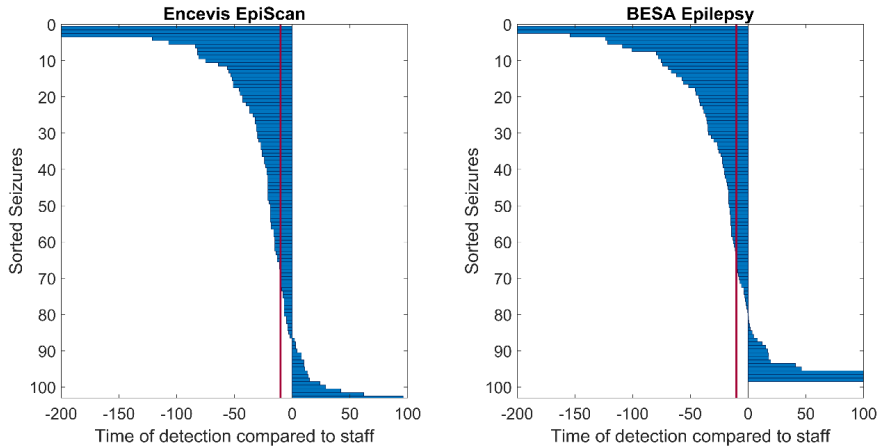


Figure 3: Time of detection of Encevis EpiScan and BESA Epilepsy compared to the staff latency (zero seconds). An extra red line is drawn to take walking time of staff into account (10 seconds). Some outliers could not be shown in the figure; for Encevis EpiScan this was -1579, -611 and -215 seconds and for BESA Epilepsy this was -552, -253, 309, 392 and 3173 seconds.

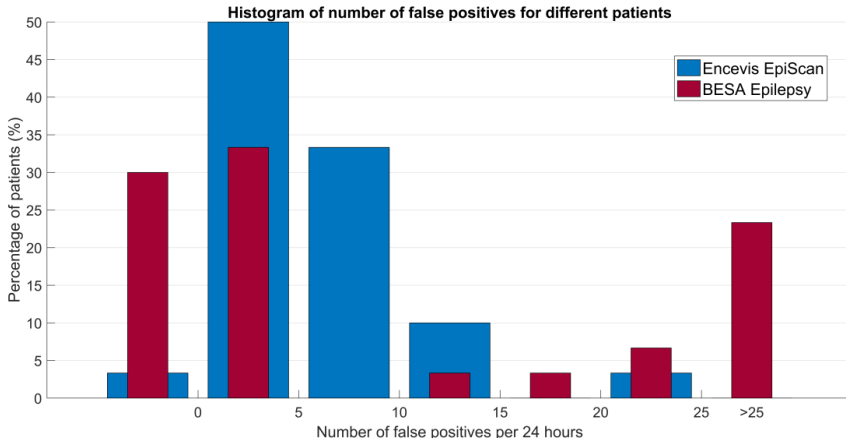


Figure 4: Histogram of number of false positives for different patients.

False positives

Encevis EpiScan had a median false positive rate of 4.9 per 24 hours per patient and BESA Epilepsy 2.1 per 24 hours per patient. Encevis EpiScan had low false positive rates for almost every patient. Whereas BESA Epilepsy had zero false positives for most patients, but also some outliers with a lot of false positives as can be seen in Figure 4. Additionally, Encevis EpiScan had most false positives during the first hours, probably due to a learning period. When the alarm of Encevis EpiScan would be turned off during the first hour, false positive rate would decrease with 36.4% and even 46.1% if it would be turned off the first two hours. Children had a higher false positive rate than adults for encevis Episcan ($p=0.0430$), with a median false

positive rate of 6.99 per 24 hours for children and 4.47 per 24 hours for adults. The difference in false positive rate between the amount of abnormalities in the EEG was not significant.

BESA Epilepsy also had a higher false positive rate in children compared to adults ($p=0.0057$), with a median false positive rate of 39.1 per 24 hours for children and 1.28 per 24 hours for adults. Additionally, EEGs with frequent epileptiform abnormalities had a significant ($p=0.0308$) higher false positive rate, with a median false positive rate of 33.1 per 24 hours (compared to 1.16-9.86 for EEGs with less abnormalities).

Table 2: Sensitivity of staff, encevis EpiScan and BESA Epilepsy for different characteristics of seizures. All characteristics were tested for statistical difference with a Chi-square test.

Table II. Sensitivity of staff, encevis EpiScan and BESA Epilepsy for different characteristics							
		Staff		encevis EpiScan		BESA Epilepsy	
		Sensitivity	p-value	Sensitivity	p-value	Sensitivity	p-value
All patients		67.0%	-	77.6%	-	65.4%	-
Age	Children under 18 year (n=54)	59.3%	0.0338	79.6%	0.681	72.2%	0.214
	Adults (n=134)	70.1%		76.9%		62.7%	
Seizure classification	Generalized onset (n=18)	88.9%		100%		100%	
	Focal onset seizures	75.0%	0.00380	86.3%	<0.001	71.3%	<0.001
	Temporal (n=80) Extratemporal (n=86)	55.8%		64.0%		53.5%	
	Unclear classification (n=4)	-		-		-	
Clinical characteristics	No visible changes (n=27)	37.0%		85.2%		66.7%	
	Subtle clinical symptoms (n=119)	67.2%	<0.001	77.3%	0.509	61.3%	0.307
	Clear clinical symptoms (n=34)	82.4%		70.6%		73.5%	
	Very clear clinical symptoms (n=8)	100%		87.5%		87.5%	
Electrographic characteristics	No visible changes (n=6)	66.7%		66.7%		0%	
	Subtle changes (n=73)	54.8%	0.0300	58.9%	<0.001	39.7%	<0.001
	Clear focal changes (n=73)	72.6%		89.0%		83.6%	
	Clear diffuse changes (n=36)	80.6%		94.4%		91.7%	

Discussion

Staff response to seizures can be improved by online EEG seizure detection algorithms by improving both the number of detected seizures and the response latency after seizure start. We were able to show that up to 66.1% of the 62 undetected seizures could be recognized by EEG seizure detection algorithms. Additionally, in most seizures the algorithm detection preceded detection by staff, as was measured by response time. The algorithms had acceptable median false positive rates. Especially children, patients with focal onset seizures (with temporal lobe semiology) and patients with seizures with clear electrographic changes could benefit from these algorithms. These seizures showed a lower response rate of staff, while the algorithms were able to detect these seizures. Using seizure detection algorithms on these patients might help to ensure patient safety and to assess consciousness and cognitive & neurological function. Seizures with none to very subtle electrographic characteristics were difficult to detect by the algorithms. Additionally, a higher false positive rate for both algorithms was found for children, and for EEGs with frequent epileptiform abnormalities for BESA Epilepsy.

The staff response and latency found in this study, is better than described in literature, where a response rate of 41% with an average response time of 142.3 seconds has been shown ⁶. This can be explained by differences between EMU settings, e.g. staff experience or EMU layout. The sensitivity and specificity of the algorithms described in this study, are comparable to literature ^{14,15}. Delay time has not been described. Additionally, to our knowledge, the added value on already present staff has never been studied. This information is crucial, since a seizure detection algorithm will not be a stand-alone system but an addition to current staff.

Staff response and sensitivity of detection algorithms are influenced by characteristics of seizures and patients. When there is a low response rate of staff but algorithms are able to detect seizures, patients could especially benefit from these algorithms. Staff response was highly dependent on the appearance of clinical characteristics, since staff mostly respond based on symptoms seen on a video stream. The algorithms, on the other hand, were mostly dependent on presence of electrographic changes. This could also be seen in the sensitivity for different seizure

classifications. For example, generalised seizures are electrographically and clinically very clear and therefore have a high response rate of staff and algorithms. On the contrary, focal onset seizures with extra-temporal lobe semiology were short with little clinical and electrographic changes and therefore have lower response rate of staff and algorithms. So, patients with clinically less clear seizures that show electrographic changes could benefit from these algorithms. Especially focal onset seizures with temporal lobe semiology had a low sensitivity of staff but a high sensitivity of the algorithms. Additionally, a lower sensitivity of staff to seizures of children was seen. Therefore, children might also benefit from seizure detection algorithms. The low sensitivity of staff is mostly likely caused by the type of seizures that children have, making it more difficult to detect. A higher false positive rate was also found for children, making it less applicable to use these algorithm. This might be caused since the EEG has more variations in children, making it more difficult to differentiate the normal EEG from ictal patterns. Also, children had more often abnormalities in the EEG, which also influenced the function of the algorithms. Encevis EpiScan still had an acceptable rate for children and can therefore be preferred when used on children.

The algorithms could not be tested online, since at time of research they were not ready for online implementation. Therefore, the true effect of these algorithms could not be researched. For example, staff might not react to all alarms or take a long time to react to alarms. Additionally, two different databases were used to test the algorithms on a high amount of seizures and long periods of continuous data. Using only full recordings can provide a better view on the function of the algorithms, since it shows the amount of false positives relatively to the true positives. However, this was not present at time of research. And lastly, staff response can vary between different EMU settings. Depending on how staff is educated and patients are monitored, response rate can be higher or lower. Therefore, the added value of these algorithms can also be different in another setting.

Online EEG seizure detection algorithms can improve the nurse response to seizures on an EMU, by detecting extra seizures and improving response time. The false positive rate is feasible for use in a clinical setting. Implementation of these algorithm can help to ensure patient safety and improve quality of diagnostics by assessing consciousness and cognitive and neurological function timely.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Cascino GD. Video-EEG Monitoring in Adults. *Epilepsia*. 2002;43(SUPPL. 3):80-93. doi:10.1046/j.1528-1157.43.s.3.14.x.
2. Ghougassian DF, D'Souza W, Cook MJ, O'Brien TJ. Evaluating the Utility of Inpatient Video-EEG Monitoring. *Epilepsia*. 2004;45(8):928-932. doi:10.1111/j.0013-9580.2004.51003.x.
3. Fahoum F, Omer N, Kipervasser S, Bar-Adon T, Neufeld M. Safety in the epilepsy monitoring unit: A retrospective study of 524 consecutive admissions. *Epilepsy Behav*. 2016;61:162-167. doi:10.1016/j.yebeh.2016.06.002.
4. Johanson M, Valli K, Revonsuo A. How to assess ictal consciousness? *Behav Neurol*. 2011;24(1):11-20. doi:10.3233/BEN-2011-0316.
5. Bauerschmidt A, Koshkelashvili N, Ezeani CC, et al. Prospective assessment of ictal behavior using the revised Responsiveness in Epilepsy Scale (RES-II). *Epilepsy Behav*. 2013;26(1):25-28. doi:10.1016/j.yebeh.2012.10.022.
6. Atkinson M, Hari K, Schaefer K, Shah A. Improving safety outcomes in the epilepsy monitoring unit. *Seizure*. 2012;21(2):124-127. doi:10.1016/j.seizure.2011.10.004.
7. Gotman J. Automatic recognition of epileptic seizures in the EEG. *Electroencephalogr Clin Neurophysiol*. 1982;54(5):530-540. doi:10.1016/0013-4694(82)90038-4.
8. Acharya UR, Vinitha Sree S, Swapna G, Martis RJ, Suri JS. Automated EEG analysis of epilepsy: A review. *Knowledge-Based Syst*. 2013;45:147-165. doi:10.1016/j.knosys.2013.02.014.
9. Alotaiby TN, Alshebeili SA, Alshawi T, Ahmad I, Abd El-Samie FE. EEG seizure detection and prediction algorithms: a survey. *EURASIP J Adv Signal Process*. 2014;2014(1):183. doi:10.1186/1687-6180-2014-183.
10. Ramgopal S, Thome-Souza S, Jackson M, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy Behav*. 2014;37:291-307. doi:10.1016/j.yebeh.2014.06.023.
11. Hartmann MM, Furbass F, Perko H, et al. EpiScan: Online seizure detection for epilepsy monitoring units. In: *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. IEEE; 2011:6096-6099. doi:10.1109/IEMBS.2011.6091506.
12. Furbass F, Hartmann M, Perko H, et al. Combining

time series and frequency domain analysis for a automatic seizure detection. In: *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. IEEE; 2012:1020-1023. doi:10.1109/EMBC.2012.6346107.

13. Hopfengärtner R, Kerling F, Bauer V, Stefan H. An efficient, robust and fast method for the offline detection of epileptic seizures in long-term scalp EEG recordings. *Clin Neurophysiol*. 2007;118(11):2332-2343. doi:10.1016/j.clinph.2007.07.017.
14. Hopfengärtner R, Kasper BS, Graf W, et al. Automatic seizure detection in long-term scalp EEG using an adaptive thresholding technique: A validation study for clinical routine. *Clin Neurophysiol*. 2014;125(7):1346-1352. doi:10.1016/j.clinph.2013.12.104.
15. Fürbass F, Ossenblok P, Hartmann M, et al. Prospective multi-center study of an automatic online seizure detection system for epilepsy monitoring units. *Clin Neurophysiol*. 2015;126(6):1124-1131. doi:10.1016/j.clinph.2014.09.023.
16. Rubboli G, Beniczky S, Claus S, et al. A European survey on current practices in epilepsy monitoring units and implications for patients' safety. *Epilepsy Behav*. 2015;44:179-184. doi:10.1016/j.yebeh.2015.02.004.

Appendix III - Technical background of the ECG algorithm

Some additional background information is given in this Appendix about different steps of the ECG algorithm.

Pan-Tompkins algorithm

The first steps of the Pan Tompkins algorithm are multiple preprocessing steps as can be seen in Figure 7.1. First, a bandpass filter between 5-15 Hz is applied to remove baseline wander and muscle noise. Next the derivative and square of the signal is taken. And lastly, a moving average filter (of 0.15 seconds) is taken to reduce noise in the signal.

The QRS-complex is detected with the second part of the Pan-Tompkins algorithm as can be seen in Figure 7.1. Two adaptive thresholds are calculated, a noise threshold (T_{noise}) and signal threshold (T_{sig}). For the first two seconds, these thresholds are normalized. The threshold signal is initialized to a third of the maximum of the ECG in the first two seconds. And the threshold noise is normalized to a half of the mean of the ECG in the first two seconds.

Next, peaks in the ECG are detected. Every peak is defined as a noise peak or a signal peak, depending on the thresholds. When a peak is above the signal threshold, it is identified as a possible QRS-complex and the parameter 'Signal level (L_{sig})' is raised based on the previous signal level and the amplitude of the peak (A_{peak}). When a peak is between the two thresholds, it is identified as a noise peak and the 'Noise level (L_{noise})' is raised based on the previous noise level and the amplitude of the peak (A_{peak}). The thresholds are adjusted to these signal and noise levels, as can be seen in Equations (7.1) to (7.4). This is done for every peak. All peaks that are identified as signal peaks, are seen as possible QRS-complexes.

$$L_{\text{sig}} = 0.125A_{\text{peak}} + 0.875L_{\text{sig}} \quad (7.1)$$

$$L_{\text{noise}} = 0.125A_{\text{peak}} + 0.875L_{\text{noise}} \quad (7.2)$$

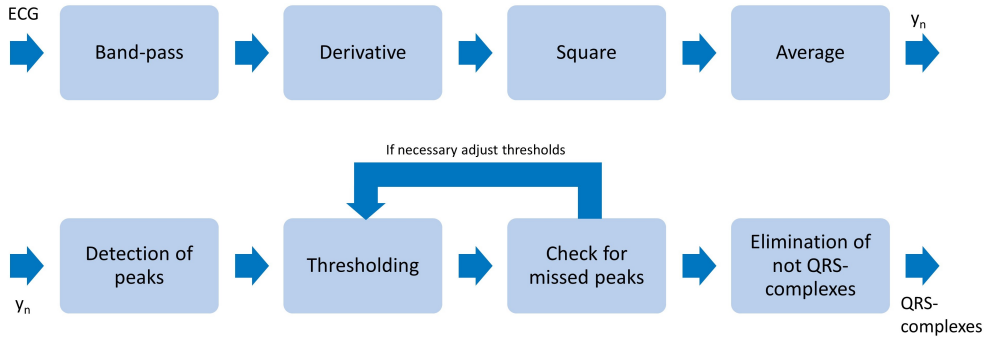


Figure 7.1: Flow-chart of the steps of the Pan-Tompkins algorithm to detect the QRS-complex. The panel above shows the pre-processings steps of the algorithm; a bandpass filter between 5-15 Hz, a derivative and the square of the signal. The panel below shows the detection of QRS-complexes; first all peaks in the signal are detected, based on adaptive threshold is determined which are possible QRS-complexes. There is checked for missed tops and thresholds are adapted based on that. And lastly, not R-tops are eliminated.

$$T_{\text{sig}} = L_{\text{noise}} + 0.25|(L_{\text{sig}} - L_{\text{noise}})| \quad (7.3)$$

$$T_{\text{noise}} = 0.5L_{\text{sig}} \quad (7.4)$$

Next is checked if QRS-complexes are possible missed due to a too high threshold. If the last RR-interval (that is the time between QRS-complexes) deviates from the mean RR-interval (of the last 8 beats), the thresholds will be halved. Additionally, when no new QRS-complex is found after 1.66 times the mean RR-interval is passed, there will be searched back for QRS-complexes. If QRS-complexes are found, the threshold levels are adjusted so that new peaks can be found. The value of 1.66 has a physiological origin, since the time value between heart beats cannot change that quickly.

In the last part of the algorithm, possible QRS-complexes are eliminated when it is not likely that it is a QRS-complex. QRS-complexes inside 200 ms after the last QRS-complex are deleted, since this is physiologically not possible due to the refractory period where ventricle depolarisation cannot occur despite a stimulus. When a QRS-complex occurs after this 200 ms but within 360 ms, it might be a T wave. This is evaluated by calculated the slope of the waveform at that position. When this slope is less than half of the previous waveform, it is considered a T-wave.

Adaptations to the Pan Tompkins algorithm

Some additions to the Pan Tompkins algorithm were necessary for a proper function of the algorithm. Four steps were added to reduce false positives and increase latency. Two of these steps were added in the adjustments of thresholds:

- If the mean RR-interval is too high (more than >220 beats/min), the thresholds (T_{sig} & T_{noise}) will be doubled. This was added, since if the RR-interval would decrease, it would influence the thresholds.
- When the step 'Check for missed tops', does not result in new QRS-complexes, the threshold are normalized to the amplitude of the ECG (in the same way it was done during the first two seconds). This was added, since in some situations thresholds remained too high and now new QRS-complexes were found for the rest of the ECG file.

The other two steps were added in the elimination of not R-tops:

- When a peak is inside 360 ms after the last QRS-complex, it is unlikely another QRS-complex. Therefore, when the RR-interval of this new peak is smaller than 0.6 times the mean RR-interval (of the last 8 beats), it is defined as a noise peak. There is chosen for this value, since the heart rate cannot change that quickly. This method was already present for when the RR-interval decreased too much, but we wanted to add this also when the RR-interval would increase since it has the same physiological meaning.
- If a QRS-complex corresponds with a RR-interval higher than 220 beats/min, it cannot be a QRS-complex and will be defined as a noise peak.

Appendix IV - Examples of performance of the ECG algorithm

These Appendix shows different examples of the performance of the ECG algorithm.

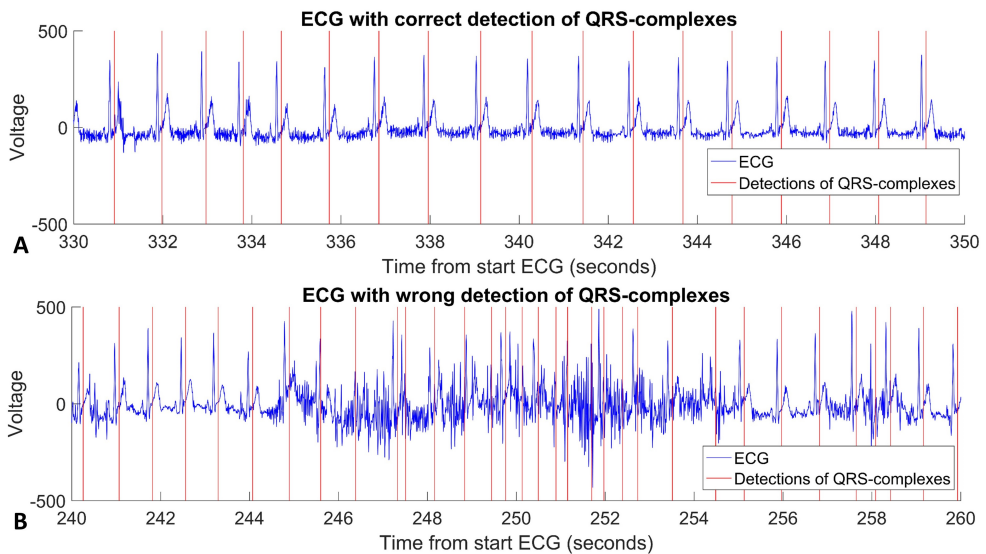


Figure 7.2: Example of detection of QRS-complexes in a patient of the 24-hour database. Figure A shows correct detections. Figure B shows wrong detections during an artefact.

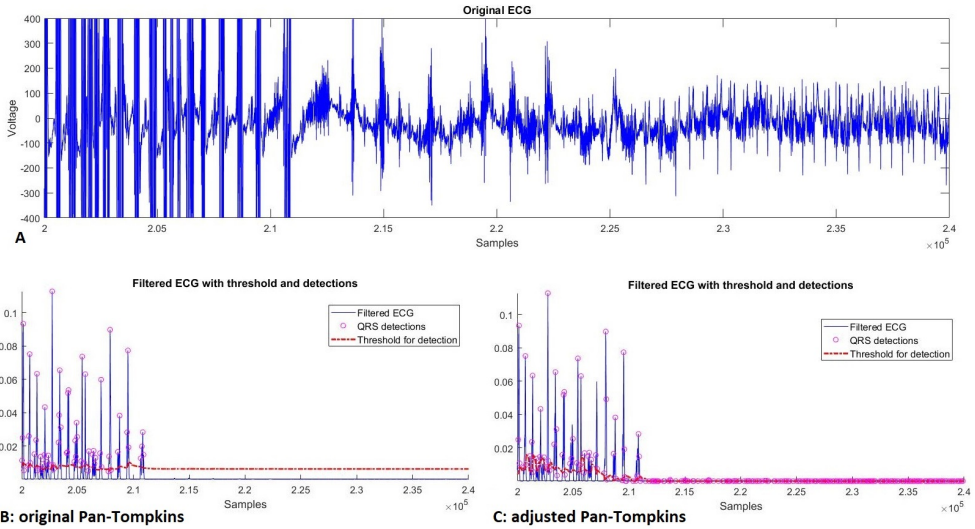


Figure 7.3: This figures shows a problem of QRS-detection with the Pan-Tompkins algorithm. Figure A shows the original ECG. Figure B shows the filtered ECG signal with adaptive threshold for QRS-complexes. This is calculated with the original Pan-Tompkins algorithm. Due to a high energy artefact, thresholds are too high and no new QRS-complexes can be detected. Figure C shows the results when improvements to the Pan-Tompkins algorithm were added. A step was added, that when the search back for QRS-complexes do not result in new found tops, thresholds will be normalized. This will always result in the detection of new QRS-complexes, as can be seen in the figure.

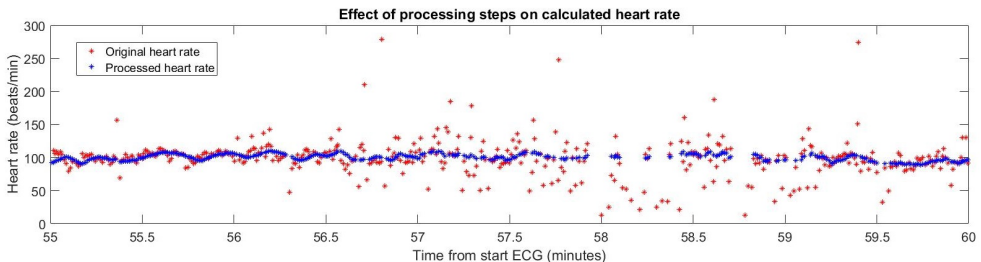


Figure 7.4: Example of the effect of the processing step of the heart rate in a patient of the 24-hour database. In red the original calculated heart rate can be seen, without any processing. In blue shows the processed heart rate, where outliers are removed and trend is saved.

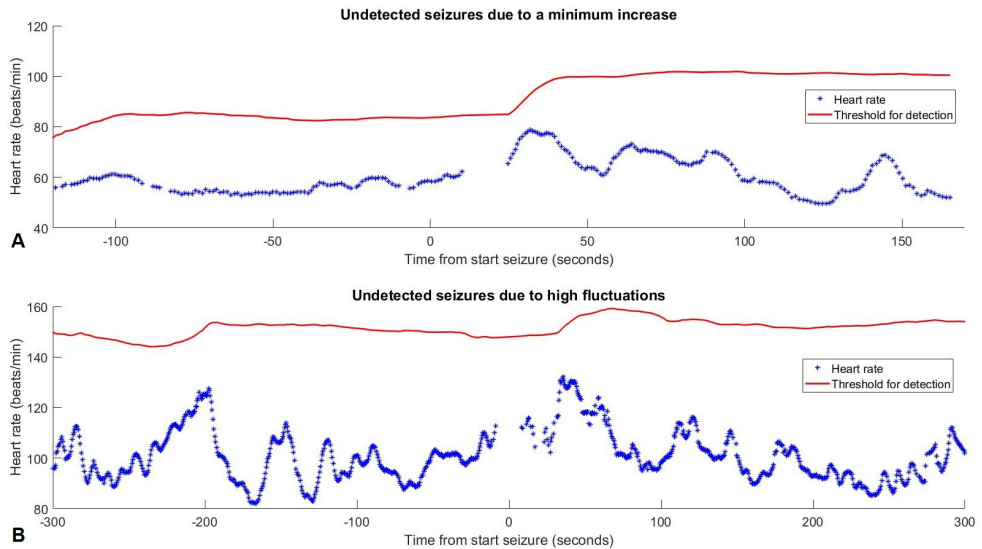


Figure 7.5: Two examples of undetected seizures in the Seizure Database. At time-point 0, the seizure started. Figure A shows a minimum increase in heart rate, by which no detection was possible. Figure B shows a high fluctuation in heart rate before the seizure started. This resulted in a higher threshold for detection, and therefore no detection.